DUDZIAK, Natalia, DROZD, Zuzanna, NIEMIEC, Bartosz, PIOSIK, Szymon, OLESIŃSKI, Bruno, PIASECKI, Łukasz, GUZOWICZ, Zuzanna, KAMIŃSKA, Monika and GĄGAŁKA, Patrycja. Esketamine in Treatment-Resistant Depression and Suicidal Ideation: A Systematic Review. Journal of Education, Health and Sport. 2025;81:66740. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.81.66740
https://apcz.umk.pl/JEHS/article/view/66740

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2025. Revised: 26.11.2025. Accepted: 26.11.2025. Published: 29.11.2025.

Esketamine in Treatment-Resistant Depression and Suicidal Ideation: A Systematic Review

Natalia Dudziak[1], https://orcid.org/0009-0000-6631-3358
[1]Medical University of Lublin, Lublin, Poland
natalia0171@gmail.com

Zuzanna Drozd[1], https://orcid.org/0009-0004-5277-9404
[1]Medical University of Lublin, Lublin, Poland
aizuzdrozd@gmail.com

Bartosz Niemiec[1], https://orcid.org/0009-0007-1168-9930
[1]Medical University of Lublin, Lublin, Poland
bartoszn1999@gmail.com

Szymon Piosik[1], https://orcid.org/0009-0003-5142-0275
[1]Medical University of Lublin, Lublin, Poland
szymon.piosikstudia@gmail.com

Bruno Olesiński[1], https://orcid.org/0009-0001-2387-4742
[1]Medical University of Lublin, Lublin, Poland
bruno.olesinski@gmail.com

Łukasz Piasecki[1], https://orcid.org/0009-0000-8545-4949
[1]Medical University of Lublin, Lublin, Poland
lukaszpiasecki131@gmail.com

Zuzanna Guzowicz[1], https://orcid.org/0009-0005-9203-4746
[1]Medical University of Lublin, Lublin, Poland
zguzowicz@gmail.com

Monika Kamińska[1], https://orcid.org/0009-0005-6138-708X
[1]Medical University of Lublin, Lublin, Poland
monikakaminskamedstudent@gmail.com

Patrycja Gągałka[1], https://orcid.org/0009-0004-9984-0241
[1]Medical University of Lublin, Lublin, Poland
patrycjagagalka@wp.pl

Corresponding Author
Natalia Dudziak, natalia0171@gmail.com

Abstract

Background. Major depressive disorder affects 20% of the global population, with treatment-resistant depression in 10-30% of cases. Patients with acute suicidal ideation need immediate intervention, yet conventional antidepressants require weeks to work. Esketamine offers rapid symptom reduction through NMDA receptor antagonism.

Aim. To systematically review current evidence on efficacy and safety of esketamine nasal spray in treating depression with active suicidal ideation and treatment-resistant depression, focusing on rapidity of response and clinical outcomes.

Material and methods. PubMed search using terms "esketamine, depression, suicide" and related. After screening, 11 studies from 2020 onwards were analyzed.

Results. ASPIRE II showed esketamine 84mg superior to placebo at 24 hours: MADRS reduction -15.7 vs -12.4 points (p=0.006), with effects at 4 hours. In 456 patients, response rates were 34.5% vs 25.3%, remission 20.4% vs 9.8% at 24 hours. Versus quetiapine, esketamine

achieved 27.1% vs 17.6% remission at week 8 (p=0.003). Long-term data (1,148 patients, 31.5 months) showed suicide attempts 0.361 and deaths 0.036 per 100 patient-years. Common side effects: dizziness (38-47%), nausea (27-33%), transient dissociation; 4-11% discontinued treatment.

Conclusions. Esketamine demonstrates rapid efficacy in reducing depressive symptoms and suicidal ideation, with effects within hours and sustained benefits. It shows superior results versus placebo and comparators with acceptable safety, making it valuable for acute suicidal ideation requiring rapid intervention.

Key words: esketamine, treatment-resistant depression, suicidal ideation, NMDA receptor, ketamine

1. Introduction

Major depressive disorder (MDD) affects approximately 20% of the global population and is projected to become the leading cause of disease burden in developed countries by 2030 (Yang et al., 2022). The disorder leads to substantial psychosocial impairment and cognitive dysfunction, and poses a particularly high risk for suicidal behaviors (Yang et al., 2022). In adolescents, MDD presents with a five-fold higher risk for suicide attempts, while treatment-resistant depression (TRD) occurs in up to 40% of young patients (Pardossi et al., 2024; Kosik-Gonzalez et al., n.d.).

Treatment-resistant depression affects between 10 and 30% of individuals with MDD, with patients experiencing markedly reduced quality of life and remission rates as low as 10-15% with further conventional antidepressant trials (Degerlund Maldi et al., 2021; Ross & Soeteman, 2020). Patients experiencing active suicidal ideation are especially vulnerable, showing more severe symptoms, higher rates of psychiatric comorbidities, and poorer functioning than those without suicidal thoughts (Canuso et al., 2021).

This clinical challenge becomes even more pressing given the often short timeframe between onset of suicidal ideation and suicide attempt, making immediate intervention essential (Kosik-Gonzalez et al., n.d.). However, current treatments present significant limitations. Traditional antidepressants, including SSRIs and SNRIs, typically require weeks or months to

demonstrate efficacy, and this prolonged delay in therapeutic response further elevates suicide risk during the critical early treatment period (Pompili, 2020; Nguyen et al., 2023).

1.1. Esketamine - Background

Esketamine offers a fundamentally different approach to treating depression, working through non-competitive antagonism of N-methyl-D-aspartate receptors (NMDAR) instead of the traditional monoamine neurotransmitter modulation (Czora-Poczwardowska et al., 2024; Vasiliu, 2023). As the isolated S-enantiomer of racemic ketamine, esketamine demonstrates approximately four times higher affinity for NMDA receptors than the R(-) enantiomer, which contributes to better therapeutic results with fewer side effects (Czora-Poczwardowska et al., 2024; Kawczak et al., 2024).

Regulatory approval of esketamine was a historic moment in psychiatric care. The FDA approved intranasal esketamine for treatment-resistant depression in March 2019, followed by European approval in December 2019 (McIntyre et al., 2021). Subsequently, esketamine received additional FDA approval for emergency treatment of patients with MDD requiring rapid symptom control (Ionescu et al., 2021).

The intranasal route allows for convenient outpatient treatment while maintaining adequate bioavailability. Esketamine is used alongside conventional SSRIs or SNRIs, combining rapid NMDA receptor antagonism with traditional monoaminergic approaches (Kawczak et al., 2024). Esketamine's rapid onset of action has opened new possibilities for acute reduction of suicidality in emergency settings, addressing a critical gap in psychiatric emergency care (Ross & Soeteman, 2020).

1.2. Esketamine in Treating Depression with Suicidal Ideation - Mechanisms of Action

Esketamine works differently from traditional monoaminergic antidepressants, primarily targeting NMDA receptors (Rizzo et al., 2025). The therapeutic mechanism begins with NMDA receptor blockade on GABAergic neurons, resulting in increased glutamate release and AMPA

receptor activation, which stimulates neuroplasticity through synaptogenesis in the prefrontal cortex and hippocampus (Czora-Poczwardowska et al., 2024).

Brain-derived neurotrophic factor (BDNF) plays a key role in esketamine's effects (Caliman-Fontes et al., 2023). Clinical evidence shows that ketamine responders demonstrate statistically significant increases in BDNF levels compared to baseline, while non-responders show no significant changes (Medeiros et al., 2022). The mechanism involves suppression of tonically activated NMDA receptors, leading to dephosphorylation of eEF2 and enhanced dendritic protein synthesis, particularly of BDNF (Krystal et al., 2024).

Recent genetic studies identified associations between clinical response to esketamine and interleukin-1 receptor associated kinase-3 (IRAK3), suggesting inflammatory pathways contribute to treatment response (Johnston et al., 2024). The action on AMPA receptors ultimately improves neural plasticity through signaling pathways that enhance BDNF production, which is typically decreased in stress and depression (Salahudeen et al., 2020).

Esketamine works quickly, with improvement often evident within 24 hours of intranasal administration (Czora-Poczwardowska et al., 2024). This rapid response is especially important for patients with acute suicidal ideation, where improvement at 4 hours after the first dose represents a potentially life-saving intervention (Canuso et al., 2021).

Meta-analyses demonstrate that one day after the first dose, esketamine reduces depression scores with a standardized mean difference of -3.18 compared to placebo (Floriano et al., 2023). Treatment extends beyond symptom reduction to include cognitive improvements, with enhanced processing speed and working memory observed within days of treatment (Lan et al., 2023). In suicidal crises, rapid resolution of suicide-associated symptoms like dysphoria and agitation provides a critical therapeutic window that traditional antidepressants cannot offer (Pompili, 2020).

Human studies provide evidence of short-term effects on hippocampal volumes, supporting pro-neuroplastic effects observed in animal models (Höflich et al., 2021). Both ketamine and esketamine demonstrate favorable safety profiles, making them effective for

treatment-resistant depression with suicidal thoughts while providing a window for longer-term interventions (Pardossi et al., 2024).

1.4. Neurobiology of Depression and Suicidal Behavior

Esketamine's therapeutic effects in depression with suicidal ideation differ fundamentally from traditional monoaminergic antidepressants. Unlike conventional treatments, esketamine primarily targets N-methyl-D-aspartate receptors (NMDAR) (Rizzo et al., 2025). The mechanism involves NMDA receptor blockade on GABAergic neurons, which results in increased glutamate release and activation of AMPA receptors, ultimately stimulating neuroplasticity by promoting synaptogenesis in the prefrontal cortex and hippocampus (Czora-Poczwardowska et al., 2024).

BDNF is central to esketamine's antidepressant action. BDNF, a growth factor from the neurotrophin family, is important for neuronal development, differentiation, survival, and neuroplasticity (Pardossi et al., 2024). The action of esketamine on AMPA receptors may ultimately improve neural plasticity and synaptogenesis through signaling pathways that enhance BDNF production, which is typically decreased in the prefrontal cortex and hippocampus during stress and depression (Salahudeen et al., 2020).

Clinical evidence supports the role of BDNF in treatment response. In longitudinal analyses, ketamine responders demonstrated statistically significant increases in BDNF levels compared to pre-treatment levels, whereas non-responders showed no significant changes (Medeiros et al., 2022). This neuroplastic effect is further supported by neuroimaging studies showing that ketamine has short-term effects on hippocampal subfield volumes in humans, confirming previous animal model findings and highlighting the hippocampus as a key region in ketamine's mechanism of action (Höflich et al., 2021).

Recent genetic research has identified additional pathways involved in esketamine's therapeutic response. A genome-wide association study of Phase 3 trial participants found significant associations between clinical response to esketamine and interleukin-1 receptor

associated kinase-3 (IRAK3), suggesting neuroinflammatory mechanisms may also contribute to treatment outcomes (Johnston et al., 2024).

1.5. Rapid Antidepressant and Anti-Suicidal Effects

The rapid onset of esketamine's therapeutic effects sets it apart from traditional antidepressants. When administered intranasally in combination with an oral antidepressant, esketamine demonstrates rapid antidepressant effects that become evident within 24 hours of administration, most commonly assessed using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Czora-Poczwardowska et al., 2024). Rapid improvement in depressive symptoms at 4 hours after the first dose is particularly important for patients with severe depression who are acutely suicidal (Canuso et al., 2021).

The fast onset of esketamine's effects may be associated with direct stimulation of the mammalian target of rapamycin complex 1 (mTORC1), a signaling pathway involved in protein synthesis regulation that stimulates synaptogenesis and BDNF production (Vasiliu, 2023). This rapid mechanism is especially important during suicidal crises, where reducing psychological suffering is essential for saving lives. Unlike traditional antidepressants, which may cause side effects without immediate beneficial effects on symptoms, esketamine can provide rapid resolution of components most associated with suicide, such as dysphoria, agitation, irritability, and anxiety (Pompili, 2020).

Clinical trial data demonstrate the sustained nature of esketamine's rapid effects. One day after the first dose, esketamine significantly reduces depression rating scale scores compared to placebo, and at 25-day follow-up, pre-dose analysis shows continued mean reduction in the esketamine group compared to placebo (Floriano et al., 2023). The rapid onset of effects, often evident within hours, and their persistence for weeks after a single dose suggest that ketamine's action involves complex processes beyond simple NMDA receptor blockade, particularly those related to synaptic plasticity and neurotrophic signaling (Pardossi et al., 2024).

For adolescents with treatment-resistant depression and suicidal ideation, both ketamine and esketamine have demonstrated favorable safety and tolerability profiles. These medications can effectively treat symptoms, reduce self-harm and suicide risks, and provide a crucial window for longer-term therapeutic interventions, potentially improving adolescents' quality of

life (Pardossi et al., 2024). Additionally, esketamine treatment shows cognitive benefits, with improvements in processing speed and working memory, without significant associations between baseline cognition and antidepressant or antisuicidal effects (Lan et al., 2023).

However, esketamine is a complex drug with low affinity for NMDAR and can bind to other targets, including opioid receptors, which may contribute to both therapeutic effects and potential withdrawal-related concerns (Rizzo et al., 2025).

Research Objective.

To systematically review and synthesize current evidence regarding the efficacy and safety of esketamine nasal spray in treating depression with active suicidal ideation and treatment-resistant depression, with particular focus on the rapidity of therapeutic response and clinical outcomes across diverse patient populations.

Research Problems.

1. What is the efficacy of esketamine nasal spray compared to placebo in rapidly reducing depressive symptoms and suicidal ideation in patients with major depressive disorder and acute suicidal ideation?
2. How does esketamine nasal spray compare to active comparators (such as quetiapine) in achieving remission and response rates in treatment-resistant depression over short-term and long-term treatment periods?
3. What is the safety profile of esketamine nasal spray, including the incidence and severity of adverse events, treatment discontinuation rates, and long-term safety outcomes in patients with treatment-resistant depression?
4. Does esketamine maintain therapeutic efficacy across diverse patient subgroups, including those with comorbid anxiety disorders, varying baseline irritability levels, and patients who do not demonstrate early treatment response?

Research Hypotheses.

Hypothesis 1: Esketamine nasal spray will demonstrate superior efficacy compared to placebo in reducing depressive symptoms (measured by MADRS score reduction) within 24 hours of administration in patients with major depressive disorder and acute suicidal ideation.

Hypothesis 2: Esketamine nasal spray will show significantly higher remission rates compared to active comparators (such as quetiapine extended-release) in patients with treatment-resistant

depression at 8 weeks and maintain these benefits through long-term follow-up (32 weeks).
Hypothesis 3: While esketamine will demonstrate higher rates of transient dissociative and neuropsychiatric adverse events compared to placebo, the overall benefit-risk profile will be favorable, with acceptable treatment discontinuation rates and no increased risk of treatment-emergent suicidal ideation or behavior compared to control groups.

2. **Research materials and methods**

A systematic search of the scientific literature was carried out using the PubMed database. The following search phrases were applied: "esketamine, depression, suicide", "esketamine treatment-resistant depression", "esketamine suicidal ideation", and "esketamine nasal spray major depressive disorder". A total of 80 articles were initially identified. After removing duplicates, 43 unique articles remained for title and abstract screening. After screening for relevance, 11 articles were selected for detailed analysis based on their focus on esketamine efficacy in treatment-resistant depression and suicidal ideation. To ensure that the review reflects the most recent evidence, only studies published from 2020 onwards were considered.

2.1. **Participants.**

Not applicable – literature review.

2.2. **Procedure / Test protocol / Skill test trial / Measure / Instruments.**

Not applicable – literature review.

2.3. Data collection and analysis / Statistical analysis.

Not applicable – literature review.

2.3.1. Statistical Software.

Not applicable – literature review.

2.3.2. AI.

Not applicable.

2.3.3. Statistical Methods.

Not applicable – literature review.

3. **Research results**

3.1. Primary Evidence from ASPIRE Studies

The ASPIRE program trials provide the strongest evidence for esketamine's anti-suicidal effects. The ASPIRE II study, a phase 3 randomized controlled trial involving 230 patients with major depressive disorder and active suicidal ideation with intent, demonstrated that esketamine 84mg nasal spray provided superior efficacy compared to placebo within 24 hours (Ionescu et al., 2021). Patients receiving esketamine showed a mean MADRS reduction of -15.7 points compared to -12.4 points with placebo, resulting in a statistically significant least squares mean difference of -3.9 (95% CI: -6.60, -1.11; p=0.006). this therapeutic effect was observable as early as 4 hours post-administration with a mean difference of -4.2 (95% CI: -6.38, -1.94). The remission rate, defined as MADRS ≤12, was 11.3% higher in the esketamine group compared to placebo (Ionescu et al., 2021). However, when examining suicidality-specific outcomes using the CGI-SS-r scale, both groups showed median reductions of -1.0 point at 24 hours, with no significant between-group difference (p=0.379), though by day 90, 86.3% of esketamine-treated patients versus 76.7% of placebo-treated patients achieved CGI-SS-r scores of 0-1, indicating normal or questionably suicidal status (Ionescu et al., 2021).

A pooled analysis of ASPIRE I and II studies including 456 patients, which showed consistent results across the larger population (Canuso et al., 2021). The pooled data revealed MADRS reductions of -16.1 for esketamine versus -12.6 for placebo at 24 hours, with a least squares mean difference of -3.8 (95% CI: -5.75 to -1.89). While the overall CGI-SS-r reduction showed no significant difference between groups (-1.5 vs -1.3, with a non-significant difference of -0.20, 95% CI: -0.43 to 0.04), subgroup analysis revealed greater benefit in patients with prior suicide attempts (-0.31, 95% CI: -0.61 to -0.01). Response rates at 24 hours favored esketamine (34.5% vs 25.3%), as did remission rates (20.4% vs 9.8%), with these benefits maintained at day 25 (response: 50.4% vs 37.3%) (Canuso et al., 2021).

Time-to-event analyses from the ASPIRE studies examined how quickly patients recovered (Fu et al., 2023). Esketamine significantly accelerated time to remission compared to placebo (15 days vs 23 days, p=0.005), with an even more pronounced difference in time to

consistent remission (23 days vs 50 days, p=0.007). The cumulative remission rates by day 25 were 65.2% for esketamine versus 55.5% for placebo, and patients in the esketamine group spent significantly more days in remission (27.1% vs 8.3% of total days, p=0.006). When combining both depression and suicidality endpoints (MADRS ≤12 plus CGI-SS-r ≤1), esketamine achieved this combined remission in 17 days compared to 25 days for placebo (p=0.003) (Fu et al., 2023).

3.2. Comparative Effectiveness Studies

Comparative effectiveness was examined in a smaller study that directly compared esketamine (0.25mg/kg IV) with racemic ketamine (0.5mg/kg IV) in 59 treatment-resistant depression patients with suicidal ideation (Vieira et al., 2021). Both treatments showed rapid and equivalent reductions in suicidal thoughts within 24 hours ($p<0.001$ for both), with effects sustained through 7 days. Baseline MADRS item 10 scores (suicidal thoughts) of 2.0 in both groups decreased to 0.0 at 24 hours and remained low through the follow-up period, demonstrating that the S-enantiomer of ketamine maintains the anti-suicidal properties of the racemic mixture (Vieira et al., 2021).

Esketamine demonstrated superior efficacy in treatment-resistant depression when compared to established treatments. The largest head-to-head comparison involved 676 patients randomized to receive either esketamine nasal spray plus SSRI/SNRI or extended-release quetiapine plus SSRI/SNRI over 32 weeks (Reif et al., 2023). The primary endpoint of remission at week 8, defined as MADRS ≤10, was achieved by 27.1% of esketamine-treated patients compared to 17.6% of quetiapine-treated patients (p=0.003). Long-term benefits were sustained, with 21.7% of esketamine patients versus 14.1% of quetiapine patients maintaining remission without relapse through week 32. By week 32, remission rates reached 49.1% versus 32.9%, respectively, while response rates were 65.5% versus 47.1% (Reif et al., 2023). Suicide attempts occurred in only 2 patients in the esketamine group versus 1 in the quetiapine group, with none considered treatment-related (Reif et al., 2023).

3.3. Long-Term Safety and Effectiveness

Long-term safety and effectiveness data from the SUSTAIN-3 study included 1,148 patients followed for a mean of 31.5 months, representing 2,769 cumulative patient-years of

exposure (Zaki et al., 2023). During the induction phase, mean MADRS scores decreased by 12.8 points, with remission rates of 35.6% and response rates of 49.2%. During the maintenance phase, these benefits were sustained with remission rates improving to 46.1% and response rates maintained at 50.9% at one year (Zaki et al., 2023). 5.6% of patients experienced suicidality-related adverse events during the extended follow-up. 49 patients (4.3%) with no prior suicide history developed new suicidal ideation, while 10 patients (0.9%) attempted suicide, corresponding to an incidence rate of 0.361 per 100 patient-years. One death by suicide occurred (0.036 per 100 patient-years), which compares favorably to expected rates in treatment-resistant depression populations (Zaki et al., 2023).

A post-hoc analysis examined 362 patients from the ASPIRE studies who lacked evidence of early response (Turkoz et al., 2023). Among patients who did not respond at 24 hours, 63.9% of those receiving esketamine achieved response by day 25 compared to 48.0% receiving placebo ($p=0.010$), with remission rates of 35.1% versus 24.4% ($p=0.074$). Even among patients who failed to respond by week 1, esketamine showed numerically superior outcomes with response rates of 48.4% versus 34.5% and remission rates of 25.0% versus 13.1% by day 25 (Turkoz et al., 2023).

3.4. Efficacy Across Patient Subgroups

Subgroup analyses showed esketamine's efficacy was maintained across diverse patient populations. In patients with comorbid anxiety symptoms or disorders, which comprised 72.6% of the study population, esketamine plus antidepressant produced MADRS reductions of -21.0 points compared to -18.3 points with placebo plus antidepressant (Daly et al., 2021). Response rates in anxious patients were 65.3% versus 54.2% for placebo, while remission rates were 47.2% versus 33.3%. Patients without comorbid anxiety showed even greater treatment differences, with response rates of 79.3% versus 46.4% and remission rates of 65.5% versus 25.0% (Daly et al., 2021). Similarly, baseline irritability levels did not influence treatment response, with pooled data from TRANSFORM-1 and TRANSFORM-2 studies showing overall response rates of 58.7% for esketamine plus antidepressant versus 45.2% for antidepressant plus placebo ($p<0.001$), and remission rates of 42.3% versus 30.8% ($p=0.004$) (Jha et al., 2023).

3.5. Safety Profile and Benefit-Risk Assessment

The safety profile of esketamine was characterized primarily by transient dissociative and neuropsychiatric effects that were generally manageable. In the ASPIRE II study, the most common adverse events included dizziness (41.2%), dissociation (38.6%), nausea (33.3%), dysgeusia (25.4%), somnolence (22.8%), headache (21.9%), and paresthesia (20.2%) (Ionescu et al., 2021). Despite the frequency of these effects, only 11.4% of patients required dose reductions due to intolerance (Ionescu et al., 2021). The pooled ASPIRE analysis showed similar patterns, with dizziness (38.3% vs 13.8% placebo), dissociation (33.9% vs 5.8%), and nausea (26.9% vs 13.8%) being the most frequent events (Canuso et al., 2021).

When compared directly to quetiapine in the 32-week comparative study, esketamine showed higher overall rates of treatment-emergent adverse events (91.9% vs 78.0%) but lower rates of treatment discontinuation due to adverse events (4.2% vs 11.0%) (McIntyre et al., 2024). The most common esketamine-related adverse events were dizziness (46.7%), nausea (29.3%), dissociation (28.1%), and headache (24.6%), while quetiapine was associated with somnolence (23.2%) and weight gain (12.5%). Treatment-emergent suicidal ideation occurred in 1.5% of esketamine-treated patients versus 2.1% of quetiapine-treated patients, while suicide attempts were rare in both groups (0.6% vs 0.3%) (McIntyre et al., 2024).

Pooled benefit-risk analyses showed favorable outcomes for esketamine. Induction studies showed 5-21 additional remitters per 100 patients treated and 14-17 additional responders per 100 patients compared to placebo, while maintenance studies demonstrated 19-32 fewer relapses per 100 patients (Katz et al., 2021). Incident post-baseline suicidal ideation was balanced between esketamine and placebo groups, with a difference of -2.1 per 100 patients (95% CI: -8.40 to 4.18), indicating no increased suicidal risk with treatment (Katz et al., 2021). The number needed to treat for response was approximately 8 overall, indicating clinically meaningful benefit (Jha et al., 2023).

4. Discussion

These 11 studies show that esketamine nasal spray represents a significant therapeutic advancement for patients with treatment-resistant depression, particularly those experiencing

acute suicidal ideation. The rapid onset of anti-suicidal and antidepressant effects, observable within 4-24 hours of administration, addresses a critical clinical need for immediate intervention in high-risk patients. This rapid action distinguishes esketamine from traditional antidepressants, which typically require weeks to achieve therapeutic effects.

Several methodological considerations influence the interpretation of these results. The ASPIRE studies' design, which required hospitalization and comprehensive standard care for both treatment groups, may have attenuated the observed treatment differences due to intensive clinical contact and optimization of conventional treatments. The characteristic dissociative effects of esketamine likely compromised blinding integrity in most studies, potentially influencing both patient and clinician assessments. Additionally, the predominance of white participants in several studies, particularly the 86.8% white representation in SUSTAIN-3, limits generalizability to more diverse populations.

The consistency of efficacy across various patient subgroups, including those with comorbid anxiety disorders, different levels of baseline irritability, and varying demographic characteristics, supports esketamine's broad clinical utility in treatment-resistant depression. The maintained efficacy in patients who do not show early response is particularly relevant, as it supports persistence with treatment rather than premature discontinuation.

Long-term safety data from SUSTAIN-3 shows sustained benefits and acceptable risk profiles over extended treatment periods, though the open-label design and potential selection bias from parent studies must be considered when interpreting these results. The observed suicide rates of 0.361 attempts and 0.036 deaths per 100 patient-years appear reasonable for this high-risk population, though direct comparisons to matched untreated cohorts are not available from these studies.

5. Conclusions

Esketamine nasal spray demonstrates robust and rapid efficacy in reducing both depressive symptoms and suicidal ideation in patients with treatment-resistant depression. The evidence supports its use for patients with acute suicidal ideation, with clinically meaningful effects observable within hours of administration and sustained benefits over weeks to months.

The treatment shows superior efficacy compared to both placebo and active comparators like quetiapine, with an acceptable safety profile characterized primarily by transient and manageable dissociative effects. Patients who do not show early response may still benefit from continued treatment, supporting clinical persistence with therapy. Long-term treatment maintains efficacy with acceptable safety over extended periods, making esketamine an important addition to the therapeutic options for treatment-resistant depression, particularly in patients with suicidal ideation where rapid intervention is crucial.

Disclossure: All authors have read and approved the final version of the manuscript for publication

Supplementary Materials

Author Contributions: Natalia Dudziak: Conceptualization, Methodology, Supervision, Writing – Original Draft, Zuzanna Drozd: Investigation, Data Curation, Formal Analysis, Writing – Review and Editing, Szymon Piosik: Resources, Validation, Writing – Review and Editing, Bartosz Niemiec: Visualization, Writing – Original Draft, Bruno Olesiński: Validation, Data Curation, Writing – Review and Editing, Piasecki Łukasz: Investigation, Validation, Writing - Original Draft; Guzowicz Zuzanna: Writing – Original Draft, Kamińska Monika – Methodology, Writing - Original Draft, Gągałka Patrycja: Resources, Writing – Review and Editing.

Funding: Dudziak Natalia

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable. This systematic review did not involve human participants. The study was based solely on the analysis of previously published scientific literature and data, and therefore did not require informed consent from any individuals.

Data Availability Statement: All data used in this systematic review are entirely contained within the published article and/or are available in the public domain through the cited scientific literature and databases (e.g., PubMed, Google Scholar). The authors confirm that the data supporting the findings of this study are available within the article.

Acknowledgements

Conflicts of Interest: The authors declare no conflict of interest.

In preparing this work, the authors used ChatGPT by OpenAI for the purpose of improving language clarity, enhancing readability, and organizing scientific content. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

References

Caliman-Fontes, A. T., Leal, G. C., Correia-Melo, F. S., Paixao, C. S., Carvalho, M. S., Jesus-Nunes, A. P., Vieira, F., Magnavita, G., Bandeira, I. D., Mello, R. P., Beanes, G., Silva, S. S., Echegaray, M., Carvalho, L. P., Machado, P., Sampaio, A. S., Cardoso, T. de A., Kapczinski, F., Lacerda, A. L. T., & Quarantini, L. C. (2023). Brain-derived neurotrophic factor serum levels following ketamine and esketamine intervention for treatment-resistant depression: secondary analysis from a randomized trial. Trends in Psychiatry and Psychotherapy, 45. https://doi.org/10.47626/2237-6089-2021-0298

Canuso, C. M., Ionescu, D. F., Li, X., Qiu, X., Lane, R., Turkoz, I., Nash, A. I., Lopena, T. J., & Fu, D. J. (2021). Esketamine Nasal Spray for the Rapid Reduction of Depressive Symptoms in Major Depressive Disorder With Acute Suicidal Ideation or Behavior. Journal of Clinical Psychopharmacology, 41(5), 516–524. https://doi.org/10.1097/JCP.0000000000001465

Czora-Poczwardowska, K., Kujawski, R., Jaworska, J., Mikołajczak, P., & Szulc, M. (2024). A review of the antidepressant effects of esketamine and arketamine in treatment-resistant depression. Pharmacotherapy in Psychiatry and Neurology, 40(2), 127–142. https://doi.org/10.5114/fpn.2024.147494

Daly, E. J., Turkoz, I., Salvadore, G., Fedgchin, M., Ionescu, D. F., Starr, H. L., Borentain, S., Trivedi, M. H., Thase, M. E., & Singh, J. B. (2021). The effect of esketamine in patients with treatment-resistant depression with and without comorbid anxiety symptoms or disorder. Depression and Anxiety, 38(11), 1120–1130. https://doi.org/10.1002/da.23193

Degerlund Maldi, K., Asellus, P., Myléus, A., & Norström, F. (2021). Cost-utility analysis of esketamine and electroconvulsive therapy in adults with treatment-resistant depression. BMC Psychiatry, 21(1). https://doi.org/10.1186/s12888-021-03601-8

Floriano, I., Silvinato, A., & Bernardo, W. M. (2023). The use of esketamine in the treatment of patients with severe depression and suicidal ideation: systematic review and meta-analysis. Revista Da Associacao Medica Brasileira, 69(4). https://doi.org/10.1590/1806-9282.2023D694

Fu, D. J., Zhang, Q., Shi, L., Borentain, S., Guo, S., Mathews, M., Anjo, J., Nash, A. I., O'Hara, M., & Canuso, C. M. (2023). Esketamine versus placebo on time to remission in major depressive disorder with acute suicidality. BMC Psychiatry, 23(1). https://doi.org/10.1186/s12888-023-05017-y

Höflich, A., Kraus, C., Pfeiffer, R. M., Seiger, R., Rujescu, D., Zarate, C. A., Kasper, S., Winkler, D., & Lanzenberger, R. (2021). Translating the immediate effects of S-Ketamine using hippocampal subfield analysis in healthy subjects-results of a randomized controlled trial. Translational Psychiatry, 11(1). https://doi.org/10.1038/s41398-021-01318-6

Ionescu, D. F., Fu, D. J., Qiu, X., Lane, R., Lim, P., Kasper, S., Hough, D., Drevets, W. C., Manji, H., & Canuso, C. M. (2021). Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). International Journal of Neuropsychopharmacology, 24(1), 22–31. https://doi.org/10.1093/ijnp/pyaa068

Jha, M. K., Williamson, D. J., Magharehabed, G., Turkoz, I., Daly, E. J., & Trivedi, M. H. (2023). Intranasal esketamine effectively treats treatment-resistant depression in adults regardless of baseline irritability. Journal of Affective Disorders, 321, 153–160. https://doi.org/10.1016/j.jad.2022.10.020

Johnston, J. N., Zarate, C. A., & Kvarta, M. D. (2024). Esketamine in depression: putative biomarkers from clinical research. European Archives of Psychiatry and Clinical Neuroscience. https://doi.org/10.1007/s00406-024-01865-1

Katz, E. G., Hough, D., Doherty, T., Lane, R., Singh, J., & Levitan, B. (2021). Benefit–Risk Assessment of Esketamine Nasal Spray vs. Placebo in Treatment-Resistant Depression. Clinical Pharmacology and Therapeutics, 109(2), 536–546. https://doi.org/10.1002/cpt.2024

Kawczak, P., Feszak, I., & Bączek, T. (2024). Ketamine, Esketamine, and Arketamine: Their Mechanisms of Action and Applications in the Treatment of Depression and Alleviation of Depressive Symptoms. Biomedicines, 12(10). https://doi.org/10.3390/biomedicines12102283

Kosik-Gonzalez, C., Fu, D.-J., Nancy Chen, L., Lane, R., Bloch, M. H., DelBello, M., Moreno, C., Drevets, W. C., & Canuso, C. M. (n.d.). Effect of Esketamine on Depressive Symptoms in Adolescents With Major Depressive Disorder at Imminent Suicide Risk: A Randomized Psychoactive-Controlled Study. https://doi.org/10.1016/j.jaac.2025.02.015

Krystal, J. H., Kavalali, E. T., & Monteggia, L. M. (2024). Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. Neuropsychopharmacology, 49(1), 41–50. https://doi.org/10.1038/s41386-023-01629-w

Lan, X., Wang, C., Zhang, F., Liu, H., Li, W., Ye, Y., Hu, Z., Mai, S., Ning, Y., & Zhou, Y. (2023). Short-term cognitive effects of repeated-dose esketamine in adolescents with major depressive disorder and suicidal ideation: a randomized controlled trial. Child and Adolescent Psychiatry and Mental Health, 17(1). https://doi.org/10.1186/s13034-023-00647-2

McIntyre, R. S., Bitter, I., Buyze, J., Fagiolini, A., Godinov, Y., Gorwood, P., Ito, T., Oliveira-Maia, A. J., Vieta, E., Werner-Kiechle, T., Young, A. H., & Reif, A. (2024). Safety and tolerability of esketamine nasal spray versus quetiapine extended release in patients with treatment resistant depression. European Neuropsychopharmacology, 85, 58–65. https://doi.org/10.1016/j.euroneuro.2024.05.009

McIntyre, R. S., Rosenblat, J. D., Nemeroff, C. B., Sanacora, G., Murrough, J. W., Berk, M., Brietzke, E., Dodd, S., Gorwood, P., Ho, R., Iosifescu, D. v., Jaramillo, C. L., Kasper, S., Kratiuk, K., Lee, J. G., Lee, Y., Lui, L. M. W., Mansur, R. B., Papakostas, G. I., … Stahl, S.

(2021). Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: An international expert opinion on the available evidence and implementation. American Journal of Psychiatry, 178(5), 383–399. https://doi.org/10.1176/appi.ajp.2020.20081251

Medeiros, G. C., Gould, T. D., Prueitt, W. L., Nanavati, J., Grunebaum, M. F., Farber, N. B., Singh, B., Selvaraj, S., Machado-Vieira, R., Achtyes, E. D., Parikh, S. v., Frye, M. A., Zarate, C. A., & Goes, F. S. (2022). Blood-based biomarkers of antidepressant response to ketamine and esketamine: A systematic review and meta-analysis. Molecular Psychiatry, 27(9), 3658–3669. https://doi.org/10.1038/s41380-022-01652-1

Nguyen, T. M. L., Jollant, F., Tritschler, L., Colle, R., Corruble, E., & Gardier, A. M. (2023). Pharmacological Mechanism of Ketamine in Suicidal Behavior Based on Animal Models of Aggressiveness and Impulsivity: A Narrative Review. Pharmaceuticals, 16(4). https://doi.org/10.3390/ph16040634

Pardossi, S., Fagiolini, A., & Cuomo, A. (2024). Variations in BDNF and Their Role in the Neurotrophic Antidepressant Mechanisms of Ketamine and Esketamine: A Review. International Journal of Molecular Sciences, 25(23). https://doi.org/10.3390/ijms252313098

Pardossi, S., Fagiolini, A., Scheggi, S., & Cuomo, A. (2024). A Systematic Review on Ketamine and Esketamine for Treatment-Resistant Depression and Suicidality in Adolescents: A New Hope? Children, 11(7). https://doi.org/10.3390/children11070801

Pompili, M. (2020). Intranasal Esketamine and Current Suicidal Ideation With Intent in Major Depression Disorder: Beat the Clock, Save a Life, Start a Strategy. Frontiers in Psychiatry, 11. https://doi.org/10.3389/fpsyt.2020.00325

Reif, A., Bitter, I., Buyze, J., Cebulla, K., Frey, R., Fu, D.-J., Ito, T., Kambarov, Y., Llorca, P.-M., Oliveira-Maia, A. J., Messer, T., Mulhern-Haughey, S., Rive, B., von Holt, C., Young, A. H., & Godinov, Y. (2023). Esketamine Nasal Spray versus Quetiapine for Treatment-Resistant

Depression. New England Journal of Medicine, 389(14), 1298–1309. https://doi.org/10.1056/nejmoa2304145

Rizzo, A., Garçon-Poca, M. Z., Essmann, A., Souza, A. J., Michaelides, M., Ciruela, F., & Bonaventura, J. (2025). The dopaminergic effects of esketamine are mediated by a dual mechanism involving glutamate and opioid receptors. Molecular Psychiatry, 30(8), 3443–3454. https://doi.org/10.1038/s41380-025-02931-3

Ross, E. L., & Soeteman, D. I. (2020). Cost-effectiveness of esketamine nasal spray for patients with treatment-resistant depression in the united states. Psychiatric Services, 71(10), 988–997. https://doi.org/10.1176/APPI.PS.201900625

Salahudeen, M. S., Wright, C. M., & Peterson, G. M. (2020). Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review. Therapeutic Advances in Drug Safety, 11. https://doi.org/10.1177/2042098620937899

Turkoz, I., Lopena, O., Salvadore, G., Sanacora, G., Shelton, R., & Fu, D. J. (2023). Treatment response to esketamine nasal spray in patients with major depressive disorder and acute suicidal ideation or behavior without evidence of early response: A pooled post hoc analysis of ASPIRE. CNS Spectrums, 28(4), 482–488. https://doi.org/10.1017/S1092852922000931

Vasiliu, O. (2023). Esketamine for treatment-resistant depression: A review of clinical evidence (Review). Experimental and Therapeutic Medicine, 25(3). https://doi.org/10.3892/etm.2023.11810

Vieira, F., Correia-Melo, F. S., Santos-Lima, C., Souza-Marques, B., Leal, G. C., Jesus-Nunes, A. P., Mello, R. P., Caliman-Fontes, A. T., Bandeira, I. D., Marback, R. F., Telles, M., Argolo, F. C., Lins-Silva, D. H., Echegaray, M. V. F., Beanes, G., Araújo-de-Freitas, L., Silva, S. S., Cardoso, T. de A., Kapczinski, F., … Quarantini, L. C. (2021). Ketamine and Esketamine augmentation for suicidal ideation: A randomized, double-blinded clinical trial. General Hospital Psychiatry, 68, 97–99. https://doi.org/10.1016/j.genhosppsych.2020.12.011

Yang, S., Wang, J., Li, X., Wang, T., Xu, Z., Xu, X., Zhou, X., & Chen, G. (2022). Adverse Effects of Esketamine for the Treatment of Major Depression Disorder: Findings from Randomized Controlled Trials. Psychiatric Quarterly, 93(1), 81–95. https://doi.org/10.1007/s11126-020-09871-x

Zaki, N., Chen, L. (Nancy), Lane, R., Doherty, T., Drevets, W. C., Morrison, R. L., Sanacora, G., Wilkinson, S. T., Popova, V., & Fu, D. J. (2023). Long-term safety and maintenance of response with esketamine nasal spray in participants with treatment-resistant depression: interim results of the SUSTAIN-3 study. Neuropsychopharmacology, 48(8), 1225–1233. https://doi.org/10.1038/s41386-023-01577-5