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Review Article

Intranasal Esketamine for Rapid Reduction of Suicidal Ideation in Treatment-Resistant Depression: A Narrative Review

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ABSTRACT

Background: Treatment-resistant depression is associated with persistent symptoms, impaired functioning, recurrent illness, and an increased burden of suicidal ideation. Conventional oral antidepressants may require several weeks to produce clinically meaningful improvement, creating a therapeutic challenge when severe depressive symptoms and suicidal thoughts require rapid stabilization. Intranasal esketamine has emerged as a supervised, rapidly acting intervention that modulates glutamatergic neurotransmission and is generally administered alongside an oral antidepressant and comprehensive psychiatric care. Objective: This narrative review examined the clinical role of intranasal esketamine in the early reduction of depressive symptoms and suicidal ideation, with particular attention to treatment-resistant depression, acute suicidal depressive episodes, sustainability of response, safety, and implementation. Methods: Relevant literature concerning intranasal esketamine, ketamine-related antidepressant mechanisms, treatment-resistant depression, and suicidality was reviewed and synthesized thematically. Evidence was organized around clinical populations, mechanisms of action, speed of response, suicidal-ideation outcomes, maintenance treatment, safety, and clinical implementation. Results: Available evidence indicates that intranasal esketamine can produce earlier improvement in depressive symptoms than conventional oral antidepressant treatment alone, particularly during the initial hours and days of supervised treatment. Reductions in selected suicidal-ideation measures have also been reported; however, improvement in suicidal thoughts does not establish prevention of suicide attempts or mortality. Interpretation is influenced by differences in populations, outcome instruments, comparator conditions, concomitant treatments, and follow-up durations. Dissociation, sedation, dizziness, nausea, perceptual disturbances, and transient elevations in blood pressure require structured monitoring. Conclusion: Intranasal esketamine represents a clinically relevant adjunctive option for selected adults with treatment-resistant depression or severe depressive episodes requiring rapid symptom reduction. Its use should remain integrated within comprehensive psychiatric management, while further research clarifies its specific effects on suicidal behaviour, long-term maintenance, comparative effectiveness, and accessibility. Keywords: Treatment-Resistant Depression, Esketamine, Suicidal Ideation, Major Depressive Disorder, NMDA Receptor Antagonists, Rapid-Acting Antidepressants, Narrative Review

INTRODUCTION

Major depressive disorder is a disabling and frequently recurrent psychiatric condition associated with substantial personal, social, occupational, and healthcare burdens. A clinically important proportion of patients continue to experience significant symptoms despite receiving antidepressant treatment. Treatment-resistant depression is generally characterized by an inadequate response to at least two antidepressant regimens administered at appropriate doses and for sufficient durations. These patients

frequently experience persistent mood symptoms, reduced quality of life, impaired functioning, recurrent episodes, and an increased burden of suicidal ideation (1,2).

Suicidal ideation is among the most serious manifestations of depressive illness. Its presence requires immediate clinical assessment because suicidal thoughts may fluctuate rapidly and may progress to suicidal intent, planning, self-harm, or attempted suicide. Nevertheless, treatment-resistant depression and an acute suicidal depressive episode are not identical clinical entities. Some patients with treatment-resistant depression experience chronic or recurrent suicidal ideation, whereas others may present with an acute suicidal crisis without having previously failed multiple adequate antidepressant treatments. This distinction is essential when evaluating rapidly acting interventions because treatment response, clinical urgency, and therapeutic objectives may differ between these populations.

Conventional oral antidepressants, including selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors, primarily influence monoaminergic neurotransmission. Although these treatments remain central to the management of major depressive disorder, their therapeutic effects commonly develop gradually. Patients with severe depressive symptoms or active suicidal ideation may therefore remain vulnerable during the initial treatment period. This delay has encouraged investigation of interventions capable of producing earlier improvement while conventional antidepressant and psychotherapeutic strategies take effect (1,3). Ketamine and esketamine have attracted substantial clinical and scientific interest because of their rapid antidepressant effects. Esketamine is the S-enantiomer of ketamine and acts primarily as a non-competitive antagonist of the N-methyl-D-aspartate receptor. Unlike conventional antidepressants, which largely target monoaminergic pathways, esketamine influences glutamatergic signalling and downstream mechanisms involved in synaptic plasticity, neural connectivity, and emotional regulation (4). Intranasal administration provides a practical route that permits supervised use in designated clinical settings.

Intranasal esketamine is not generally used as a simple substitute for oral antidepressant therapy. It is typically administered as an adjunct to a newly initiated or ongoing oral antidepressant and forms one component of a broader treatment plan. Such care may also include psychiatric observation, suicide-risk assessment, psychological intervention, treatment of comorbid conditions, safety planning, family involvement, and hospitalization when clinically required (2,5).

Previous reviews have examined ketamine and esketamine in relation to treatment-resistant depression, suicidality, cognitive outcomes, long-term maintenance, sleep, and special populations (1–10). Interpretation of this literature remains challenging because studies differ in ketamine formulation, route of administration, diagnostic criteria, definition of treatment resistance, comparator treatment, outcome measure, treatment schedule, and duration of follow-up. In addition, improvement in total depression scores, reduction in suicidal-ideation ratings, resolution of suicidal intent, prevention of suicide attempts, and reduction in suicide mortality are distinct outcomes and should not be interpreted as interchangeable. This narrative review therefore examined the clinical evidence concerning intranasal esketamine as a rapidly acting intervention for depressive symptoms and suicidal ideation. Particular attention was given to the distinction between treatment-resistant depression and acute suicidal depression, the biological rationale for rapid action, timing and sustainability of response, interpretation of suicidal-ideation outcomes, safety, treatment monitoring, and clinical implementation.

Literature Review and Narrative Synthesis Approach

The literature was reviewed using a clinically focused narrative approach. Relevant publications addressing intranasal esketamine, ketamine-related antidepressant mechanisms, treatment-resistant depression, major depressive disorder with suicidal ideation, rapid antidepressant response, long-term treatment, cognitive outcomes, sleep-related outcomes, and safety were considered. The evidence base included systematic reviews, meta-analyses, narrative reviews, and clinically relevant comparative literature concerning intranasal esketamine and related ketamine formulations.

The literature was synthesized thematically rather than statistically. Evidence concerning intravenous racemic ketamine, intranasal esketamine, and other formulations was interpreted separately where route of administration or pharmacological formulation affected clinical relevance. Particular attention was given to whether intranasal esketamine was administered alone or alongside an oral antidepressant and comprehensive psychiatric care. Findings were organized around treatment populations, neurobiological mechanisms, speed of antidepressant response, suicidal-ideation outcomes, maintenance treatment, safety, cognitive effects, and practical implementation. Because the available literature used heterogeneous populations, outcome instruments, comparator conditions, and follow-up periods, no common quantitative treatment estimate was assumed. Findings concerning suicidal ideation were interpreted separately from suicidal behaviour, suicide attempts, and mortality. Greater interpretive weight was given to evidence directly concerning intranasal esketamine in adults with treatment-resistant depression or severe depressive episodes than to evidence derived from other ketamine formulations or clinically distinct populations.

Results and Narrative Synthesis

The reviewed literature consistently identified intranasal esketamine as a rapidly acting adjunctive treatment for adults with treatment-resistant depression. The principal areas addressed across the evidence included early antidepressant response, reduction in suicidal ideation, maintenance of treatment benefit, neurobiological mechanisms, cognitive and sleep-related outcomes, safety, and comparison with other emerging interventions. The available evidence was heterogeneous in population, formulation, treatment setting, comparator condition, outcome measure, and follow-up duration. Consequently, the findings were interpreted thematically rather than combined into a single quantitative estimate.

Characteristics of the Reviewed Evidence

The literature included systematic reviews, meta-analyses, and narrative reviews examining intranasal esketamine alone or alongside broader evidence concerning ketamine formulations. Most publications focused on adults with treatment-resistant depression, although some examined older adults, adolescents, suicidality, sleep, cognition, or comparative emerging therapies. The principal characteristics of the evidence are summarized in Table 1.

Table 1. Characteristics and thematic contributions of the reviewed literature

Reference	Review type	Principal population or topic	Intervention or exposure	Main contribution
Boudieu et al. (1)	Systematic review	Major depressive disorder	Intranasal ketamine and esketamine	Efficacy, tolerability, and safety of intranasal formulations
Capuzzi et al. (2)	Systematic review	Treatment-resistant major depression	Long-term intranasal esketamine	Continuation treatment, persistence of response, and maintenance
Gupta et al. (3)	Systematic review	Older adults with depression	Ketamine-based treatment	Effectiveness and tolerability in older populations
Kang et al. (4)	Systematic review	Depression and treatment-resistant depression	Ketamine-related mechanisms	Glutamatergic signalling, neuroplasticity, and rapid response
Salahudeen et al. (5)	Narrative review	Treatment-resistant depression	Esketamine	Clinical indications, administration, efficacy, and safety
Kwaśny et al. (6)	Systematic review	Treatment-resistant depression and sleep disturbance	Ketamine	Relationship between sleep and antidepressant response
Pardossi et al. (7)	Systematic review	Adolescents with treatment-resistant depression or suicidality	Ketamine and esketamine	Emerging paediatric and adolescent evidence
Wang et al. (8)	Systematic review and meta-analysis	Treatment-resistant depression with suicidal ideation	Ketamine and esketamine	Effects on suicidal-ideation outcomes
Psiuk et al. (9)	Systematic review	Depression	Esketamine and psilocybin	Comparison of emerging rapidly acting treatments
Guglielmo et al. (10)	Systematic review	Treatment-resistant depression	Esketamine	Cognitive effects and cognitive safety
Kucuker et al. (11)	Systematic review	Psychiatric populations with suicidality	Neuromodulation	Comparative non-pharmacological context
Hyde et al. (12)	Systematic review and meta-analysis	Multiple mental disorders	Neurostimulation	Broader evidence for neurostimulation across psychiatric disorders

Treatment-Resistant Depression and Acute Suicidal Depression

Treatment-resistant depression represents a heterogeneous clinical condition rather than a single uniform disorder. Patients differ in illness duration, number and adequacy of previous treatments, psychiatric and medical comorbidities, medication adherence, psychosocial stressors, and severity of functional impairment. Apparent treatment resistance may also be influenced by inaccurate diagnosis, subtherapeutic treatment, insufficient treatment duration, poor adherence, substance use, bipolar-spectrum illness, personality-related factors, or unrecognized medical conditions.

The therapeutic objective in treatment-resistant depression is generally to achieve sustained symptom remission and functional recovery after inadequate response to conventional treatment. By contrast, the immediate objective during an acute suicidal depressive crisis is stabilization, reduction of imminent risk, and prevention of self-harm. Although rapid improvement in depressive symptoms may contribute to stabilization, emergency management cannot depend solely on pharmacological reduction in a rating-scale score.

This distinction has direct implications for interpreting esketamine evidence. Findings generated in patients with established treatment resistance should not automatically be generalized to every patient presenting with suicidal ideation. Similarly, findings from acutely suicidal patients receiving intensive inpatient or emergency psychiatric care may not directly represent routine outpatient treatment-resistant depression. Clinical interpretation should therefore account for the diagnostic population, previous treatment history, baseline suicide risk, treatment setting, and intensity of concomitant care.

Pharmacological Basis of Esketamine

Esketamine primarily acts through antagonism of N-methyl-D-aspartate receptors. Its antidepressant action is believed to involve a wider cascade of glutamatergic effects rather than simple receptor blockade. Modulation of glutamate transmission may increase activity through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, promote brain-derived neurotrophic factor signalling, activate intracellular pathways involved in synaptic protein synthesis, and enhance synaptic plasticity in neural networks associated with mood regulation (4).

These mechanisms differ from the delayed adaptations commonly associated with conventional monoaminergic antidepressants. The rapid neurobiological effects of esketamine provide a plausible explanation for clinical improvement occurring within hours or days rather than several weeks. However, the relationship between these neurobiological changes and improvement in suicidal ideation remains incompletely understood. Rapid reduction in overall depressive distress may indirectly reduce suicidal thoughts, while effects on anxiety, agitation, hopelessness, cognitive flexibility, or emotional processing may also contribute.

The clinical response to esketamine may therefore reflect several overlapping processes, including rapid improvement in depressive symptoms, modification of negative cognitive and emotional processing, increased engagement with treatment, and the effects of intensive clinical contact during supervised administration. The therapeutic environment surrounding administration should consequently be considered when interpreting treatment outcomes.

Rapid Antidepressant Response

The strongest and most consistent theme across the literature was the earlier onset of antidepressant effects associated with ketamine-related interventions compared with conventional oral antidepressant treatment. Reviews of intranasal esketamine reported clinically meaningful improvement during the initial treatment period, frequently within hours or the first several days of administration (1,2,5). This rapid onset is particularly relevant for patients with severe, persistent, or treatment-resistant symptoms who have not obtained adequate benefit from conventional antidepressants.

The magnitude and timing of improvement vary among patients and studies. Differences may reflect baseline severity, degree of treatment resistance, dose, administration schedule, concomitant oral medication, inpatient or outpatient setting, and choice of depression-rating scale. Some patients experience substantial early improvement, whereas others have partial, transient, or clinically insufficient responses. Rapid action should therefore not be interpreted as universal effectiveness.

Esketamine is generally administered during an induction phase involving repeated supervised doses, followed by less frequent maintenance administration when clinically indicated. Early improvement may support continued engagement with treatment, but sustained benefit depends on subsequent management. Oral antidepressant therapy, psychotherapy, relapse-prevention strategies, management of comorbidities, and regular reassessment remain essential components of care.

Evidence concerning longer-term efficacy suggests that continuation or maintenance treatment may help sustain response in selected patients with treatment-resistant depression (2). Nevertheless, optimal treatment duration, frequency of maintenance administration, criteria for tapering, and management after discontinuation remain clinically important areas of uncertainty.

Effects on Suicidal Ideation

The possibility that esketamine may rapidly reduce suicidal ideation has generated particular interest. Meta-analytic and review-level evidence concerning ketamine and esketamine suggests that rapidly acting glutamatergic treatments may reduce suicidal thoughts during the early period following administration (8). Interpretation of intranasal esketamine remains more complex because the broader literature includes different ketamine formulations and clinically heterogeneous populations.

Some studies have reported early improvement in suicidal-ideation items or structured suicidality scales among patients receiving esketamine alongside comprehensive standard care. These findings indicate that esketamine-containing treatment may contribute to earlier relief of selected suicide-related symptoms. Their clinical significance should be interpreted carefully because single-item depression-scale measures and multidimensional suicide-assessment instruments do not measure identical constructs.

Suicidal ideation may include passive wishes for death, active suicidal thoughts, intent, planning, perceived controllability, preparatory behaviour, and previous attempts. A reduction in one dimension does not necessarily indicate resolution of all components of suicide risk. Suicidal thoughts may also fluctuate independently of overall depression severity and may recur after initial symptomatic improvement.

Observed reductions in suicidal ideation may partly reflect improvement in broader depressive symptoms rather than a distinct anti-suicidal pharmacological effect. This distinction remains difficult to establish because depression severity and suicidal ideation are closely related, and many studies evaluate both over short periods. Demonstrating a specific anti-suicidal effect would require evidence that improvement in suicidality exceeds that expected from the general antidepressant response.

Available evidence does not establish that intranasal esketamine prevents suicide attempts or reduces suicide mortality. Trials evaluating symptom change are generally not designed or powered to detect differences in these rare but critical behavioural outcomes. Clinical decisions should therefore continue to be guided by comprehensive suicide-risk assessment rather than improvement in a single rating-scale score.

Esketamine should be understood as one component of acute management rather than a stand-alone suicide-prevention intervention. Patients with active suicidal intent or imminent risk of self-harm may require hospitalization, continuous observation, environmental safety measures, crisis intervention,

treatment of agitation or psychosis, involvement of family or caregivers, and coordinated follow-up. Symptomatic improvement after administration does not remove the need for continued monitoring.

Maintenance and Sustainability of Response

The early effects of intranasal esketamine are clinically meaningful only when considered alongside durability of response. Available evidence suggests that some patients maintain improvement with continued treatment, whereas differences between esketamine-containing and comparator treatments may become less pronounced over time as oral antidepressants and comprehensive care exert their effects (2).

A narrowing of treatment differences at later assessment points does not necessarily indicate treatment failure. It may reflect delayed improvement in comparator groups, continued standard psychiatric treatment, regression toward the mean, natural reduction in acute crisis intensity, or differences in continuation schedules. Conversely, an early response does not guarantee durable remission. Relapse may occur when treatment intervals are extended or administration is discontinued.

Maintenance decisions should therefore be individualized. Relevant considerations include degree and stability of response, number of previous treatment failures, recurrence history, adverse effects, comorbid conditions, patient preference, accessibility, cost, and ability to comply with supervised treatment. Periodic reduction in treatment frequency may be appropriate for some patients, whereas others may require ongoing maintenance to preserve benefit.

Further research is needed to identify reliable predictors of sustained response. Potential predictors may include clinical subtype, duration of illness, previous treatment history, baseline symptom profile, comorbid anxiety, cognitive symptoms, inflammatory or neurobiological markers, and characteristics of the initial response.

Safety and Tolerability

Intranasal esketamine requires supervised administration because of its acute physiological and psychological effects. Commonly reported adverse effects include dissociation, dizziness, sedation, nausea, perceptual disturbance, vertigo, headache, altered taste, and transient elevation of blood pressure (1,2,5). These effects are generally most prominent shortly after administration and often diminish during the observation period.

Dissociation is particularly important because it may affect treatment acceptability and compromise blinding in clinical trials. Participants and assessors may infer treatment allocation when characteristic perceptual or dissociative symptoms occur. This functional unblinding can influence expectations and subjective outcome ratings, especially for depression and suicidal-ideation scales.

Blood-pressure monitoring is necessary because transient increases may occur following administration. Patients with unstable cardiovascular disease, uncontrolled hypertension, or other relevant medical conditions require careful evaluation before treatment. Sedation and perceptual changes also justify restrictions on driving, operating machinery, and making safety-sensitive decisions after administration.

The potential for misuse or psychological dependence should be considered, particularly in patients with current or previous substance-use disorders. Supervised administration, controlled dispensing, clear eligibility criteria, and longitudinal monitoring reduce but do not eliminate this concern.

Cognitive safety has also been examined because repeated exposure to ketamine-related treatments raises questions regarding memory, attention, and executive function. Available reviews have not demonstrated a uniform pattern of clinically significant cognitive deterioration with appropriately monitored intranasal esketamine treatment, although long-term real-world evidence remains limited (10). Cognitive functioning should be monitored when treatment is prolonged or when patients have

pre-existing cognitive vulnerability. The principal evidence patterns and their clinical interpretation are summarized in Table 2.

Table 2. Thematic synthesis of intranasal esketamine evidence

Clinical domain	Overall evidence pattern	Clinical interpretation	Important limitations
Speed of antidepressant response	Earlier improvement is commonly reported during the initial hours or days	May benefit selected patients requiring rapid symptom reduction	Response is not universal, and outcome measures vary
Overall depressive symptoms	Reduction in depressive symptom severity is reported in treatment-resistant populations	Supports adjunctive use following inadequate response to conventional treatment	Long-term comparative effectiveness remains uncertain
Suicidal ideation	Early reduction in selected suicidal-ideation measures has been reported	May contribute to short-term stabilization within comprehensive care	Does not establish prevention of attempts or mortality
Treatment-resistant depression	Evidence is most clinically relevant to patients with inadequate response to previous antidepressants	Provides an additional treatment option for selected adults	Definitions and degrees of treatment resistance vary
Acute suicidal depression	Rapid symptom improvement may be useful during severe episodes	May complement observation, safety planning, hospitalization, and crisis treatment	Acute suicidal depression is not synonymous with treatment-resistant depression
Maintenance treatment	Continued treatment may sustain response in selected patients	Frequency should be individualized according to response and relapse risk	Optimal duration, tapering, and discontinuation remain uncertain
Dissociation and perceptual effects	Common acute treatment-related effects	Require supervised administration and post-dose monitoring	May compromise blinding and influence subjective assessment
Cardiovascular safety	Transient blood-pressure elevation may occur	Pre-treatment assessment and monitoring are necessary	Evidence is less certain in medically unstable populations
Cognitive outcomes	No consistent major cognitive decline is evident in reviewed evidence	Cognitive safety appears acceptable under structured monitoring	Long-term real-world data remain limited
Accessibility and implementation	Administration requires trained staff, monitoring, and repeated attendance	Best suited to organized psychiatric services	Cost, infrastructure, transport, and unequal access may restrict use

Comparison With Conventional Antidepressants

Comparisons between intranasal esketamine and conventional oral antidepressants require careful interpretation. Esketamine is generally administered in addition to oral antidepressant treatment rather than as an isolated competing therapy. Many studies therefore evaluate the incremental effect of adding active intranasal treatment to an oral antidepressant and standard psychiatric care.

The principal comparative advantage of esketamine appears to be the potential for earlier symptom reduction. Conventional antidepressants remain essential for ongoing management because they are more widely available, easier to administer, and supported by extensive long-term clinical experience. The relevant clinical question is therefore not simply whether esketamine is superior to oral antidepressants, but which patients benefit from adding esketamine, when it should be introduced, and how it should be integrated with longer-term treatment.

Direct comparisons are also complicated by differences in intensity of care. Patients receiving esketamine generally undergo structured clinical contact, repeated monitoring, and frequent reassessment. These components may independently influence symptom reporting, adherence, and safety. Comparative effectiveness in routine practice may therefore differ from efficacy observed in highly supervised clinical settings.

Comparison With Other Rapid-Acting Interventions

Esketamine is one of several interventions used or investigated for rapid relief of severe depressive symptoms. Intravenous ketamine, electroconvulsive therapy, repetitive transcranial magnetic stimulation, accelerated neuromodulation protocols, and other emerging treatments may also produce relatively rapid improvement in selected patients (9,11,12).

Electroconvulsive therapy remains an established intervention for severe depression, psychotic depression, catatonia, and situations requiring a rapid clinical response. Neuromodulation approaches may offer alternatives for patients who do not respond to pharmacological treatment or cannot tolerate specific medications. Comparative research is needed to determine how intranasal esketamine should be positioned relative to these interventions.

Treatment choice should account for urgency, previous treatment history, comorbidity, patient preference, local expertise, availability, safety, expected speed of response, and likelihood of sustained benefit. A precision-treatment framework may ultimately be more useful than universal ranking of interventions.

Table 3. Clinical comparison of rapidly acting interventions for severe or treatment-resistant depression

Intervention	Typical clinical role	Potential advantage	Principal limitations
Intranasal esketamine	Adjunctive treatment for selected adults with treatment-resistant depression	Rapid onset, standardized delivery, supervised administration	Dissociation, sedation, blood-pressure effects, cost, repeated attendance
Intravenous ketamine	Off-label rapid antidepressant intervention in specialist settings	Rapid response and flexible dosing	Intravenous access, monitoring, variable protocols, misuse concerns
Electroconvulsive therapy	Severe depression, psychotic depression, catatonia, or urgent deterioration	Established efficacy and potentially rapid response	Anaesthesia, cognitive adverse effects, stigma, infrastructure requirements
Repetitive transcranial magnetic stimulation	Non-invasive treatment after inadequate medication response	No anaesthesia and limited systemic adverse effects	Multiple sessions, variable speed of response, equipment availability
Accelerated neuromodulation	Emerging option for rapid symptom reduction	Potentially shorter treatment course	Limited availability, evolving protocols, need for comparative evidence
Conventional oral antidepressants	First-line and maintenance treatment	Wide availability, extensive long-term experience	Delayed onset and incomplete response in treatment-resistant populations

Taken together, the literature supports intranasal esketamine as a rapidly acting adjunctive option for selected adults with treatment-resistant depression. Its most consistent clinical contribution is earlier reduction of depressive symptom burden during the initial treatment period. Selected evidence also indicates early improvement in suicidal ideation, although this outcome remains distinct from prevention of suicidal behaviour, attempts, or death. The balance of evidence supports supervised use within comprehensive psychiatric care rather than isolated medication administration. Patient selection, cardiovascular assessment, suicide-risk evaluation, monitoring for dissociation and sedation, concurrent antidepressant treatment, and longer-term relapse-prevention planning remain central to clinical effectiveness and safety. The evidence base is promising but remains limited by clinical heterogeneity, short follow-up, variation in suicidality measures, and incomplete long-term comparative data.

DISCUSSION

This narrative review indicates that intranasal esketamine occupies an important but carefully defined role in the management of treatment-resistant depression. Its principal clinical advantage is the possibility of producing meaningful improvement in depressive symptoms during the initial hours and days of treatment, substantially earlier than is commonly expected with conventional oral antidepressants. This rapid action may be particularly valuable in patients with severe symptom burden, recurrent treatment failure, functional deterioration, or a need for earlier stabilization.

The findings are consistent with the broader ketamine literature, which links rapid antidepressant effects to glutamatergic modulation and enhanced synaptic plasticity rather than conventional monoaminergic mechanisms (4). This neurobiological distinction provides a plausible explanation for the difference in onset between esketamine and standard oral antidepressants. However, rapid improvement should not be interpreted as universal response or sustained remission. Some patients experience partial, transient, or minimal benefit, and continued treatment remains necessary to consolidate and maintain clinical improvement.

Evidence concerning suicidal ideation is clinically important but requires particularly cautious interpretation. Reviews of ketamine and esketamine suggest that suicidal thoughts may decrease during the early treatment period (8). Nevertheless, suicidal ideation is a complex and multidimensional construct. Passive wishes for death, active suicidal thoughts, intent, planning, preparatory behaviour, and previous attempts represent different levels of risk and are not adequately captured by a single rating-scale item.

Improvement in suicidal ideation may occur partly through reduction in overall depressive severity. Intensive clinical contact, structured observation, initiation of an oral antidepressant, hospitalization, psychological support, and safety planning may also contribute. The existing evidence therefore does

not establish that intranasal esketamine has an independent suicide-preventive effect or that it reduces suicide attempts or mortality.

This distinction has major clinical implications. Esketamine should not replace comprehensive suicide-risk management. Patients presenting with active intent, planning, access to lethal means, severe agitation, psychosis, intoxication, or inability to maintain safety require an appropriate level of psychiatric containment and monitoring. A rapid reduction in reported suicidal thoughts after treatment does not eliminate the possibility of recurrence or behavioural escalation.

The longer-term role of esketamine remains less clearly defined than its short-term effects. Maintenance treatment may preserve response in selected patients, but optimal frequency, duration, tapering, and discontinuation strategies remain uncertain (2). Clinical decisions should be individualized according to stability of response, previous relapse pattern, adverse effects, comorbidity, patient preference, access, and cost.

Safety and implementation requirements distinguish esketamine from conventional oral treatment. Dissociation, perceptual alteration, dizziness, sedation, nausea, and transient blood-pressure elevation necessitate supervised administration and post-treatment observation (1,2,5). These requirements improve safety but create barriers related to infrastructure, staffing, transport, repeated attendance, and affordability.

The recognizable psychoactive effects of esketamine also complicate clinical research. Functional unblinding may influence expectations and subjective outcome ratings. This issue is especially important when outcomes rely on clinician-rated depression scales or patient-reported suicidal ideation. Future studies should incorporate objective functional outcomes, independent assessments, active control conditions where feasible, and longer follow-up.

Cognitive safety appears generally acceptable under structured monitoring, but available evidence is insufficient to exclude subtle or long-term effects in all patient groups (10). Older adults, individuals with neurological disorders, and patients receiving prolonged treatment may require closer cognitive monitoring. Cardiovascular risk assessment is similarly important because acute blood-pressure elevations may be clinically relevant in vulnerable patients.

The position of intranasal esketamine relative to other rapidly acting interventions remains an important research question. Electroconvulsive therapy has an established role in severe and psychotic depression, catatonia, and urgent clinical deterioration. Intravenous ketamine offers rapid antidepressant effects but requires specialist administration and remains off-label in many settings. Repetitive and accelerated transcranial magnetic stimulation provide non-invasive alternatives but differ in speed, accessibility, and evidence base (11,12).

Rather than treating these interventions as universally competing options, clinical decision-making should consider individual patient characteristics and treatment context. The most appropriate treatment may depend on urgency, psychotic symptoms, previous treatment failures, cognitive vulnerability, cardiovascular status, substance-use history, availability, cost, and patient preference.

The current evidence base has several limitations. Definitions of treatment-resistant depression vary, and studies of acute suicidal depression do not always confirm prior treatment resistance. Suicidal ideation is assessed using different instruments and time points, limiting direct comparison. Follow-up is frequently too short to determine effects on relapse, attempts, mortality, long-term cognition, misuse, or functional recovery. The influence of concomitant treatments and intensive clinical contact also complicates attribution of benefit exclusively to esketamine.

Future research should distinguish clearly between treatment-resistant depression and acute suicidal major depression. Suicidal ideation, intent, planning, behaviour, attempts, and mortality should be

reported as separate outcomes. Studies should also document oral antidepressant treatment, psychotherapy, hospitalization, and other components of standard care so that the incremental effect of esketamine can be evaluated more accurately.

Long-term comparative studies should examine maintenance schedules, relapse following discontinuation, cardiovascular and cognitive safety, misuse potential, functional recovery, quality of life, and cost-effectiveness. Direct comparisons with electroconvulsive therapy, intravenous ketamine, accelerated neuromodulation, and optimized pharmacological combinations would further clarify the place of intranasal esketamine within treatment algorithms.

CONCLUSION

Intranasal esketamine is a rapidly acting adjunctive treatment that may provide earlier improvement in depressive symptoms and selected measures of suicidal ideation among carefully selected adults with treatment-resistant depression or severe depressive episodes. Its clinical value lies primarily in reducing acute symptom burden while broader psychiatric treatment is established or optimized. Improvement in suicidal-ideation scores should not be interpreted as confirmed prevention of suicide attempts or mortality, and treatment must remain integrated with comprehensive risk assessment, monitoring, psychological care, and longer-term relapse-prevention strategies. Further comparative and longitudinal research is required to define its specific anti-suicidal effects, durability, safety, cost-effectiveness, and appropriate position relative to other rapidly acting interventions.

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