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EFFECTS OF KETAMINE AND ESKETAMINE ON SUICIDAL IDEATION WITHIN THE FIRST 24 HOURS IN ADULTS WITH DEPRESSIVE DISORDERS: VARIABILITY IN CLINICAL FINDINGS AND INTERPRETATIVE CHALLENGES - A NARRATIVE REVIEW

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ABSTRACT

Background: Ketamine and esketamine have been studied as rapid-acting interventions in adults with depressive disorders and suicidal ideation, but findings vary across populations, settings, comparators, routes, and outcome measures.

Aim: To examine their effects on suicidal ideation within the first 24 hours and to identify factors contributing to variability across studies.

Methods: This narrative review used a structured PubMed and Scopus search for English-language studies published from January 2000 through April 30, 2026. Clinical trials and relevant secondary studies were considered. No formal risk-of-bias assessment or quantitative synthesis was performed.

Results: Intravenous ketamine studies reported rapid reductions in suicidal ideation, although findings were inconsistent. One midazolam-controlled trial showed a 4.96-point greater reduction in the Scale for Suicide Ideation score at 24 hours, whereas another found no significant difference in the primary Beck Scale for Suicide Ideation outcome. Intranasal esketamine added to intensive standard-of-care treatment improved depressive symptoms at 24 hours, but clinician-rated suicidality did not differ significantly between groups in either ASPIRE trial.

Conclusions: Intravenous ketamine may rapidly reduce suicidal ideation in selected adults. Intranasal esketamine has shown clearer early effects on depressive symptoms than on suicidality-specific outcomes. Standardized measures and longer follow-up are needed.

KEYWORDS

Ketamine, Esketamine, Suicidal Ideation, Major Depressive Disorder, Treatment-Resistant Depression, Rapid-Acting Antidepressants, Early Treatment Response

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1. Introduction

Major depressive disorder is a common and disabling psychiatric disorder associated with suicidal ideation, suicide attempts, and increased mortality.(1,2) Suicidal ideation in the context of depression is particularly concerning when accompanied by intent, planning, recent suicidal behavior, marked hopelessness, agitation, or the need for psychiatric hospitalization. In such circumstances, rapid reduction in suicidal ideation is clinically important.

Ketamine and esketamine have therefore attracted considerable interest as rapid-acting interventions for depressive disorders. Racemic ketamine, most commonly administered as a subanesthetic intravenous infusion, has been studied in adults with major depressive disorder, treatment-resistant depression, and clinically significant suicidal ideation.(3,4) Esketamine, the S-enantiomer of ketamine, has been developed as an intranasal formulation and evaluated in adults with treatment-resistant depression and in adults with major depressive disorder accompanied by acute suicidal ideation with intent.(5–7) Their rapid antidepressant effects have raised the question of whether these agents may also reduce suicidal ideation within the first 24 hours after administration.(8–10)

However, the interpretation of ketamine- and esketamine-related effects on suicidal ideation remains complex.(11,12) Available clinical trials differ substantially in patient populations, baseline suicide risk, chronicity of suicidal ideation, treatment setting, route of administration, dosing schedule, comparator condition, concomitant standard-of-care treatment, and follow-up duration. These differences are particularly relevant when interpreting outcomes within the first 24 hours, because early changes may reflect pharmacological effects, rapid improvement in depressive or anxiety-related symptoms, crisis stabilization, close monitoring, hospitalization, or a combination of these factors.

The measurement of suicidal ideation is another important source of interpretative difficulty. Some studies used dedicated suicidal ideation scales, whereas others relied on single suicide-related items from

depression rating scales or clinician-rated global assessments of suicide risk.(13,14) These instruments do not necessarily capture the same clinical construct and may differ in sensitivity to early change. Consequently, the apparent effect of ketamine or esketamine on suicidal ideation may depend not only on the intervention itself but also on how suicidal ideation is defined and measured.

The first 24 hours after treatment represent a clinically relevant assessment window, particularly in patients experiencing an acute suicidal crisis. However, findings during this period have not been fully consistent and appear to vary according to the clinical population, treatment context, assessment instrument, and intervention studied.(3,4,6,7)

Therefore, this narrative review aims to examine the effects of ketamine and esketamine on suicidal ideation within the first 24 hours in adults with depressive disorders, with particular emphasis on variability in clinical findings and methodological factors that complicate interpretation of trial results. Rather than estimating a pooled treatment effect, this review focuses on the clinical and methodological reasons why findings differ across studies and how the current evidence should be interpreted in research and clinical practice.

2. Methods

This narrative review was designed to synthesize and critically discuss evidence on the effects of ketamine and esketamine on suicidal ideation within the first 24 hours in adults with depressive disorders. Particular emphasis was placed on variability in clinical findings and methodological factors that may complicate the interpretation of suicidal ideation outcomes assessed within the first 24 hours.

A structured literature search was conducted in PubMed and Scopus, covering publications available through April 30, 2026. Search terms included combinations of keywords related to ketamine and esketamine, depressive disorders, suicidal ideation, and early treatment response, including “ketamine”, “esketamine”, “S-ketamine”, “suicid*”, “suicidal ideation”, “depression”, “major depressive disorder”, “treatment-resistant depression”, “24 hours”, “24 h”, “day 1”, “rapid”, and “acute”. Searches were limited to human studies published in English from January 2000 through April 30, 2026. Studies conducted exclusively in children or adolescents were excluded because the review focused on adult populations.

Searches were conducted iteratively to identify primary clinical studies reporting suicidal ideation outcomes within the first 24 hours, as well as relevant pooled and post hoc analyses, systematic reviews, meta-analyses, and methodological studies addressing the measurement of suicidal ideation. Scopus was used as a supplementary database to identify additional relevant publications and supplement the PubMed search.

Primary clinical studies were considered if they involved adults with depressive disorders, evaluated ketamine or esketamine, and reported suicidal ideation outcomes within the first 24 hours after administration. Studies involving mixed psychiatric populations were included as contextual evidence when they reported findings relevant to participants or subgroups with depressive disorders. Randomized and controlled trials of intravenous ketamine and intranasal esketamine were prioritized because they provided the most direct evidence relevant to the review question. Studies of alternative routes of administration and repeated-dose protocols were included as contextual evidence because their designs differed substantially from the core single-dose intravenous ketamine and intranasal esketamine trials. Systematic reviews, meta-analyses, pooled analyses, post hoc analyses, and methodological studies were used to contextualize the primary findings and discuss limitations in the measurement and interpretation of suicidal ideation outcomes.

As this was a narrative review, no formal risk-of-bias assessment, certainty-of-evidence grading, or quantitative synthesis was performed. The aim was not to estimate a pooled treatment effect, but to provide a clinically oriented and methodologically informed synthesis of the factors contributing to variability across studies and the interpretation of suicidal ideation outcomes within the first 24 hours.

3. Ketamine and esketamine as rapid-acting interventions in depressive disorders

Ketamine and esketamine differ from conventional monoaminergic antidepressants in their pharmacological profiles and expected time courses of clinical response. Racemic ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist that has most commonly been studied in depression as a single subanesthetic intravenous infusion. Esketamine, the S-enantiomer of ketamine, has been developed as an intranasal formulation and evaluated as an adjunctive treatment for treatment-resistant depression and for major depressive disorder accompanied by acute suicidal ideation with intent.(3,5–7)

The clinical relevance of these agents for suicidal ideation is related primarily to their rapid onset of action. In trials of intravenous ketamine, changes in depressive symptoms and suicidal ideation have been assessed within hours and at approximately 24 hours after dosing. Similarly, intranasal esketamine trials in patients with major depressive disorder and acute suicidal ideation with intent included assessments at several early post-dose time points, including approximately 24 hours after the first dose.(3,6,7) This early assessment window is clinically important because patients with active suicidal ideation may require immediate clinical stabilization while longer-term treatment strategies are initiated.

However, findings on rapid improvement should not be considered directly comparable across ketamine and esketamine studies. Intravenous ketamine trials often examined a single infusion and frequently used midazolam as an active comparator. By contrast, intranasal esketamine trials in patients with major depressive disorder and acute suicidal ideation with intent evaluated esketamine in addition to comprehensive standard-of-care treatment, including psychiatric hospitalization and newly initiated or optimized oral antidepressant therapy. Therefore, differences in route of administration, comparator condition, treatment setting, and concomitant care must be considered when interpreting suicidal ideation outcomes within the first 24 hours.(3,4,6,7)

4. Evidence for effects on suicidal ideation within the first 24 hours

4.1 Intravenous ketamine

Evidence for the rapid effects of intravenous ketamine on suicidal ideation comes primarily from clinical studies involving adults with major depressive disorder or treatment-resistant depression, some of whom were selected for clinically significant suicidal ideation. These studies generally evaluated a single subanesthetic intravenous ketamine infusion, most commonly 0.5 mg/kg, and assessed depressive symptoms and suicidal ideation at one or more time points within the first 24 hours after administration.(3,4,15,16)

A key randomized, midazolam-controlled trial included 80 adults with major depressive disorder and clinically significant suicidal ideation. Ketamine produced a significantly greater reduction in suicidal ideation at 24 hours than midazolam, with a between-group difference of 4.96 points on the Scale for Suicide Ideation.(3) The use of midazolam as an active comparator strengthened the trial design and may have reduced expectancy effects relative to an inert placebo, although the sample size was moderate and the primary randomized comparison focused on the 24-hour outcome.

Other intravenous ketamine studies also reported early reductions in suicidal ideation, but findings varied according to the outcome measure and assessment time point.(4,17) In the trial by Murrough et al., ketamine did not differ significantly from midazolam on the primary BSI outcome at 24 hours, although the MADRS suicidal ideation item showed a borderline between-group difference favoring ketamine; a significant between-group difference in BSI emerged at 48 hours.(4) These findings illustrate how the apparent effect of ketamine on suicidal ideation may depend on the instrument used and the timing of assessment.

A larger placebo-controlled trial by Abbar et al. included hospitalized adults with severe suicidal ideation across bipolar, depressive, and other psychiatric disorders. Participants received two intravenous infusions of ketamine or saline, administered at baseline and 24 hours, with suicidal ideation assessed at several early time points, including Day 1 before the second infusion. Although ketamine increased the overall rate of suicidal remission at Day 3, treatment effects differed according to diagnosis, and the between-group difference was not statistically significant in the subgroup with depressive disorders. The mixed diagnostic population and the primary endpoint after two infusions limit the direct comparability of this trial with single-infusion studies focused specifically on depressive disorders.(18)

An additional interpretative issue is whether the reduction in suicidal ideation represents an effect specific to suicidal ideation or is largely associated with broader improvement in depressive and anxiety-

related symptoms. A post hoc analysis of a ketamine–midazolam trial found that changes in suicidal ideation were closely related to improvements in core mood and anxiety-related symptoms.(11) Therefore, intravenous ketamine appears to show a clinically relevant early signal in selected patients with depression, but the specificity and durability of this effect remain uncertain.

A 2026 systematic review and meta-analysis of 21 studies involving 927 high-risk participants found a significant overall reduction in suicidal ideation after ketamine treatment. However, the evidence was rated as low quality, and differences in study populations, designs, treatment protocols, and assessment time points limit its direct applicability to suicidal ideation outcomes within the first 24 hours in adults with depressive disorders.(19)

4.2 Intranasal esketamine

Intranasal esketamine has been evaluated primarily as an adjunctive treatment in adults with major depressive disorder and acute suicidal ideation with intent, rather than as a standalone intervention specifically targeting suicidal ideation.(5–7) This distinction is important because the pivotal ASPIRE trials were conducted in the context of intensive standard-of-care treatment, including psychiatric hospitalization and initiation or optimization of oral antidepressant therapy.(6,7)

In an early double-blind, randomized proof-of-concept study, intranasal esketamine added to standard of care was associated with rapid improvement in depressive symptoms in patients with major depressive disorder at imminent risk for suicide. A greater reduction in the MADRS suicidal thoughts item was observed with esketamine at 4 hours, but not at 24 hours. Between-group differences in clinician-rated global suicide risk were not statistically significant at any assessed time point.(5)

The phase 3 ASPIRE I and ASPIRE II trials further evaluated intranasal esketamine in hospitalized adult patients with major depressive disorder and active suicidal ideation with intent. In both trials, esketamine plus standard-of-care treatment produced greater improvement in depressive symptom severity at 24 hours compared with placebo plus standard of care. However, clinician-rated suicidality scores improved rapidly in both treatment groups, and between-group differences were not statistically significant in the individual trials.(6,7)

Taken together, the esketamine data support rapid improvement in depressive symptom severity in patients with major depressive disorder and acute suicidal ideation with intent, but provide less definitive evidence for an effect specific to suicidal ideation.(6,7,20) The interpretation of esketamine outcomes within the first 24 hours is therefore strongly influenced by the intensity of concurrent clinical care, the use of global clinician-rated measures of suicidality, and the overlap between improvement in depressive symptoms and reduction in suicidal ideation.(6,7,20,21)

4.3 Other routes and repeated-dose protocols

Evidence from repeated-dose ketamine protocols and alternative routes of administration is more heterogeneous than evidence from single-infusion intravenous ketamine studies and phase 3 intranasal esketamine trials. These studies differ in dosing schedule, route of administration, comparator, treatment setting, baseline chronicity of suicidal ideation, and timing of outcome assessment. For this reason, these studies are useful for understanding the broader clinical landscape but should be interpreted as contextual evidence because their designs and assessment schedules differ substantially from those of the core single-dose intravenous ketamine and intranasal esketamine trials.(12,22–24)

Repeated-infusion protocols have been investigated in treatment-resistant depression with suicidal ideation, including populations with more persistent or chronic suicidal thoughts. Some studies suggest that suicidal ideation may decrease during a course of repeated ketamine administration. However, controlled evidence is not uniformly positive. In a randomized, double-blind, placebo-controlled trial in medicated outpatients with severe treatment-resistant depression and chronic suicidal ideation, repeated intravenous ketamine infusions did not show a statistically significant advantage over placebo for either depressive symptoms or suicidal ideation. Suicidal ideation outcomes were assessed 240 minutes after each infusion. However, because the study evaluated a repeated-infusion protocol in patients with chronic suicidal ideation, it is considered contextual to the main evidence from single-dose intravenous ketamine and intranasal esketamine trials.(12)

Evidence from oral and intramuscular ketamine protocols is limited and less directly comparable with the core intravenous ketamine and intranasal esketamine trials. Available studies differ in dose, comparator,

treatment schedule, and timing of assessment, which limits conclusions about a consistent effect on suicidal ideation within the first 24 hours.(23,24)

Overall, evidence from alternative routes and repeated-dose protocols reinforces the conclusion that ketamine-related effects on suicidal ideation are context-dependent. These studies highlight the importance of the chronicity of suicidal ideation, dosing strategy, route of administration, and comparator design, and underscore the need for well-controlled trials using standardized suicidal ideation measures and prespecified assessment time points within the first 24 hours.

The clinical studies and analyses discussed in Sections 4.1–4.3 are summarized in Table 1.

Table 1. Clinical studies and analyses evaluating the early effects of ketamine or esketamine on suicidal ideation in depressive disorders

Author, year	Study design	Population	N	Intervention	Comparator	Suicidality measure	Time point	Main finding	Interpretative issue	PMID
A. Intravenous ketamine										
Price et al., 2009	Open-label preliminary study	Patients with treatment-resistant depression	26; 10 completed the IAT	Single intravenous ketamine infusion, 0.5 mg/kg over 40 min	No placebo control in main single-infusion sample	MADRS suicidal item; Implicit Association Test	24 h after infusion	At 24 hours, the MADRS suicidal ideation item decreased significantly after a single ketamine infusion. Implicit self–escape associations also decreased in the subgroup completing the IAT.	Preliminary uncontrolled study with a small sample; suicidal ideation was assessed primarily using a single MADRS item, and participants were not selected specifically for clinically significant suicidal ideation. The publication also included a separate repeated-infusion sample of nine participants, which is not summarized here because this row focuses on the 24-hour findings after a single infusion.	19545857
DiazGranados et al., 2010	Open-label clinical trial	Patients with treatment-resistant MDD	33	Single intravenous ketamine infusion, 0.5 mg/kg over 40 min	No comparator	Scale for Suicide Ideation; suicide items of the MADRS, HDRS, and BDI	40, 80, 120, 230 min after infusion; no 24-hour assessment	Suicidal ideation decreased significantly on the SSI and suicide-related items of depression scales within 40 minutes, and the improvement remained significant through 230 minutes after infusion.	The open-label design and absence of a comparator limit causal conclusions. Only 10 of 33 participants had an SSI score of at least 4 at baseline, limiting generalizability to patients with clinically significant suicidal ideation. Because outcomes were assessed only through 230 minutes, the study provides evidence for very early effects rather than for the 24-hour endpoint.	20673547
Price et al., 2014	Randomized, double-blind, midazolam-controlled trial	Patients with treatment-resistant unipolar major depression	57; 36 ketamine, 21 midazolam; 54 completed the IAT	Single intravenous ketamine infusion, 0.5 mg/kg over 40 min	Intravenous midazolam, 0.045 mg/kg over 40 min	Composite explicit suicidal ideation index comprising the BSS, MADRS-SI, and QIDS-SI; Implicit Association Test	24 h after infusion	Ketamine produced a significantly greater reduction in the composite explicit suicidal ideation score than midazolam at 24 hours. Fifty-three percent of ketamine-treated participants scored zero on all three explicit measures, compared with 24% of the midazolam group. No significant between-group effects were observed for the implicit IAT outcomes.	Participants were not selected specifically for clinically significant suicidal ideation. A statistical mediation analysis suggested that improvement in non-suicidal depressive symptoms partly accounted for the reduction in explicit suicidal cognition, limiting conclusions about an independent effect specific to suicidal ideation.	24668760
Murrough et al., 2015	Randomized, double-blind, midazolam-controlled trial	Patients with mood and anxiety spectrum disorders with clinically significant suicidal ideation	24; 12 ketamine, 12 midazolam	Single intravenous ketamine infusion, 0.5 mg/kg over 40 min, plus standard of care	Intravenous midazolam, 0.045 mg/kg over 40 min, plus standard of care	Beck Scale for Suicide Ideation, BSI; MADRS-SI	24 h primary endpoint; also 48 h and 7 days	Ketamine did not differ significantly from midazolam on the primary BSI outcome at 24 hours. The MADRS suicidal ideation item showed a borderline between-group difference favoring ketamine, while a significant between-group difference in BSI emerged at 48 hours.	The small and diagnostically heterogeneous sample, failure to meet the primary 24-hour BSI endpoint, and discrepant findings across suicidal ideation measures limit the strength of the conclusions.	26266877

Author, year	Study design	Population	N	Intervention	Comparator	Suicidality measure	Time point	Main finding	Interpretative issue	PMID
Grunebaum et al., 2018	Randomized, double-blind, midazolam-controlled clinical trial	Adults with MDD and clinically significant suicidal ideation	80; 40 ketamine, 40 midazolam	Single intravenous ketamine infusion, 0.5 mg/kg over 40 min	Intravenous midazolam, 0.02 mg/kg over 40 min	Scale for Suicide Ideation, SSI	24 h after infusion	Intravenous ketamine produced a greater reduction in clinically significant suicidal ideation at 24 hours compared with midazolam in adults with major depressive disorder.	The randomized active-comparator design and assessment of SSI at 24 hours strengthen the evidence, but the observed reduction in suicidal ideation may partly overlap with improvements in depressive and anxiety-related symptoms. Because 54% of participants were receiving antidepressant medication, the findings do not represent ketamine monotherapy in the entire sample.	29202655
Hochschild et al., 2022	Exploratory post hoc analysis of a randomized, double-blind, midazolam-controlled trial	Patients with MDD and clinically significant suicidal ideation	80; 40 ketamine, 40 midazolam	Intravenous ketamine, 0.5 mg/kg over 40 min	Intravenous midazolam, 0.02 mg/kg over 40 min	SSI; factor-derived subscales of the HDRS, BDI, and POMS	Baseline and 1 day after infusion	Reduction in suicidal ideation after ketamine was largely associated with improvement in core mood and anxiety-related symptom domains.	Exploratory post hoc analysis based on associations between symptom changes; the findings do not establish that mood and anxiety improvement causally mediated the reduction in suicidal ideation.	34953926
Phillips et al., 2020	Secondary analysis of a randomized, double-blind crossover trial followed by open-label repeated and maintenance ketamine phases	Patients with treatment-resistant depression and baseline suicidal ideation	37	Intravenous ketamine, 0.5 mg/kg over 40 min; subsequently six open-label infusions administered three times weekly for 2 weeks, followed by four weekly maintenance infusions in responders	Intravenous midazolam, 0.03 mg/kg, in the initial crossover phase; no comparator in the repeated and maintenance phases	MADRS-SI; QIDS-SI	2 h, 24 h, and 7 days after the single infusion; assessments during the repeated and maintenanc e phases and 3 days after completion of these phases	Ketamine produced a greater reduction in MADRS-SI than midazolam at 2 hours and 7 days, but not at 24 hours. Repeated ketamine infusions were associated with cumulative reductions in suicidal ideation, which were maintained during the maintenance phase.	The controlled phase did not demonstrate a significant between-treatment difference at 24 hours. The subsequent phases were open-label, and suicidal ideation was assessed using single items from depression rating scales.	31759333
Ionescu et al., 2019	Randomized, double-blind, placebo-controlled trial	Medicated outpatients with severe TRD and chronic suicidal ideation	26	Six intravenous ketamine infusions, 0.5 mg/kg over 45 min, administered over 3 weeks	Intravenous saline placebo	Columbia-Suicide Severity Rating Scale, ideation severity and intensity subscales	Baseline, 240 min after each infusion, and during a 3-month follow-up	Repeated intravenous ketamine infusions did not demonstrate superiority over placebo for reducing depressive symptoms or suicidal ideation in medicated outpatients with severe treatment-resistant depression and chronic suicidal ideation.	The small sample size, uncontrolled concomitant medication regimens, and restriction to outpatients limit generalizability to patients with acute suicidal crises requiring hospitalization.	30286416

Author, year	Study design	Population	N	Intervention	Comparator	Suicidality measure	Time point	Main finding	Interpretative issue	PMID
Abbar et al., 2022	Prospective, double-blind, randomized, placebo-controlled multicenter trial	Hospitalized adults with severe suicidal ideation and bipolar, depressive, or other psychiatric disorders	156; 73 ketamine, 83 placebo	Two intravenous ketamine infusions, 0.5 mg/kg over 40 min, administered at baseline and 24 h, plus usual treatment	Intravenous saline placebo administered at baseline and 24 h, plus usual treatment	Clinician-rated Scale for Suicide Ideation, SSI	40 min, 2 h, 4 h, and Day 1 before the second infusion; primary endpoint at Day 3	In the overall diagnostically mixed sample, suicidal remission occurred more frequently with ketamine than with placebo, with changes observed from 40 minutes and a significant between-group difference at Day 3.	The study included a mixed diagnostic population, and the primary endpoint was assessed at Day 3 after two infusions. Treatment effects differed by diagnosis, and the between-group difference was not statistically significant in the subgroup with depressive disorders. The study therefore provides contextual rather than direct evidence for adults with depressive disorders within the first 24 hours.	35110300
B. Intranasal esketamine										
Canuso et al., 2018	Double-blind, randomized, placebo-controlled, proof-of-concept multicenter study	Patients with MDD at imminent risk for suicide	68 randomized; 66 received treatment and were included in the intent-to-treat and safety analyses: 35 esketamine, 31 placebo	Intranasal esketamine 84 mg twice weekly + standard of care	Matching intranasal placebo plus comprehensive standard of care	MADRS total score; MADRS suicidal thoughts item; clinician global judgment of suicide risk	4 h and approximately 24 h after the first dose; Day 25	Intranasal esketamine added to standard of care produced greater improvement in overall depressive symptoms at approximately 24 hours. The MADRS suicidal thoughts item favored esketamine at 4 hours, but not at 24 hours, while clinician-rated global suicide risk did not differ significantly between groups at any assessed time point.	The primary efficacy outcome assessed overall depressive symptom severity rather than suicidal ideation specifically. Intensive standard-of-care treatment and the absence of significant between-group differences in clinician-rated global suicide risk complicate interpretation of an independent effect on suicidal ideation.	29656663
Fu et al., 2020	Phase 3, double-blind, randomized, placebo-controlled multicenter study; ASPIRE I	Adults with MDD, active suicidal ideation with intent, requiring psychiatric hospitalization	226 randomized: 114 esketamine, 112 placebo; 225 received treatment and 224 were included in the full efficacy analysis	Esketamine nasal spray 84 mg twice weekly for 4 weeks plus comprehensive standard-of-care treatment	Matching placebo nasal spray twice weekly for 4 weeks plus comprehensive standard-of-care treatment	MADRS total score; CGI-SS-r for suicidality	4 h and 24 h after the first dose; subsequent assessments through Day 25	Esketamine plus standard of care produced greater improvement in depressive symptom severity at 24 hours than placebo plus standard of care in patients with major depressive disorder and active suicidal ideation with intent.	The CGI-SS-r score improved rapidly in both groups, but the between-group difference in suicidality severity at 24 hours was not statistically significant.	32412700

Author, year	Study design	Population	N	Intervention	Comparator	Suicidality measure	Time point	Main finding	Interpretative issue	PMID
Ionescu et al., 2021	Phase 3, double-blind, randomized, placebo-controlled study; ASPIRE II	Adults with MDD and active suicidal ideation with intent requiring psychiatric hospitalization	230 randomized; 115 per group; 227 received treatment and were included in the analyses	Esketamine nasal spray 84 mg twice weekly for 4 weeks plus comprehensive standard-of-care treatment	Matching placebo nasal spray twice weekly for 4 weeks plus comprehensive standard-of-care treatment	MADRS total score; CGI-SS-r for suicidality	4 h and 24 h after the first dose; subsequent assessments through Day 25	Esketamine plus standard of care produced greater improvement in depressive symptom severity at 24 hours than placebo plus standard of care in patients with major depressive disorder and active suicidal ideation with intent.	The CGI-SS-r score improved rapidly in both groups, but the between-group difference in suicidality severity at 24 hours was not statistically significant.	32861217
Canuso et al., 2021	Pooled post hoc analysis of ASPIRE I and ASPIRE II	Adults with MDD and active suicidal ideation with intent requiring psychiatric hospitalization	456; 229 esketamine, 227 placebo	Esketamine nasal spray 84 mg twice weekly for 4 weeks plus comprehensive standard-of-care treatment	Matching placebo nasal spray twice weekly for 4 weeks plus comprehensive standard-of-care treatment	MADRS total; CGI-SS-r	4 h, 24 h, Day 25	Pooled ASPIRE data showed significantly greater improvement in depressive symptom severity with esketamine plus standard of care at 4 hours, 24 hours, and Day 25. CGI-SS-r scores improved in both groups, and the overall between-group difference in suicidality severity at 24 hours was not statistically significant.	This was a post hoc pooled analysis, and intensive standard-of-care treatment may have contributed to improvement in both groups, limiting conclusions about an independent effect on suicidal ideation.	34412104
C. Other routes or comparative protocols										
Kheirabadi et al., 2020	Randomized, open-label, three-arm pilot study	Patients with MDD suitable for ECT	45; 15 participants per group	Intramuscular ketamine, 0.5 mg/kg, or oral ketamine, 1 mg/kg, administered in 6–9 sessions over 3 weeks	ECT administered in 6–9 sessions over 3 weeks	HAM-D; Beck Scale for Suicide Ideation	Baseline; 24 h; 1, 2, and 3 weeks; and 1 week and 1 month after the end of treatment	Depressive symptoms and suicidal ideation improved in all three groups. In time-point-specific comparisons, suicidal ideation scores were significantly lower in the oral and intramuscular ketamine groups than in the ECT group at 24 hours and 2 weeks, although the overall analysis showed no significant differences between the three treatment groups.	The small sample size, open-label design, absence of a placebo group, and repeated-treatment protocol limit conclusions about an early treatment-specific effect.	33060432
Seraj et al., 2025	Midazolam-controlled randomized clinical trial	Adults with MDD and expressed suicidal ideation	80; 40 ketamine, 40 midazolam	Single oral racemic ketamine 3 mg/kg	Oral midazolam 0.3 mg/kg	Modified Scale for Suicide Ideation; HAM-D	4 h after treatment (Day 1), Day 3, and Day 7	MSSI scores were significantly lower in the oral ketamine group than in the midazolam group at 4 hours, Day 3, and Day 7.	No assessment was performed at 24 hours; therefore, this study provides contextual rather than direct evidence for the present review question.	40015180

Abbreviations: BDI, Beck Depression Inventory; BSI, Beck Scale for Suicide Ideation; BSS, Beck Scale for Suicide Ideation; CGI-SS-r, Clinical Global Impression–Severity of Suicidality–Revised; ECT, electroconvulsive therapy; HAM-D, Hamilton Depression Rating Scale; HDRS, Hamilton Depression Rating Scale; IAT, Implicit Association Test; IM, intramuscular; IV, intravenous; MADRS, Montgomery–Åsberg Depression Rating Scale; MADRS-SI, Montgomery–Åsberg Depression Rating Scale suicidal thoughts item; MDD, major depressive disorder; MSSI, Modified Scale for Suicide Ideation; POMS, Profile of Mood States; QIDS-SI, suicidal ideation item of the Quick Inventory of Depressive Symptomatology–Self-Report; SI, suicidal ideation; SSI, Scale for Suicide Ideation; TRD, treatment-resistant depression.

5. Variability in clinical findings

Clinical findings regarding the early effects of ketamine and esketamine on suicidal ideation vary because the available studies examined substantially different clinical populations and treatment contexts. Differences between trials are evident in patient populations, baseline suicide risk, chronicity of suicidal ideation, treatment setting, route of administration, comparator design, concomitant standard-of-care treatment, and outcome measurement. These factors are particularly important when interpreting outcomes within the first 24 hours, because early changes may reflect pharmacological effects, rapid improvement in depressive symptoms, crisis stabilization, close monitoring, or a combination of these factors.

Overall, variability in clinical findings should not be interpreted simply as evidence for or against ketamine-based interventions. Rather, it indicates that suicidal ideation outcomes are highly sensitive to the clinical population, study design, comparator condition, background care, and measurement strategy.(13,14) A clinically meaningful interpretation of the evidence therefore requires moving beyond a binary conclusion of efficacy versus lack of efficacy and toward a more nuanced understanding of when, in whom, and under what conditions early changes in suicidal ideation are observed.

6. Interpretative challenges

6.1 Differences in study populations

The study population is one of the most important determinants of how ketamine and esketamine findings should be interpreted. Patients with major depressive disorder and acute suicidal ideation with intent, patients with treatment-resistant depression, patients with chronic suicidal ideation, and patients treated in emergency, inpatient, and outpatient settings may differ substantially in illness duration, baseline suicide risk, prior treatment exposure, clinical instability, and responsiveness to short-term interventions.

This distinction is clinically important because acute suicidal ideation may fluctuate rapidly in response to hospitalization, crisis intervention, close observation, and initiation of treatment. By contrast, chronic suicidal ideation may represent a more persistent symptom dimension, particularly in patients with severe treatment-resistant depression. Therefore, a reduction in suicidal ideation within the first 24 hours in an acutely suicidal inpatient population should not be interpreted in the same way as changes observed in an outpatient population with chronic suicidal ideation.

The ASPIRE trials enrolled hospitalized patients with major depressive disorder and active suicidal ideation with intent, representing a high-acuity clinical population receiving intensive standard-of-care treatment.(6,7) In contrast, repeated-infusion ketamine studies included patients with persistent or baseline suicidal ideation, treatment-resistant depression, and different clinical trajectories.(12,22) These population-level differences limit direct comparisons between studies and indicate that future trials should define the phenotype and chronicity of suicidal ideation, as well as the treatment setting, more precisely.

6.2 Differences between ketamine and esketamine

Although ketamine and esketamine are pharmacologically related, findings from clinical trials should not be interpreted as fully interchangeable. Racemic ketamine contains both R- and S-enantiomers and has most commonly been investigated in depression as a single subanesthetic intravenous infusion. Esketamine is the S-enantiomer of ketamine and, in the studies most relevant to acute suicidal ideation in depression, was administered intranasally as an adjunct to standard-of-care treatment.(3,5–7)

Consequently, differences between ketamine and esketamine studies may reflect not only pharmacological differences between the compounds but also differences in route of administration, comparator condition, treatment setting, regulatory trial design, and background care. Conclusions drawn from intravenous ketamine studies should therefore not be directly extrapolated to intranasal esketamine, and findings from esketamine trials should not be assumed to represent the effects of racemic intravenous ketamine.

6.3 Differences in comparators and standard of care

Comparator design is a major methodological factor in trials evaluating the effects of ketamine and esketamine on suicidal ideation. In several intravenous ketamine studies, midazolam was used as an active comparator.(3,4) This approach may reduce expectancy effects and partially improve blinding compared with

an inert placebo, because midazolam produces psychoactive effects that may mimic some subjective effects of ketamine administration.

By contrast, the pivotal esketamine trials in patients with major depressive disorder and acute suicidal ideation with intent compared intranasal esketamine plus standard-of-care treatment with placebo nasal spray plus standard-of-care treatment. Both treatment groups received intensive clinical management, including psychiatric hospitalization and initiation or optimization of antidepressant therapy.(6,7) This design was clinically appropriate for a high-risk population, but it also means that suicidal ideation could improve rapidly in both groups as a result of hospitalization, close observation, and concurrent treatment.

This difference in comparator condition and background care is central to interpreting outcomes within the first 24 hours. A statistically significant between-group difference in intravenous ketamine trials may reflect the pharmacological effect of ketamine relative to an active comparator. In contrast, the absence of a statistically significant between-group difference in clinician-rated suicidality in esketamine trials should not be interpreted as an absence of clinical improvement, because both esketamine and placebo groups received intensive standard-of-care interventions. However, this design limits conclusions about whether improvement in clinician-rated suicidality was specifically attributable to esketamine itself.(6,7,20)

6.4 Measurement of suicidal ideation

Measurement of suicidal ideation is a central interpretative challenge in ketamine and esketamine studies. Suicidal ideation is a multidimensional clinical construct, and clinical trials have assessed it using different instruments, including dedicated suicidal ideation scales, single suicide-related items from depression rating scales, and clinician-rated global assessments of suicidality. These instruments differ in their content, scoring structure, sensitivity to rapid change, and clinical interpretation.(13,14)

Dedicated suicidal ideation scales, such as the Scale for Suicide Ideation or the Beck Scale for Suicide Ideation, provide a more direct assessment of suicidal thoughts than single items embedded within depression rating scales. By contrast, suicide-related items from scales such as the MADRS or HAM-D may be easier to implement in depression trials, but they may not capture the multidimensional nature of suicidal ideation. As a result, apparent treatment effects may differ depending on whether suicidal ideation is assessed as a distinct clinical construct or as one component of depressive symptom severity.(13)

This measurement problem is evident across both ketamine and esketamine trials. In ketamine studies, findings varied according to whether dedicated clinician-rated scales, self-report measures, or single suicide-related items were used. In the ASPIRE trials, clinician-rated global suicidality measures showed less clear between-group differences than depressive symptom scales, possibly reflecting differences in sensitivity to rapid change.(3,4,6,7,13,14)

Overall, differences in the measurement of suicidal ideation limit direct comparisons across ketamine and esketamine studies. Future trials should use standardized suicidal ideation measures, prespecified assessment time points within the first 24 hours, and transparent reporting of both clinician-rated and self-reported outcomes.

6.5 Relationship between antidepressant effects and effects specific to suicidal ideation

A key interpretative question is whether ketamine and esketamine exert a direct effect on suicidal ideation or whether the observed reduction occurs primarily through rapid improvement in depressive symptom severity. This distinction is clinically important because suicidal ideation may decrease when mood, anxiety, agitation, hopelessness, or psychological distress improve, even if the intervention does not directly target suicidal ideation as an independent symptom domain.

Several intravenous ketamine studies reported rapid reductions in suicidal ideation, but a post hoc analysis of a ketamine–midazolam trial found that changes in suicidal ideation were closely related to improvements in core mood and anxiety-related symptoms.(11) This does not make the observed reduction clinically irrelevant. In a patient experiencing acute suicidal ideation, rapid improvement in the symptoms contributing to suicidal ideation may still be clinically meaningful. However, this limits the strength of claims that ketamine exerts an effect on suicidal ideation independently of its broader antidepressant action.

The same interpretative issue is evident in esketamine trials. In ASPIRE I and ASPIRE II, esketamine plus standard of care produced greater improvement in depressive symptom severity at 24 hours than placebo plus standard of care. However, clinician-rated suicidality scores improved in both groups, and the between-group differences were not statistically significant at 24 hours.(6,7) This pattern suggests that the early clinical

benefit of esketamine in patients with acute suicidal ideation with intent is more clearly demonstrated for overall depressive symptom reduction than for an effect specific to suicidal ideation.

Future studies should distinguish between reduction of suicidal ideation as an independent outcome and reduction secondary to broader symptom improvement. This will require dedicated suicidal ideation measures, prespecified assessment time points within the first 24 hours, mediation analyses, and trial designs capable of distinguishing pharmacological effects from those of hospitalization, close monitoring, and concurrent standard-of-care interventions.(11,13,14)

The main interpretative challenges affecting suicidal ideation outcomes within the first 24 hours in ketamine and esketamine studies are summarized in Table 2.

Table 2. Main interpretative challenges in assessing suicidal ideation outcomes within the first 24 hours in ketamine and esketamine studies

Interpretative challenge	Why it matters	Example in current evidence	Implication for interpretation
Acute vs chronic suicidal ideation	Acute suicidal ideation may fluctuate rapidly during crisis stabilization, hospitalization, and initiation of treatment, whereas chronic suicidal ideation may represent a more persistent and treatment-resistant symptom dimension.	The ASPIRE trials enrolled hospitalized patients with MDD and active suicidal ideation with intent, whereas the repeated-dose ketamine trial by Ionescu et al. included outpatients with treatment-resistant depression and chronic suicidal ideation.	Findings from acute suicidal crisis trials should not be directly generalized to chronic suicidal ideation.
Comparator design	Active-comparator trials and placebo-controlled trials conducted alongside intensive standard-of-care treatment estimate different treatment contrasts and may produce different magnitudes of between-group differences.	Intravenous ketamine trials often used midazolam as an active comparator; esketamine trials used placebo nasal spray plus intensive standard-of-care treatment.	Observed treatment effects may vary depending on whether the comparator is pharmacologically active or embedded within intensive standard-of-care treatment.
Standard-of-care effects	Hospitalization, close monitoring, crisis stabilization, and optimization of pharmacotherapy may rapidly reduce suicidal ideation in both treatment groups.	In ASPIRE I and ASPIRE II, both the esketamine and placebo groups received psychiatric hospitalization and standard-of-care treatment.	Improvement in both groups may reduce the apparent between-group difference and complicate identification of an effect specific to suicidal ideation.
Suicidality measurement	Dedicated suicidal ideation scales, single suicide-related items from depression rating scales, and global clinician-rated measures may capture different aspects of suicidality and differ in sensitivity to rapid change.	Measures used across studies included the SSI or BSI, the MADRS suicidal thoughts item, and the CGI-SS-r. In the Murrough et al. trial, the primary BSI outcome was not statistically significant at 24 hours, whereas the MADRS suicidal ideation item showed a borderline between-group difference favoring ketamine.	Observed findings may depend on the instrument used, limiting direct comparisons across studies and supporting the use of standardized suicidal ideation measures.
Antidepressant effect vs effect specific to suicidal ideation	Reduction in suicidal ideation may reflect broader improvement in depression, anxiety, agitation, hopelessness, or psychological distress rather than an effect specific to suicidal ideation.	Analyses of ketamine trials suggest that mood-related improvement may partly explain reductions in suicidal ideation.	Claims of an effect specific to suicidal ideation require cautious interpretation and should not be based solely on early reductions in suicidal ideation.
Timing of assessment	Effects observed at 4 hours, 24 hours, day 3, and later follow-up points may differ in magnitude and clinical meaning.	Some studies report improvement within hours, whereas others assess outcomes at approximately 24 hours or during longer-term follow-up.	A response observed within the first 24 hours may be clinically meaningful, but it does not necessarily indicate a durable benefit or a reduction in long-term suicide risk.

Interpretative challenge	Why it matters	Example in current evidence	Implication for interpretation
Route and dosing protocol	Intravenous, intranasal, oral, intramuscular, single-dose, and repeated-dose protocols differ clinically, pharmacologically, and logistically.	Available evidence includes single-dose and repeated-dose intravenous ketamine, intranasal esketamine, oral ketamine, and intramuscular ketamine.	Findings from one route or dosing protocol should not be assumed to apply directly to another.

Abbreviations: BSI, Beck Scale for Suicide Ideation; CGI-SS-r, Clinical Global Impression–Severity of Suicidality–Revised; IM, intramuscular; IV, intravenous; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; SI, suicidal ideation; SSI, Scale for Suicide Ideation.

7. Clinical implications

The available evidence suggests that ketamine and esketamine may contribute to early symptom reduction in selected patients with depressive disorders and suicidal ideation, particularly when used within structured psychiatric care. Intravenous ketamine has shown rapid reductions in suicidal ideation in some trials, whereas intranasal esketamine has more consistently improved depressive symptom severity when added to intensive standard-of-care treatment. Neither intervention should be regarded as a standalone replacement for comprehensive suicide risk assessment and crisis management.(3,6,7,11)

The distinction between rapid antidepressant effects and effects specific to suicidal ideation is especially important in clinical communication. Overstating the specific efficacy of ketamine or esketamine for suicidal ideation may create unrealistic expectations, whereas dismissing early symptomatic improvement may underestimate their potential value in selected patients. Clinicians should therefore interpret outcomes observed within the first 24 hours as potentially clinically meaningful but methodologically complex, particularly when improvement occurs alongside intensive standard-of-care treatment.(6,7,14)

8. Limitations

This review has several limitations. First, it was designed as a narrative review rather than a systematic review or meta-analysis. Although structured searches of PubMed and Scopus were conducted, study selection was guided by clinical and methodological relevance. No formal risk-of-bias assessment, certainty-of-evidence evaluation, or quantitative synthesis was performed. Because this was a narrative review, the literature search and study-selection process was not intended to be exhaustive, and some potentially eligible studies may not have been included.

Second, substantial heterogeneity across studies limits direct comparison of findings. Studies differed in patient populations, baseline severity and chronicity of suicidal ideation, treatment setting, route and schedule of administration, comparator condition, concurrent standard-of-care treatment, and timing of assessment.(3,6,7,12,22–24)

Third, suicidal ideation was not measured consistently across studies. Dedicated suicidal ideation scales, single suicide-related items from depression rating scales, and global clinician-rated assessments may capture different aspects of suicidality and differ in sensitivity to rapid change.(13,14)

Finally, most included studies were not designed to determine whether reductions in suicidal ideation were independent of broader antidepressant improvement, and longer-term effects on suicidal ideation and suicidal behavior remain insufficiently characterized.(6,7,11) Improvement within the first 24 hours should therefore not be interpreted as evidence of a sustained reduction in suicide risk or prevention of suicidal behavior.(3,6–8)

9. Conclusions

Ketamine and esketamine have generated substantial interest as rapid-acting interventions in depressive disorders accompanied by suicidal ideation. The available evidence suggests that intravenous ketamine may produce rapid reductions in suicidal ideation in selected patients with depression, including effects observed within the first 24 hours. Intranasal esketamine, when added to intensive standard-of-care treatment, has demonstrated rapid improvement in depressive symptom severity in patients with major depressive disorder and acute suicidal ideation with intent, although outcomes specifically assessing suicidal ideation have shown less consistent between-group differences.

The interpretation of these findings remains challenging. Differences in patient populations, chronicity of suicidal ideation, route of administration, comparator condition, concomitant treatment, and the measurement of suicidal ideation substantially influence observed outcomes. In particular, it remains unclear whether improvement in suicidal ideation represents an effect specific to suicidal ideation or occurs primarily as a consequence of broader antidepressant improvement.

Overall, ketamine and esketamine may contribute to early clinical improvement in selected patients with depression and suicidal ideation, but current evidence does not support a simplistic conclusion that these interventions exert a uniform, specific, and durable effect on suicidal ideation across different clinical contexts. Future trials should use standardized suicidal ideation measures, prespecified assessment time points within the first 24 hours, longer follow-up, and designs capable of distinguishing pharmacological effects from the effects of intensive clinical care.

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