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THE IMPACT OF INTRANASAL ESKETAMINE ON TREATMENT-RESISTANT DEPRESSION: A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Treatment-resistant depression (TRD) is a major public health and societal challenge, associated with persistent symptoms, functional impairment, and increased healthcare and economic burden. Intranasal esketamine has emerged as a rapid-acting adjunctive therapy with a distinct glutamatergic mechanism of action. This systematic review summarizes current evidence on its effectiveness and implementation-relevant outcomes in TRD.
Methods: A systematic literature review was conducted in accordance with PRISMA 2020. PubMed/MEDLINE and EMBASE were searched for English-language systematic reviews and meta-analyses published between 2010 and 2026 using database-specific but equivalent Boolean strategies combining intranasal esketamine terms with TRD terms. Titles/abstracts were screened and eligible records underwent full-text assessment. Five studies were included in qualitative synthesis. The last search was conducted on 5 March 2026.
Results: Meta-analytic evidence from randomized trials reported greater symptom improvement with intranasal esketamine versus control (MADRS SMD = −3.88; 95% CI −5.71 to −2.05) and higher response rates (RR = 1.99; 95% CI 1.28–3.10), alongside improvements in disability (SDS SMD = −3.01) and patient-reported symptoms (PHQ-9 SMD = −2.32). Adverse events were more frequent, including dizziness (RR = 3.55) and nausea (RR = 3.88). Real-world data showed substantial symptom reduction (Hedges' g = −1.98) and higher remission likelihood at three months (OR = 5.1), with high overall adverse-event prevalence (82%) and dissociation commonly reported (49%).
Conclusions: Intranasal esketamine shows clinically relevant benefits in TRD with convergent trial and real-world signals, but requires supervised delivery and sustained follow-up. Further research should clarify long-term outcomes, clinical meaningfulness, and health-system cost-effectiveness.

KEYWORDS

Intranasal Esketamine; Esketamine Nasal Spray; Treatment-Resistant Depression; Major Depressive Disorder; Adjunctive Therapy

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Introduction

Treatment-resistant depression (TRD) represents a significant public health and societal challenge due to its chronic course, substantial impact on quality of life, and associated economic burden. Beyond persistent low mood and loss of interest, many individuals experience long-lasting functional impairment that affects social relationships, family roles, and occupational performance. In everyday terms, TRD can translate into reduced ability to maintain employment, increased reliance on informal caregiving, and prolonged disruption of social and educational pathways. As a consequence, TRD contributes not only to increased healthcare utilization but also to broader socioeconomic costs related to absenteeism, reduced productivity, and long-term disability. These consequences are often amplified by the recurrent nature of depression: even when partial improvement occurs, residual symptoms may persist and continue to limit functioning, thereby sustaining societal costs over time.

TRD is commonly described as a condition in which patients experience less than a 25% reduction in the severity of major depressive disorder (MDD) symptoms despite undergoing at least two adequate trials of different antidepressant medications administered at appropriate doses and duration during the current depressive episode [1,2]. This operational definition highlights an important clinical reality: in a substantial subset of patients, standard pharmacological strategies are insufficient to achieve meaningful symptom relief within a reasonable timeframe. Despite the availability of numerous antidepressant treatment options, remission after first-line therapy is achieved in only about one-third of patients, while a similar proportion eventually develops treatment resistance [3]. In practice, repeated treatment failures may increase hopelessness, undermine treatment adherence, and intensify psychosocial consequences, thereby reinforcing the societal burden associated with chronic and recurrent depression. TRD is also frequently associated with persistent cognitive symptoms (e.g., impaired concentration, slowed information processing), reduced motivation, and difficulties with decision-making, which may further limit return to normal social and occupational functioning even when mood symptoms partially improve. Importantly, these cognitive and motivational deficits can interfere with psychotherapy engagement and rehabilitation efforts, potentially delaying recovery even when pharmacological strategies are escalated.

The clinical and societal burden associated with TRD has stimulated growing interest in the development of novel therapeutic approaches with faster onset of action and improved effectiveness. Traditional antidepressant medications primarily target monoaminergic neurotransmission and often require several weeks before clinically meaningful effects become apparent. For patients who have already experienced multiple inadequate responses, such delays can be especially problematic and may prolong a period of severe impairment. This is clinically important not only because of symptom suffering, but also because extended episodes can increase cumulative functional decline and complicate reintegration into everyday roles. Furthermore, standard approaches do not always address the full spectrum of depressive pathology, including cognitive symptoms, motivational deficits, and reduced capacity for everyday functioning. From a care-delivery perspective, prolonged trial-and-error pharmacotherapy also places demand on healthcare resources, increases the frequency of follow-up visits, and can contribute to treatment discontinuation when patients perceive repeated strategies as ineffective.

In recent years, increasing attention has been directed toward interventions that modulate glutamatergic neurotransmission, which is believed to play an important role in the neurobiology of depression [4]. Glutamatergic pathways are closely linked to synaptic signaling, neuroplasticity, and adaptive stress responses—processes that are increasingly considered relevant in depressive disorders, particularly when symptoms persist despite adequate monoaminergic treatment. From an innovation perspective, therapies targeting these pathways represent a shift toward mechanistically differentiated antidepressant strategies and a more “technology-enabled” model of depression care, in which treatment can be delivered within structured clinical settings and monitored using standardized protocols. This shift is also aligned with the broader trend toward measurement-based mental health care, where symptom change, functioning, and tolerability are tracked systematically to guide treatment decisions.

One of the most notable developments in this area has been the introduction of intranasal esketamine, a novel rapid-acting antidepressant approved for the treatment of adults with TRD. The intranasal route is clinically important because it enables controlled administration within supervised environments, typically accompanied by observation and safety monitoring. As a result, intranasal esketamine can be viewed not only as a pharmacological innovation but also as a structured service-delivery intervention that requires defined clinical pathways, trained staff, and healthcare system capacity—factors that directly influence real-world access and broader societal impact. In other words, the “treatment effect” is not solely a function of the molecule, but also of the clinical delivery model that ensures safe administration and follow-up, which may vary across health systems and influence equitable availability. Practical considerations such as travel distance to treatment sites, the ability to attend repeated visits, and continuity of follow-up may therefore shape how benefits are realized outside controlled trial settings.

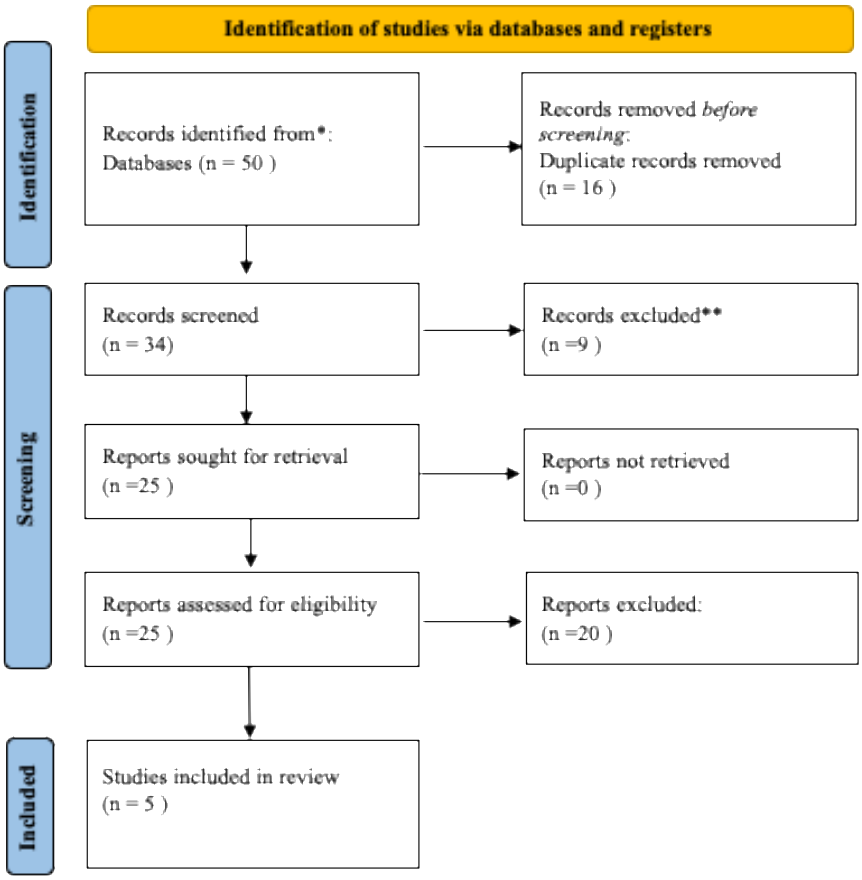
Esketamine, the S-enantiomer of ketamine, produces its antidepressant effects primarily by modulating glutamatergic neurotransmission in the brain. It acts as an antagonist of N-methyl-D-aspartate (NMDA) receptors, a type of glutamate receptor involved in synaptic signaling. Blocking these receptors leads to a temporary increase in glutamate release, which subsequently activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This process promotes neuroplasticity and supports the formation of new synaptic connections in brain regions associated with mood regulation. In addition, esketamine may influence dopaminergic pathways involved in motivation and reward processing, which could contribute to the rapid improvement of symptoms such as anhedonia. Its fast antidepressant action has also been linked to activation of intracellular signaling pathways, including the mammalian target of rapamycin complex 1 (mTORC1), which enhances the production of brain-derived neurotrophic factor (BDNF) and supports synaptic plasticity [5,6]. Importantly, the proposed neurobiological cascade provides a mechanistic rationale for the rapid onset observed with esketamine compared with traditional antidepressants, while also raising clinically relevant questions regarding durability of benefit, optimal treatment schedules, and long-term outcomes.

There is an increasing number of publications in the literature on the impact of intranasal esketamine on TRD. However, the expanding evidence base includes a range of study designs and outcome measures, making it necessary to synthesize findings in a structured and transparent way. Moreover, given the rapid expansion of the evidence base, a concise synthesis may help clinicians and stakeholders interpret findings consistently and identify practical gaps relevant to long-term care planning and service organization. The aim of this analysis is to gather available data from the literature and analyze it in terms of intranasal esketamine and its impact on treatment-resistant depression (TRD), with attention to both clinical effectiveness and the broader implications of implementing a supervised, rapid-acting treatment model in routine care.

Material and Methods

The literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, and the study selection process was documented using the PRISMA 2020 flow diagram for updated systematic reviews. Searches were performed in PubMed/MEDLINE and EMBASE using database-specific but equivalent Boolean strategies combining intranasal esketamine terms (“intranasal esketamine”, “esketamine nasal spray”) with treatment-resistant depression terms (“treatment-resistant depression”, “TRD”).

PRISMA 2020 flow diagram for updated systematic reviews which included searches of databases.



The databases were searched for English-language systematic reviews and meta-analyses published between 2010 and 2026. Titles and abstracts were screened for relevance, and potentially eligible records underwent full-text assessment. Based on predefined inclusion and exclusion criteria, five studies were selected and included in the qualitative synthesis presented in the Results section. The last search was conducted on 5 March 2026.

Results

The following articles were included in the analysis:

1.Ouyang Y, Li J. Efficacy of esketamine nasal spray for treatment-resistant depression: A meta-analysis of randomized controlled studies [7].

2.de Oliveira Lapa C, Viola T, Delfino R, et al. Systematic review and meta-analysis of intranasal esketamine for treatment-resistant depression: Evidence from real-world studies [8].

3.Capuzzi E, Caldiroli A, Capellazzi M, et al. Long-Term Efficacy of Intranasal Esketamine in Treatment-Resistant Major Depression: A Systematic Review [9].

4.Sapkota A, Khurshid H, Qureshi IA, et al. Efficacy and Safety of Intranasal Esketamine in Treatment-Resistant Depression in Adults: A Systematic Review [10].

5.Naudet F, Pellen C, Fodor LA, et al. Efficacy and safety of esketamine for "treatment resistant depression": registered report for a systematic review with an individual patient data meta-analysis of randomized, double-blind, placebo-controlled trials [11].

Across the included publications, intranasal esketamine was most commonly evaluated as an adjunct to ongoing oral antidepressant therapy in adults with treatment-resistant depression. The evidence base covered both randomized controlled trial–derived quantitative syntheses and real-world observational outcomes. In addition, one included paper contributed an evidence-planning framework (registered report) designed to reassess efficacy and safety using individual patient data meta-analysis, reflecting ongoing methodological discussion in this field [11]. Taken together, the selected studies provide complementary perspectives: controlled trial estimates of symptom change and response/remission [7], effectiveness and tolerability signals from routine practice [8], longer-term and maintenance-oriented evidence [9], and a broader structured overview of pivotal and supportive evidence relevant for clinical implementation [10].

The meta-analysis by Ouyang and Li [7] integrated evidence from five randomized controlled trials that evaluated intranasal esketamine nasal spray in treatment-resistant depression, with depressive symptom severity commonly measured using MADRS as the primary endpoint. The pooled estimates were primarily derived from pivotal randomized trials within the TRANSFORM program [12–15]. Compared with control conditions, intranasal esketamine was associated with significantly lower depressive symptom severity (SMD = −3.88; 95% CI −5.71 to −2.05; P <.0001) [7]. This result reflects a consistent direction of effect across included trials, supporting the concept that esketamine may provide clinically relevant symptom improvement when added to standard antidepressant regimens.

Beyond overall symptom scores, Ouyang and Li [7] included outcomes that are particularly relevant to everyday functioning and patient-centered recovery. Functional impairment was assessed using the Sheehan Disability Scale, and pooled results indicated improvements favoring intranasal esketamine (SMD = −3.01; 95% CI −4.39 to −1.64; P <.0001) [7]. Depressive symptom burden from the patient perspective was reflected by PHQ-9, which also improved in pooled analysis (SMD = −2.32; 95% CI −3.51 to −1.13; P =.0001) [7]. These outcomes extend the results beyond clinician-rated symptom change and reinforce the relevance of intranasal esketamine as a therapeutic innovation with potential implications for social and occupational functioning. In the social context, such measures can be interpreted as intermediate markers of broader societal outcomes, such as improved participation in work, education, and interpersonal roles.

In addition to continuous outcomes, Ouyang and Li [7] assessed categorical endpoints that are commonly used to communicate clinical effectiveness in practice. Response rates were higher in the intranasal esketamine group than in controls (RR = 1.99; 95% CI 1.28–3.10; P =.002) [7]. Such endpoints often carry practical value in clinical decision-making because they correspond to clinically recognizable improvement thresholds rather than mean score differences alone. The inclusion of response-based evidence strengthens interpretability of the pooled results for non-specialist audiences and health-system stakeholders.

Safety and tolerability were also addressed in the meta-analysis [7]. Intranasal esketamine was associated with higher rates of specific adverse events, particularly dizziness (RR = 3.55; 95% CI 2.37–5.32; P <.00001) and nausea (RR = 3.88; 95% CI 2.10–7.18; P <.0001) [7]. While these effects are often described as transient within supervised treatment environments, their increased incidence is relevant for service

planning, patient counseling, and acceptability. In real-world service delivery, side effects such as dizziness and nausea may influence patient willingness to continue treatment and can shape operational protocols (e.g., observation periods, advice regarding transport home, and on-site clinical monitoring). Thus, even when adverse events do not lead to severe outcomes, their frequency has implications for treatment logistics and resource utilization.

The systematic review and meta-analysis by de Oliveira Lapa et al. [8] focused on real-world studies of intranasal esketamine in treatment-resistant depression. This perspective is important because routine clinical practice often involves greater heterogeneity in patient characteristics, comorbidities, and treatment histories than randomized trials. The authors synthesized nine observational studies and reported a large pooled improvement in depressive symptoms (Hedges' g = −1.98; 95% CI −2.94 to −1.03; P <.0001) [8]. The magnitude of the pooled effect indicates substantial symptom reduction across settings; however, the observational nature of the included studies implies that confounding, selection bias, and differences in baseline severity may contribute to effect size estimates. Nevertheless, the convergence in direction of symptom improvement across real-world cohorts provides supportive evidence that intranasal esketamine can retain effectiveness when implemented beyond controlled trial conditions.

A key result highlighted in this synthesis was remission trajectory over time. de Oliveira Lapa et al. [8] reported that remission was more likely at three months compared with the induction phase (OR = 5.1; 95% CI 2.29–11.39). This finding suggests that clinical gains may consolidate with ongoing treatment exposure and structured follow-up, emphasizing that the benefits of intranasal esketamine may depend on continuity of care rather than solely the early phase of treatment initiation. From a system-level perspective, such a pattern implies that clinical programs need mechanisms for sustained engagement, monitoring, and retention if longer-term remission outcomes are to be achieved in real-world settings.

Safety findings in real-world cohorts were prominent. The pooled prevalence of any adverse event was high (82%; 95% CI 69–92), with dissociation being most common (49%; 95% CI 37–62) [8]. While dissociation is a well-recognized phenomenon in esketamine administration, the quantification of prevalence under real-world conditions is particularly relevant for routine practice implementation. High rates of reported adverse events can influence patient expectations and contribute to early discontinuation if not adequately managed through education, monitoring, and supportive clinical processes. Additionally, real-world practice often includes variability in staff experience and clinic infrastructure; therefore, documenting safety patterns supports the rationale for standardized protocols, staff training, and structured supervision.

Importantly, the real-world synthesis underscores that intranasal esketamine is intrinsically linked to an organized model of care. In many jurisdictions, esketamine is administered under supervision with mandatory observation periods after dosing. This organizational requirement functions as a "technology of care delivery," not merely a pharmacological detail, because it structures patient flow, clinic scheduling, and resource allocation. As a result, real-world evidence is especially relevant to questions of access and equity: if treatment delivery requires specialized sites and trained staff, geographic and socioeconomic barriers can influence who receives the intervention. Although these broader outcomes are not quantified directly in the included observational studies, the reported adverse-event prevalence and monitoring requirements provide practical inputs to implementation considerations that extend beyond symptom reduction alone [8].

The systematic review by Capuzzi et al. [9] addressed long-term efficacy of intranasal esketamine in treatment-resistant major depression. The authors identified seven relevant studies involving 1,024 adult patients [9]. Long-term evidence is particularly important in treatment-resistant depression because chronicity and relapse risk are major contributors to disability, healthcare utilization, and societal burden. Capuzzi et al. [9] emphasized that continuation of intranasal esketamine following induction may be associated with maintenance of benefit and relapse prevention in certain cohorts, while discontinuation may be followed by loss of sustained antidepressant effectiveness [9,16]. These findings highlight the importance of maintenance strategies and long-term follow-up structures when interpreting the real-world value of intranasal esketamine programs.

The review by Capuzzi et al. [9] also underscored limitations across the long-term evidence base, including heterogeneity in study designs, duration of follow-up, and outcome reporting. Such heterogeneity complicates synthesis and may limit generalizability across healthcare systems. For instance, long-term observational cohorts may reflect patients who tolerated and benefited from induction phases, while those who discontinued earlier due to side effects or lack of response may be underrepresented. This can lead to "survivor bias" in longer-term effectiveness estimates. Capuzzi et al. [9] noted moderate-to-high risk of bias in some

included studies, which constrains the certainty of long-term conclusions and underlines the need for cautious interpretation of durability.

From an implementation standpoint, long-term evidence also intersects with questions of resource allocation and service sustainability. Maintenance treatment implies repeated supervised administrations, ongoing monitoring, and potential cumulative staffing and facility demands. The clinical implications of relapse prevention can be substantial, but the operational implications are also significant: long-term service delivery requires stable funding models, reliable scheduling capacity, and patient adherence support. The long-term review provides context for these considerations by framing continuation and discontinuation as factors linked to sustained outcomes [9].

The systematic review by Sapkota et al. [10] provided a broader overview of efficacy and safety evidence for intranasal esketamine in adults with treatment-resistant depression. The authors included 10 studies, incorporating phase III clinical trials, post-hoc analyses, and other supportive evidence types [10]. Such a synthesis is useful because it situates pooled results within a wider body of evidence, including pivotal trial structures that informed regulatory approval and clinical adoption.

Across the included evidence, Sapkota et al. [10] described intranasal esketamine as generally effective as an adjunctive intervention when combined with oral antidepressants in TRD, with improvements typically assessed using MADRS and related standardized measures. The review also addressed relapse-prevention evidence in maintenance settings, consistent with the idea that sustained administration pathways may be required for long-term benefit [10]. By integrating both acute and maintenance-phase evidence, this review provides a structured narrative of how intranasal esketamine is positioned across different treatment stages.

Sapkota et al. [10] reported a consistent adverse-event profile across studies, commonly including transient dissociation/sedation-related phenomena, dizziness/vertigo, nausea, and headache. These effects align with supervised administration protocols and reinforce that safety considerations are intertwined with the care model. Even when adverse events are transient, their predictability and frequency require structured monitoring, which can influence patient satisfaction, clinic efficiency, and overall acceptability. In practical terms, these safety features can affect indirect costs (e.g., time off work for supervised dosing sessions) and may contribute to differential access across patient groups, particularly those with limited flexibility for repeated clinic visits.

From a health-systems perspective, Sapkota et al. [10] also implicitly highlights the organizational "cost" of delivering intranasal esketamine. Unlike standard oral antidepressants prescribed for home use, intranasal esketamine is typically delivered in supervised clinical settings, often with a required observation period. This changes the unit of care from "prescription" to "session-based service," requiring clinic capacity planning and sometimes dedicated infrastructure. Such an arrangement can be conceptualized as a technology-integrated care pathway: the pharmacological intervention is inseparable from the delivery technology (supervised administration protocols, monitoring procedures, and service logistics).

Naudet et al. [11] contributed a registered report describing an ongoing systematic review with an individual patient data (IPD) meta-analysis of randomized, double-blind, placebo-controlled trials of intranasal esketamine. The paper does not provide pooled clinical outcome estimates, but it is highly relevant to the interpretation of the evidence base because it explicitly addresses methodological transparency and clinical meaningfulness [11]. The planned analysis aims to reassess efficacy and safety using IPD, with data access described via the Yale Open Data Access (YODA) Project [11]. This is notable because IPD meta-analysis allows more granular evaluation of subgroups, baseline severity effects, and outcome distributions than aggregate data meta-analyses.

The planned primary endpoint is MADRS at ≥4 weeks in initiation trials, benchmarked against a 6.5-point clinical significance threshold used in pivotal trial design, with evidence certainty assessed using GRADE [11]. This approach is directly relevant to ongoing debate in the field: whether statistically significant improvements in symptom scales necessarily translate into clinically meaningful benefit at the patient level. While this registered report does not provide results, its inclusion in the synthesis highlights that the evidence base is still evolving, and that methodological refinement remains central to how esketamine's value is judged by clinicians, guideline developers, and payers. It also underscores the importance of transparency and reproducibility—factors that can affect public and professional trust in innovative interventions.

From a broader perspective, the methodological emphasis of Naudet et al. [11] has implications for real-world adoption and societal impact. When a therapy is resource-intensive to deliver, stakeholders often demand robust evidence not only of statistical benefit but also of meaningful clinical impact, durability, and safety. An IPD approach is positioned to clarify these issues, potentially informing how intranasal esketamine is

prioritized within treatment algorithms and how healthcare systems justify investment in supervised delivery models.

Across the included publications, there is a consistent pattern indicating that intranasal esketamine can reduce depressive symptom severity in adults with treatment-resistant depression when used as an adjunct to oral antidepressant therapy [7–10]. Evidence from randomized trials supports significant improvements in standardized symptom scores and response outcomes, while real-world observational studies suggest that effectiveness signals persist in routine practice, with remission likelihood increasing over time in some cohorts [7,8]. Long-term reviews highlight the potential for sustained benefit with continuation treatment but also reveal limitations in evidence quality and heterogeneity of follow-up methods [9]. The broader overview literature reinforces a consistent adverse-event profile and positions intranasal esketamine within a supervised care framework that can influence access and delivery feasibility [10].

Functional and patient-reported measures were explicitly captured in the RCT meta-analysis by Ouyang and Li [7], emphasizing that improvements may extend beyond symptom severity and include disability reduction as measured by the Sheehan Disability Scale. In the context of TRD, functional recovery is closely related to broader societal outcomes, such as productivity, employment stability, and social participation. While these downstream outcomes are not directly quantified in the included studies, the presence of functional measures provides a useful bridge between clinical efficacy and social impact narratives [7]. Similarly, real-world data that describe remission trajectories and high adverse-event prevalence contribute practical insights into how benefits might materialize—or be constrained—within real healthcare systems [8].

Safety findings across analyses underscore that tolerability is a central component of implementation. Increased dizziness and nausea were reported in trial-based synthesis [7], and dissociation was prominent in real-world meta-analysis [8]. These effects, in conjunction with supervised administration requirements, shape how intranasal esketamine is experienced by patients and delivered by services. In practical terms, they can influence patient acceptability, adherence, and overall treatment persistence—factors that ultimately determine real-world effectiveness and longer-term outcomes. In addition, because the intervention requires repeated clinic-based sessions, the cumulative time and resource burden can influence not only healthcare costs but also patient opportunity costs (e.g., time away from work or caregiving).

At the same time, the evidence base is characterized by methodological challenges that are important to acknowledge even within Results. Differences between controlled trials and observational cohorts, variability in study designs and follow-up durations, and potential biases in long-term datasets limit the certainty of conclusions about durability and optimal maintenance strategies [9]. The inclusion of a registered report planning an IPD meta-analysis highlights that re-evaluation of clinical meaningfulness, subgroup responsiveness, and robustness of effects remains an active area of research [11]. This methodological evolution is relevant to how esketamine's role is perceived in clinical guidelines and how healthcare systems justify the investment in supervised delivery infrastructure.

Overall, the reviewed evidence base provides a coherent picture of short-term symptom reduction and emerging real-world effectiveness, while also highlighting uncertainty around long-term durability, heterogeneity of evidence quality, and the distinction between statistical and clinically meaningful benefit. These combined strengths and limitations inform how intranasal esketamine may be positioned within stepped-care pathways for TRD and how services might prioritize monitoring, follow-up, and equitable access. The next section discusses these findings in the context of methodological quality, implementation feasibility, and broader societal implications.

Discussion

This systematic review synthesized the available evidence on intranasal esketamine for treatment-resistant depression (TRD) by integrating five secondary sources (systematic reviews and meta-analyses) and, where appropriate, referencing pivotal primary trials that underpin pooled estimates and maintenance conclusions [7–16]. Overall, the evidence indicates that intranasal esketamine—typically used as an adjunct to oral antidepressant therapy—produces measurable improvements in depressive symptom severity and response outcomes in adults with TRD, with convergent signals across trial-based syntheses and real-world observational data [7–10,12–16]. This finding is clinically and socially relevant because TRD is associated with persistent symptoms, functional impairment, and disproportionate direct and indirect costs, making it a high-priority public health and societal issue [20,24,25,30].

A key strength of the current evidence base is the apparent convergence across study contexts. Trial-derived meta-analytic findings point toward symptom improvement and higher response likelihood [7], while

real-world evidence supports the translation of benefit into routine care and suggests that remission outcomes may improve over time when treatment pathways are sustained [8]. In practical terms, this combination of evidence suggests that esketamine may offer value not only as an acute intervention but also as part of a structured treatment pathway in which induction is followed by continuation strategies, monitoring, and follow-up. This is important for TRD because short-lived symptom reduction without durable recovery may have limited impact on long-term disability and societal burden [20,24,30]. From the perspective of technology-enabled care, intranasal esketamine is also distinctive because it sits at the boundary between pharmacotherapy and a supervised procedure-like model of delivery, meaning that treatment benefit is partly "co-produced" by the clinical infrastructure that enables safe dosing and monitoring [29].

At the same time, the evidence also highlights important interpretive challenges that matter for both clinicians and health-system decision makers. A central issue is the distinction between statistical significance and clinical meaningfulness. The registered report by Naudet et al. [11] underscores that interpretation may differ when individual patient data are analyzed against prespecified clinical thresholds and with rigorous evidence grading [11]. This question is not merely academic: for a therapy embedded in supervised delivery models, the balance of benefit and burden is shaped by whether improvements are sufficiently large, meaningful at the individual level, and sustained over time to justify infrastructure, staffing, and financing requirements. More broadly, TRD research is complicated by heterogeneity in definitions and staging. Even when two studies use the label "TRD," the underlying populations may differ substantially with respect to illness duration, baseline severity, comorbidity, and previous treatment exposure [28]. These differences can influence observed outcomes and complicate cross-study comparisons, especially when secondary evidence sources aggregate trials with varying inclusion criteria and varying thresholds for "treatment resistance."

Long-term durability is particularly important in TRD because relapse and recurrence are major drivers of cumulative impairment and costs. The long-term evidence summarized in the included reviews suggests that continuation treatment may contribute to maintenance of benefit and relapse prevention, while discontinuation may increase the probability of symptom recurrence [9,16]. However, long-term evidence is frequently less uniform than acute trial data and may be affected by selection effects (e.g., continuation cohorts enriched for responders and those tolerating treatment). Therefore, long-term conclusions should be viewed as supportive but not definitive, reinforcing the need for additional comparative studies, pragmatic follow-up research, and improved reporting of functional outcomes over extended time horizons [9,11,28]. These limitations are common in chronic depression research and are consistent with broader clinical experience indicating that remission and functional recovery often require sustained, multi-step care [24]. Importantly, durability also intersects with the patient experience of repeated supervised visits: the longer the treatment pathway, the more likely logistical constraints (transport, work scheduling, caregiving responsibilities) influence adherence and continuation, which may indirectly influence long-term outcomes in routine practice [8,29].

Safety and tolerability findings are central to interpretation because they determine both individual acceptability and system feasibility. The evidence base consistently identifies a recognizable adverse-event profile that includes dissociation/sedation-related phenomena, dizziness, and nausea [7,8,10,12–15]. While these events are commonly transient and manageable in supervised environments, their predictability and frequency are precisely what drives the requirement for structured monitoring and observation. This is a major reason why esketamine differs from conventional antidepressants: it is not simply prescribed for independent home use, but delivered as a supervised session-based intervention. Consequently, the technology is not only the nasal spray formulation but also the delivery model—clinic procedures, monitoring protocols, staff training, and scheduling systems that enable safe administration and follow-up. In implementation terms, this means that a portion of esketamine's real-world value is contingent on systems being able to provide standardized monitoring and to respond consistently to adverse effects, thereby maintaining patient confidence and reducing discontinuation driven by avoidable anxiety or insufficient preparation [8,10,29].

This delivery model has direct implications for access and equity. Regulatory risk-management requirements in the United States emphasize supervised administration and monitoring [29], which can create practical barriers for patients who live far from certified sites, have limited transport options, or cannot attend frequent appointments due to work or caregiving responsibilities. These barriers can translate into inequities in access, where availability depends on geography, service organization, and socioeconomic constraints rather than purely on clinical need. The link between supervised delivery and access is particularly relevant when considering that TRD often co-occurs with functional impairment and reduced work capacity, which can further reduce patients' ability to travel or to allocate time for repeated sessions [20,30]. From a societal

perspective, an intervention intended to reduce disability may paradoxically be least accessible to those with the greatest disability unless delivery pathways are designed with equity and feasibility in mind. This strengthens the case for implementation-focused research and for service innovations that reduce logistical burden while preserving safety monitoring [18,29].

From a public health perspective, TRD exists within the broader context of a large and persistent global burden of depressive disorders. Global burden analyses highlight that depressive disorders remain among leading contributors to health loss worldwide [25] and that population mental health burden increased further during the COVID-19 pandemic [26]. These findings frame TRD as a subset within a wider population-level challenge, where even modest improvements in effective treatments could have meaningful aggregate impact if implemented at scale. However, scale itself is constrained by workforce limitations, infrastructure, and financing. Therefore, the societal case for esketamine is not just "does it work," but "under what conditions can it be delivered widely enough to shift outcomes in the populations that most need it." These considerations are aligned with policy and guideline frameworks that increasingly emphasize measurement-based care and systematic follow-up, because the system needs to identify non-responders efficiently and move through treatment steps with minimal delay [17,19,24].

Health-economic evidence further contextualizes the societal relevance of the intervention. TRD is associated with high direct healthcare costs, including more frequent consultations, hospitalizations, and complex treatment regimens, as well as substantial indirect costs linked to productivity loss and disability [20,30]. This helps explain why rapid-acting interventions have attracted interest: faster improvement could theoretically reduce time spent in severe episodes and accelerate functional recovery. However, cost-effectiveness is not guaranteed. Modeling work has suggested that esketamine may not meet conventional cost-effectiveness thresholds under certain payer perspectives and assumptions [21]. Formal appraisal processes similarly evaluate esketamine within health technology assessment frameworks that explicitly consider clinical effectiveness, cost, and feasibility of implementation [18]. Importantly, cost-effectiveness results can vary by context, because healthcare prices, reimbursement structures, and service organization differ across systems, and because model assumptions about durability and downstream outcomes can substantially alter conclusions [18,21]. As a result, a therapy can be clinically effective yet face restricted adoption if financing models do not support supervised delivery at scale.

The evidence landscape is evolving toward comparative effectiveness, which may influence how clinicians and systems position esketamine relative to other augmentation strategies. The head-to-head randomized trial comparing esketamine nasal spray with quetiapine extended release (as augmentation strategies alongside SSRI/SNRI) provides an example of how comparative data can influence treatment positioning beyond placebo-controlled trial evidence [23]. Comparative evidence is particularly valuable for decision-making in TRD because clinical pathways often involve multiple augmentation options with trade-offs in efficacy, tolerability, and feasibility. While one comparative trial does not resolve all questions of durability and cost-effectiveness, it strengthens the clinical positioning of esketamine within augmentation pathways and may affect guideline evolution, reimbursement debates, and real-world prescribing patterns [17,18,23].

Guideline frameworks emphasize systematic monitoring, individualized treatment sequencing, and the use of evidence-based interventions for major depressive disorder, including difficult-to-treat cases [17,19]. Within such frameworks, intranasal esketamine can be conceptualized as a specialized intervention for a subset of patients with TRD who remain symptomatic despite adequate conventional therapy. However, guideline-consistent implementation requires careful patient selection, standardized monitoring, and integration with broader mental health services. This includes practical considerations such as ensuring that patients have access to supervised dosing sites, that monitoring protocols are feasible within clinic schedules, and that follow-up is sufficiently structured to support continuation when beneficial and to adjust strategies when response is insufficient [17–19,29]. From an organizational standpoint, implementation success also depends on workforce readiness: staff must be trained not only in administration and monitoring, but also in communication strategies that prepare patients for transient adverse effects and reduce discontinuation driven by fear or misunderstanding. These "soft" system components are rarely captured in trial outcomes but can materially affect real-world effectiveness and societal impact.

Several limitations of the present review should be acknowledged. First, the synthesis is based on secondary sources, meaning that conclusions reflect the scope, inclusion criteria, and analytical decisions of the included systematic reviews and meta-analyses [7–11]. Second, heterogeneity in TRD definitions, baseline severity, outcome reporting, and study designs limits direct comparability across sources and may influence

the magnitude of pooled effects [28]. Third, real-world observational data, while valuable for generalizability and implementation insights, remain subject to confounding and selection biases [8]. Fourth, because the present review emphasizes systematic reviews and meta-analyses, it may under-represent emerging evidence streams that are not yet captured in secondary syntheses, although the inclusion of a registered report indicates that further high-quality syntheses are in progress [11]. Finally, the evidence base continues to evolve, and future IPD-based analyses may refine conclusions regarding subgroup response patterns and clinically meaningful thresholds, potentially altering how stakeholders interpret the balance of benefits and harms [11].

Future research should prioritize long-term comparative outcomes and patient-centered endpoints, with particular attention to functional recovery rather than symptom scales alone. Pragmatic implementation studies should evaluate how different service models influence retention, adverse-event management, and equitable access in diverse settings. In parallel, health-economic evaluations should incorporate indirect costs (productivity loss, disability) and patient opportunity costs (time and travel burden) in addition to direct healthcare costs, as these factors can materially influence societal value assessments [18,20,21,30]. Finally, the societal impact of esketamine will depend on how health systems design pathways to minimize barriers—through improved scheduling systems, coordinated care models, and policies that address geographic inequities—while maintaining safety requirements [18,29].

In summary, intranasal esketamine appears to represent a meaningful innovation for TRD, with evidence supporting symptom improvement and emerging real-world effectiveness [7–10,12–16]. However, its broader impact depends on durability, clinical meaningfulness at the individual level, and health-system capacity to implement supervised delivery pathways efficiently and equitably, alongside cost-effectiveness considerations and evolving comparative evidence [11,18,20–23,29–31].

Conclusions

Intranasal esketamine demonstrates measurable antidepressant effects in treatment-resistant depression, supported by convergent signals across randomized trial syntheses and real-world evidence [7–10,12–16]. The available evidence suggests that structured continuation strategies may support maintenance of benefit and relapse prevention for some patients, although long-term durability, subgroup responsiveness, and the clinical meaningfulness of observed effects require further clarification, including higher-resolution individual patient data approaches [9,11,16,28].

Because TRD carries a substantial clinical, societal, and economic burden, the potential value of intranasal esketamine should be considered not only in terms of symptom reduction but also in relation to functioning, service utilization, and equity of access [20,25,30]. Future research should prioritize long-term comparative studies and pragmatic implementation research designed to optimize supervised delivery pathways while minimizing logistical barriers for patients [18,23,29]. Robust health-economic evaluations, including indirect costs and patient opportunity costs, are also needed to inform reimbursement decisions and sustainable adoption in different healthcare contexts [18,21]. Ultimately, the extent to which esketamine's clinical benefits translate into broader societal gains will depend on whether health systems can deliver the intervention consistently, safely, and fairly, while balancing resource constraints and cost-effectiveness requirements [18,20,29–31].

REFERENCES

1. Boudieu, L., Mennetrier, M., Llorca, P. M., & Samalin, L. (2023). The efficacy and safety of intranasal formulations of ketamine and esketamine for the treatment of major depressive disorder: A systematic review. *Pharmaceutics, 15*(12), 2773. https://doi.org/10.3390/pharmaceutics15122773
2. Sforzini, L., Worrell, C., Kose, M., Anderson, I. M., Aouizerate, B., Arolt, V., Bauer, M., Baune, B. T., Blier, P., Cleare, A. J., Cowen, P. J., Dinan, T. G., Fagiolini, A., Ferrier, I. N., Hegerl, U., Krystal, A. D., Leboyer, M., McAllister-Williams, R. H., McIntyre, R. S., . . . Pariante, C. M. (2022). A Delphi-method-based consensus guideline for definition of treatment-resistant depression for clinical trials. *Molecular Psychiatry, 27*(3), 1286–1299. https://doi.org/10.1038/s41380-021-01381-x
3. Rush, A. J., Thase, M. E., & Dubé, S. (2003). Research issues in the study of difficult-to-treat depression. *Biological Psychiatry, 53*(8), 743–753. https://doi.org/10.1016/S0006-3223(03)00088-X
4. Dębowska, W., Więdłocha, M., Dębowska, M., Kownacka, Z., Marcinowicz, P., & Szulc, A. (2023). Transcranial magnetic stimulation and ketamine: Implications for combined treatment in depression. *Frontiers in Neuroscience, 17*, 1267647. https://doi.org/10.3389/fnins.2023.1267647
5. Bhavya, Shetty, S., & Sadasivam, B. (2025). A new era for esketamine in managing treatment-resistant depression: A systematic review of its use from adjunct to first-line therapy. *Cureus, 17*(9), e91829. https://doi.org/10.7759/cureus.91829
6. Hashimoto, K., Kakiuchi, T., Ohba, H., Nishiyama, S., & Tsukada, H. (2017). Reduction of dopamine D2/3 receptor binding in the striatum after a single administration of esketamine, but not R-ketamine: A PET study in conscious monkeys. *European Archives of Psychiatry and Clinical Neuroscience, 267*(2), 173–176. https://doi.org/10.1007/s00406-016-0692-7
7. Ouyang, Y., & Li, J. (2025). Efficacy of esketamine nasal spray for treatment-resistant depression: A meta-analysis of randomized controlled studies. *Medicine, 104*(9), e41495. https://doi.org/10.1097/MD.0000000000041495
8. de Oliveira Lapa, C., Viola, T., Delfino, R., Dutra, L., Rubira, G., Rodrigues, R. J. K., Coral, S. C., Ramos-Quiroga, J. A., & Spanemberg, L. (2026). Systematic review and meta-analysis of intranasal esketamine for treatment-resistant depression: Evidence from real-world studies. *Journal of Affective Disorders, 401*, 121257. https://doi.org/10.1016/j.jad.2026.121257
9. Capuzzi, E., Caldiroli, A., Capellazzi, M., Tagliabue, I., Marcatili, M., Colmegna, F., Clerici, M., Buoli, M., & Dakanalis, A. (2021). Long-term efficacy of intranasal esketamine in treatment-resistant major depression: A systematic review. *International Journal of Molecular Sciences, 22*(17), 9338. https://doi.org/10.3390/ijms22179338
10. Sapkota, A., Khurshid, H., Qureshi, I. A., Jahan, N., Went, T. R., Sultan, W., & Alfonso, M. (2021). Efficacy and safety of intranasal esketamine in treatment-resistant depression in adults: A systematic review. *Cureus, 13*(8), e17352. https://doi.org/10.7759/cureus.17352
11. Naudet, F., Pellen, C., Fodor, L. A., Gastaldon, C., Barbui, C., Turner, E. H., Le Pabic, E., & Cristea, I. A. (2025). Efficacy and safety of esketamine for "treatment resistant depression": Registered report for a systematic review with an individual patient data meta-analysis of randomized, double-blind, placebo-controlled trials. *BMC Medicine, 23*(1), 677. https://doi.org/10.1186/s12916-025-04435-x
12. Daly, E. J., Singh, J. B., Fedgchin, M., Cooper, K., Lim, P., Shelton, R. C., Thase, M. E., Winokur, A., Van Nueten, L., Manji, H., & Drevets, W. C. (2018). Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry, 75*(2), 139–148. https://doi.org/10.1001/jamapsychiatry.2017.3739
13. Fedgchin, M., Trivedi, M., Daly, E. J., Melkote, R., Lane, R., Lim, P., Vitagliano, D., Blier, P., Fava, M., Liebowitz, M., Ravindran, A., Gaillard, R., Van den Ameele, H., Preskorn, S., Manji, H., & Drevets, W. C. (2019). Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in treatment-resistant depression: Results of a randomized, double-blind, active-controlled study (TRANSFORM-1). *International Journal of Neuropsychopharmacology, 22*(10), 616–630. https://doi.org/10.1093/ijnp/pyz039
14. Popova, V., Daly, E. J., Trivedi, M., Cooper, K., Lane, R., Lim, P., Mazzucco, C., Hough, D., Thase, M. E., Shelton, R. C., Molero, P., Vieta, E., Bajbouj, M., Manji, H., & Drevets, W. C. (2019). Efficacy and safety of flexibly dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: A randomized double-blind active-controlled study. *American Journal of Psychiatry, 176*(6), 428–438. https://doi.org/10.1176/appi.ajp.2019.19020172
15. Ochs-Ross, R., Daly, E. J., Zhang, Y., Lane, R., Lim, P., Morrison, R. L., Hough, D., Thase, M. E., Manji, H., & Drevets, W. C. (2020). Efficacy and safety of esketamine nasal spray plus an oral antidepressant in elderly patients with treatment-resistant depression (TRANSFORM-3): A randomized, double-blind, active-controlled study. *American Journal of Geriatric Psychiatry, 28*(2), 121–141. https://doi.org/10.1016/j.jagp.2019.10.008
16. Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., Lane, R., Lim, P., Duca, A. R., Hough, D., Manji, H., & Drevets, W. C. (2019). Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: A randomized clinical trial. *JAMA Psychiatry, 76*(9), 893–903. https://doi.org/10.1001/jamapsychiatry.2019.1189

17. Lam, R. W., Kennedy, S. H., Adams, C., Bahji, A., Beaulieu, S., Bhat, V., & CANMAT Depression Work Group. (2024). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 update on clinical guidelines for management of major depressive disorder in adults. *Canadian Journal of Psychiatry, 69*, 641–687. https://doi.org/10.1177/07067437241245384
18. National Institute for Health and Care Excellence. (2022). *Esketamine nasal spray for treatment-resistant depression (Technology appraisal guidance TA854).* https://www.nice.org.uk/guidance/ta854
19. McQuaid, J. R., Buelt, A., Capaldi, V., Fuller, M., Issa, F., Lang, A. E., Hoge, C., Oslin, D. W., Sall, J., Wiechers, I. R., & Williams, S. (2022). The management of major depressive disorder: Synopsis of the 2022 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guideline. *Annals of Internal Medicine, 175*(11), 1440–1451. https://doi.org/10.7326/M22-1603
20. Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., Sheehan, J. J., & Williamson, T. (2021). The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. *Journal of Clinical Psychiatry, 82*(2), 20m13699. https://doi.org/10.4088/JCP.20m13699
21. Ross, E. L., Zivin, K., Maixner, D. F., & Valenstein, M. (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.202000020
22. Institute for Clinical and Economic Review. (2019). *Esketamine for the treatment of treatment-resistant depression: Final evidence report.* https://icer.org/wp-content/uploads/2020/10/ICER_TRD_Final_Evidence_Report_062019.pdf
23. 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
24. Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry, 163*(11), 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905
25. Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., & Ferrari, A. J. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry, 9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3
26. Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Zheng, P., Ashbaugh, C., Pigott, D. M., & Ferrari, A. J. (2021). Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet, 398*(10312), 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7
27. Swainson, J., Thomas, R. K., Archer, S., Chokka, P., Frey, B. N., Jha, M. K., & Milev, R. (2021). The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the use of racemic ketamine in adults with major depressive disorder. *Canadian Journal of Psychiatry, 66*(2), 113–125. https://doi.org/10.1177/0706743720965142
28. McIntyre, R. S., Alsuwaidan, M., Baune, B. T., Berk, M., Demyttenaere, K., Goldberg, J. F., Gorwood, P., Ho, R., Kasper, S., Kennedy, S. H., Ly-Uson, J., Mansur, R. B., McAllister-Williams, R. H., Murrough, J. W., Nemeroff, C. B., Nierenberg, A. A., Rosenblat, J. D., Sanacora, G., Schatzberg, A. F., . . . Maj, M. (2023). Treatment-resistant depression: Definition, prevalence, detection, management, and investigational interventions. *World Psychiatry, 22*(3), 394–412. https://doi.org/10.1002/wps.21120
29. U.S. Food and Drug Administration. (2025). *Spravato (esketamine) nasal spray, CIII: Prescribing information.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/211243s019lbl.pdf
30. Prasartpornsirichoke, J., Pityaratstian, N., Poolvoralaks, C., Sirinimnualkul, N., Ormtavesub, T., Hiranwattana, N., & Rungnirundorn, T. (2023). The prevalence and economic burden of treatment-resistant depression in Thailand. *BMC Public Health, 23*, 1541. https://doi.org/10.1186/s12889-023-16477-y
31. McIntyre, R. S., Filteau, M.-J., Martin, L., Patry, S., Carvalho, A., Cha, D. S., Barakat, M., & Miguelez, M. (2014). Treatment-resistant depression: Definitions, review of the evidence, and algorithmic approach. *Journal of Affective Disorders, 156*, 1–7. https://doi.org/10.1016/j.jad.2013.10.043