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Effectiveness of esketamine nasal spray in TRD: A review on symptoms severity, assessment scales, and regional practice pattern's

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Abstract
Treatment-resistant depression (TRD) remains a major clinical challenge, defined commonly as failure to respond to two or more adequate antidepressant trials despite adherence. Esketamine (Spravato®), the S-enantiomer of ketamine delivered via intranasal route, has emerged as a promising rapid-acting adjunctive option. This review synthesizes evidence on the effectiveness of esketamine nasal spray in reducing depressive symptom severity, the assessment scales used in trials and practice, and regional variations in its adoption. Controlled clinical trials such as TRANSFORM and ESCAPE-TRD have demonstrated that esketamine plus an oral antidepressant leads to significantly greater reductions in Montgomery–Åsberg Depression Rating Scale (MADRS) scores compared with placebo plus antidepressant, and higher rates of response and remission. Relapse-prevention studies (e.g. SUSTAIN) suggest that maintenance use of esketamine reduces the risk of relapse relative to discontinuation. Common assessment tools include MADRS (primary), HAM-D, PHQ-9 (patient-reported), CGI, and functional/quality-oflife scales; MADRS is the most sensitive to change in esketamine trials. Safety profiles indicate primarily transient adverse effects (dissociation, dizziness, nausea, blood pressure rise), with low discontinuation rates. Regional uptake of intranasal esketamine varies: the U.S. has implemented it under a REMS (Risk Evaluation and Mitigation Strategy) framework, Europe uses more centralized or hospital-based protocols, and adoption in Asia (including India) remains limited due to regulatory, infrastructure, and cost barriers.

Keywords: Treatment- resistant depression, assessment scales, safety and tolerability, adjunctive therapy, s-enantiomer of ketamine.

Introduction
Another name of esketamine is spravoto. TRD is adopted by the US Food and Drug Administration (FDA) [1] and the European medicines agency is failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment [2]. Although many definitions for TRD have been proposed, the general consensus appears to be 2 unsuccessful trails of anti-depressant pharmacotherapy (AD) [3]. The term "difficult-to-treat depression" has been suggested with the benefit of not introducing any "therapeutic nihilism" to the psychiatric -patient relationship [4]. Treatment- resistant depression, which affects 10 to 30% of patients with major depressive disorder, is associated with increased hospitalizations and coexisting conditions, higher mortality and suicide rates, and a greater economic burden [5]. According to the World Health Organization (WHO), Major Depressive Disorder is the single largest contribution has apparently further increased during the COVID-19 Pandemic [6]. However, although numerous molecules have been studied in phases II and phase III of clinical research is difficult to predict which will reach the market in decades [7]. A maximum of seven points can be as signed for the treatment dimension: one point for failure on 1- 2 medications; two points for failure on 3- 4 medications; three points for failure on 5- 6 medications; four points for failure on 7- 10 medications; five points for failure on more than 10 medications [8]. While depressive symptoms are at times part of normal human behaviour, MDD can be debilitating and at its worst, life threatening. MDD can present at any age across the life span, age of onset, risk factors, symptomatic presentation and comorbidities are present among people with the same diagnosis [9].

This condition, termed treatment-resistant depression (TRD), is associated with substantial morbidity, impaired quality of life, elevated healthcare costs, and increased risk of suicide [10].

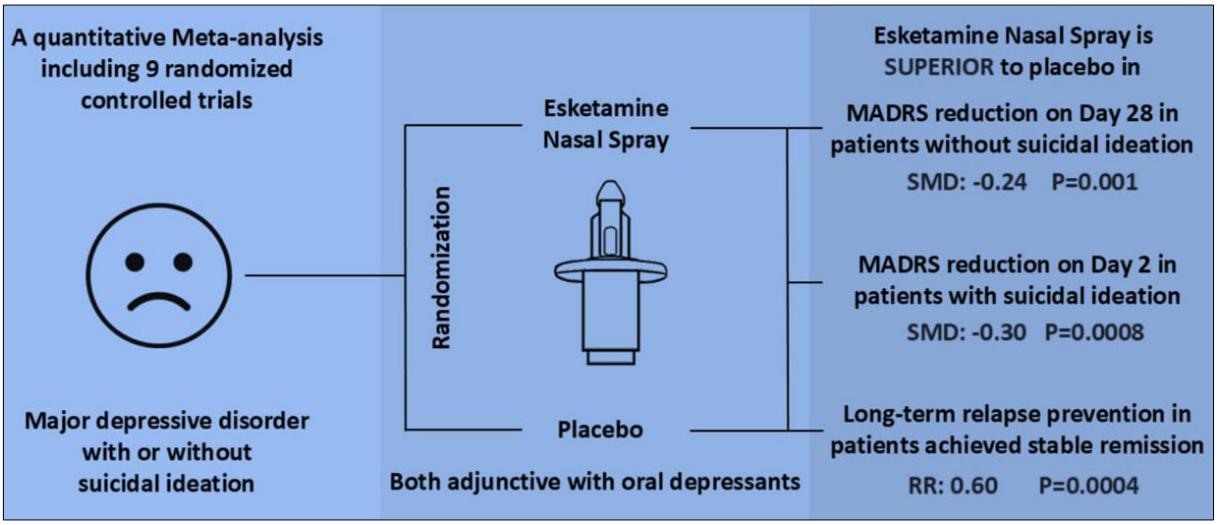

Fig 1: Clinical outcomes of esketamine nasal spray in treatment-resistant depression

Dreimüller N, Michael N, Böhringer A, Grohmann R, Schüle C. Esketamine nasal spray for treatment-resistant depression: an evidence-based review. Expert Opin Pharmacother. 2022;23(6):597–609.

2. Esketamine In Treatment Resistant Depression [TRD]

Esketamine, the S-enantiomer of ketamine, has recently emerged as a novel treatment option for patients suffering from treatment-resistant depression (TRD), a condition affecting nearly one-third of individuals with major depressive disorder (MDD) who fail to respond to at least two adequate antidepressant trials [11]. The limitations of these therapies have driven the search for new approaches, and esketamine represents one of the most promising breakthroughs in modern psychiatry. Esketamine exerts its antidepressant action primarily through non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor, resulting in enhanced glutamatergic neurotransmission and subsequent stimulation of synaptic plasticity via activation of the brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) signaling pathways [12-13]. In pivotal studies, such as TRANSFORM-2, patients receiving esketamine plus an oral antidepressant achieved significantly greater improvement in Montgomery–Åsberg Depression Rating Scale (MADRS) scores compared to those receiving placebo with an oral antidepressant [14]. Importantly, esketamine has shown potential for acute relief of suicidal thoughts, an area where traditional antidepressants fall short [15]. The safety profile of esketamine is generally acceptable but requires careful monitoring. Common adverse effects include dizziness, dissociation, increased blood pressure, nausea, perceptual disturbances, and sedation [16-17]. The nasal spray is typically given twice weekly during the induction phase, followed by individualized maintenance dosing schedules depending on patient response and tolerability [18].

2.1. Mechanism of action of esketamine

NMDA Receptor Antagonism: Esketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, a subtype of glutamate receptor. By blocking NMDA receptors on GABAergic interneurons, it reduces inhibitory control, leading to increased glutamate release. Activation of AMPA Receptors: The excess glutamate stimulates AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, enhancing excitatory neurotransmission. This AMPA activation is considered crucial for the antidepressant effect, more than NMDA antagonism itself. BDNF and mTOR Pathway Activation: AMPA receptor activation increases release of brain-derived neurotrophic factor (BDNF).This activates the mTOR (mammalian target of rapamycin) signaling pathway, which promotes synaptogenesis, dendritic spine growth, and synaptic plasticity in the prefrontal cortex. Restoration of Neural Circuit Function: Through enhanced neuroplasticity, esketamine helps restore connectivity in brain regions such as the prefrontal cortex and hippocampus, which are impaired in depression. Monoaminergic Effects (Indirect): Esketamine also influences dopaminergic, serotonergic, and noradrenergic pathways, partly contributing to mood improvement and its rapid antidepressant effect.

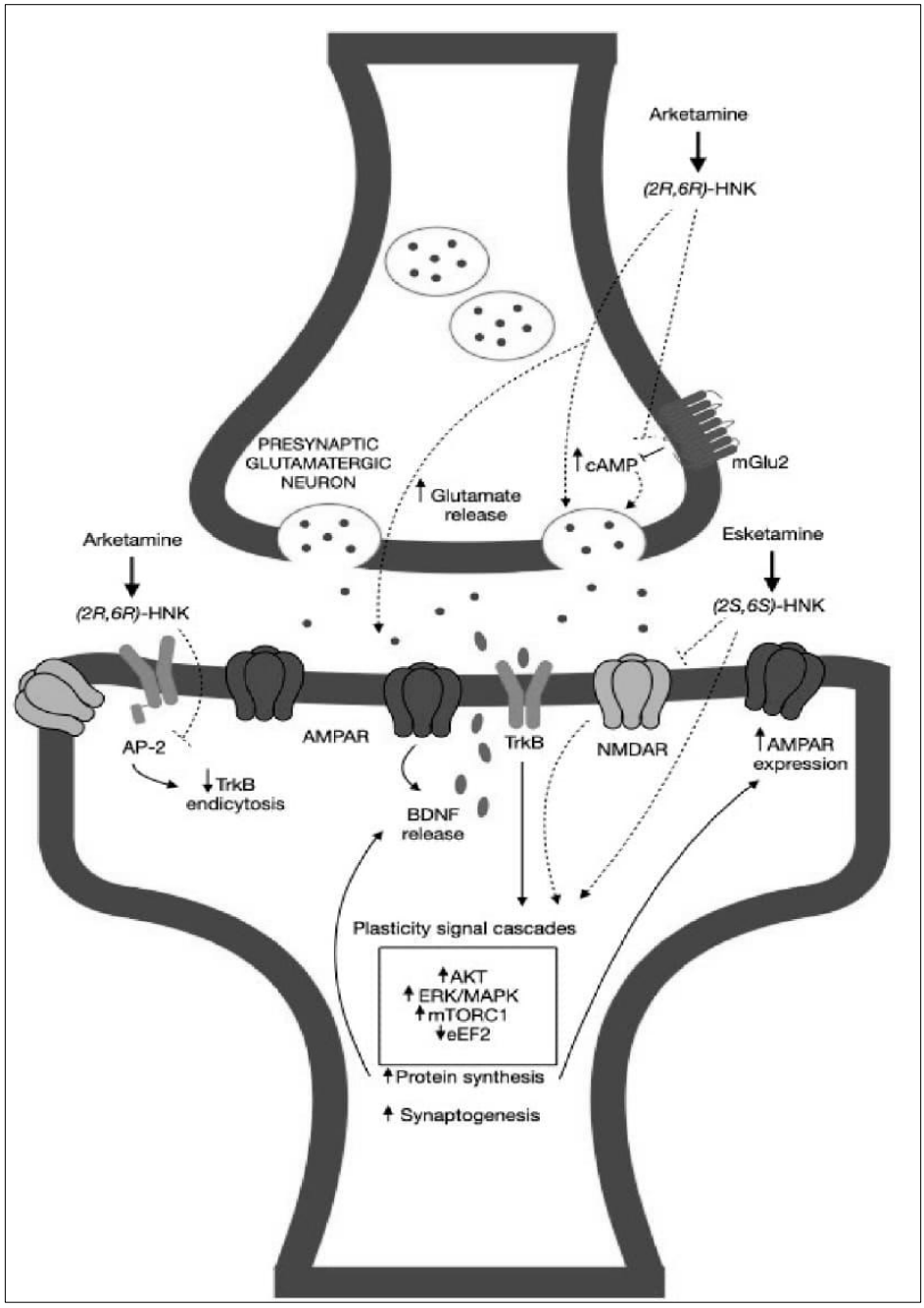

Fig 2: Mechanism of action of Esketamine nasal spray

Zanos P, Gould TD. Mechanisms of ketamine and its metabolites as antidepressants: insights from preclinical studies. Pharmacol Rev. 2018;70(3):621-660. doi:10.1124/pr.117.015198.

2.2. Pharmacokinetics

Absorption: Administered mainly as a nasal spray (intranasal route).Bioavailability after intranasal use: ~48%.Peak plasma concentration (Tmax): 20–40 minutes after intranasal administration.

Distribution: Highly lipophilic, rapidly crosses the blood–brain barrier.Volume of distribution (Vd): ~709 L, indicating extensive tissue distribution.Plasma protein binding: about 43–45%.

Metabolism: Extensively metabolized in the liver via CYP enzymes.

Elimination: Primarily excreted via urine (~90% as metabolites).Elimination half-life: 7–12 hours (longer than ketamine).Clearance: ~89 L/h.

2.3. Routes of administration

Intranasal (Main clinical use): Marketed as Spravato® nasal spray for treatment-resistant depression. Dosing is done under medical supervision to monitor blood pressure and dissociative side effects.

Intravenous (IV): Used in some off-label settings (similar to racemic ketamine for depression or analgesia).Provides rapid onset of action but less convenient for routine psychiatric use.

2.4. Clinical rational for intranasal delivery

Avoidance of First-Pass Metabolism: Oral ketamine has very low and variable bioavailability (~20%) due to

extensive hepatic first-pass metabolism. Intranasal administration bypasses the gastrointestinal tract and liver's first-pass effect, improving bioavailability (~48%).

Rapid Onset of Action: Intranasal delivery allows direct absorption through the nasal mucosa into systemic circulation. Peak plasma concentration occurs within 20–40 minutes.

Improved Patient Compliance: Outpatient-friendly compared to IV infusion therapy. Reduces hospital burden and improves accessibility for long-term treatment.

Controlled Dosing and Safety Monitoring: The nasal spray device delivers a standardized dose with controlled absorption. Administration is still done under supervision, allowing monitoring of adverse effects like dissociation and hypertension [19-23].

3. Symptoms sevierity in TRD

3.1. Definition

In treatment-resistant depression (TRD), symptom severity refers to the intensity and persistence of depressive symptoms despite adequate treatment attempts with antidepressant medications. Patients with TRD often present with moderate to severe symptom burden, including persistent low mood, anhedonia, cognitive impairment, suicidal ideation, sleep disturbances, and functional disability, even after receiving at least two trials of antidepressants from different pharmacological classes at adequate dose and duration (≥6 weeks each) [24-25].

Fig 3: Common signs of treatment resistant depression

Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. Can J Psychiatry. 2007;52(1):46–54.

TRD patients typically remain in the moderate-to-severe range, which is associated with poor quality of life, increased healthcare utilization, and elevated suicide risk [26-27].

3.2. Common clinical presentations

The common clinical presentation typically includes: High severity of symptoms, often quantified by scales such as the Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) [28].

3.3 Impacts of symptoms severity on treatment outcomes

Patients with higher baseline severity of depressive symptoms often experience lower response rates to pharmacological and non-pharmacological interventions compared with those with moderate severity. Severe symptoms, such as profound anhedonia, cognitive impairment, psychomotor retardation, and suicidality, contribute to treatment refractoriness and are associated with poor prognosis [29].

Greater symptom severity is also linked with longer duration to remission and an increased probability of relapse or recurrence[30].Furthermore, studies indicate that patients with higher severity often require multimodal interventions, including augmentation strategies (e.g., antipsychotics, lithium), neuromodulation techniques, or novel agents [31-32].

4. Assessment scales for symptoms evaluation

Standardized assessment scales provide a structured framework for clinicians and researchers to quantify depressive symptoms, monitor treatment response, and compare outcomes across studies. Widely used scales, such as the Hamilton Depression Rating Scale (HAM-D), Montgomery–Åsberg Depression Rating Scale (MADRS),patient health quetionarrie-9(PHQ-9), have been validated for assessing depressive symptomatology in various clinical and research contexts (Zimmerman *et al*., 2008) [33].

4.1. Montgomery-Asberg Depression Rating Scales (MADRS)

The MADRS is the most widely used primary outcome measure in esketamine clinical trials. It consists of 10 items that assess core symptoms of depression such as sadness, tension, sleep disturbances, appetite changes, concentration

difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal ideation. Each item is rated from 0 to 6, yielding a total score ranging from 0 (no symptoms) to 60 (severe depression)

Limitations: Requires trained raters, which can limit its practicality in routine outpatient settings [34-35].

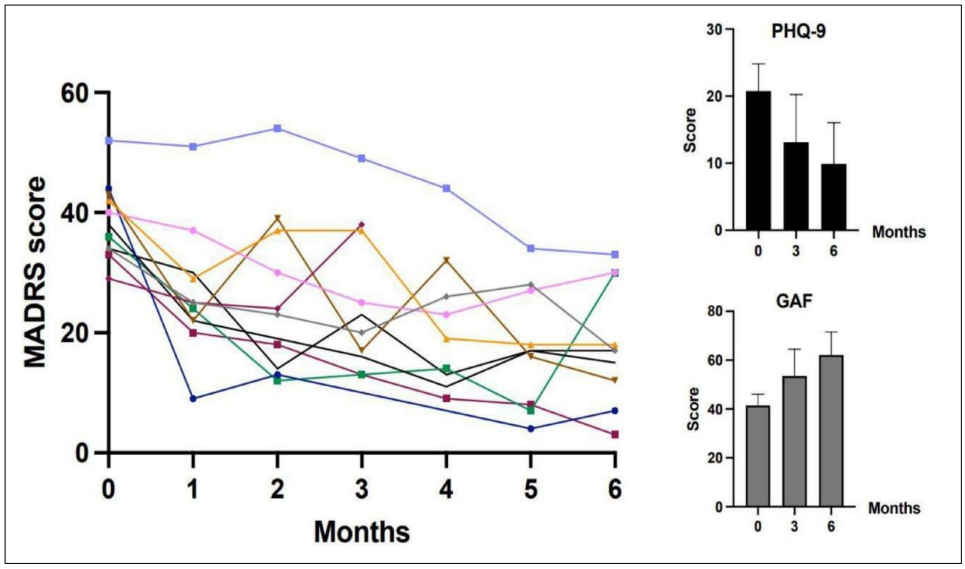

Fig 4: Changes in depression severity over time assessed by MADRS,GAF,and PHQ-9 scores.

Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134(4):382–389.

4.2. Hamilton Depression Rating Scale (HAM-D)

The HAM-D, developed in the 1960s, remains one of the oldest and most commonly used depression rating scales. It typically includes 17–24 items covering mood, somatic symptoms, insomnia, and psychomotor changes.

Use in Esketamine Trials: While not the primary endpoint, HAM-D has been used as a secondary measure to validate MADRS findings.

Limitations: More focused on somatic and sleep symptoms, less sensitive to mood changes compared with MADRS [36].

4.3. Patient Health Questionnarie-9 (PHQ-9)

The PHQ-9 is a self-administered questionnaire consisting of nine items based on DSM diagnostic criteria for major depressive disorder. Scores range from 0 to 27, with higher scores indicating greater symptom severity.

Use in Clinical Practice: Particularly valuable in real-world esketamine studies where patient-reported outcomes are emphasized.

Limitations: Subjective responses may vary depending on patient insight and willingness to disclose symptoms [37].

5. Effect of esketamine nasal spray on symptom severity

Esketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a novel therapeutic option for adults with treatment-resistant depression (TRD). In the TRANSFORM-2 trial, esketamine combined with an oral antidepressant produced a mean change in MADRS score of –21.4 compared to –17.0 in the placebo plus antidepressant group after 28 days, demonstrating superior efficacy [38].

5.1. Short term Vs long term efficacy

Short- term efficacy

Short-term randomized controlled trials (RCTs) have demonstrated that esketamine nasal spray produces rapid and robust reductions in depressive symptom severity when combined with oral antidepressants.

In the TRANSFORM trials, patients receiving esketamine plus an antidepressant showed significantly greater reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) scores within 24 hours compared to placebo [39-40].Response and remission rates at 4 weeks were consistently higher with esketamine, supporting its rapid antidepressant effect [41].

Long-Term Efficacy

Long-term extension studies and relapse prevention trials suggest that esketamine is effective in maintaining symptom improvement: Patients who achieved stable remission or response and continued esketamine treatment demonstrated a significantly lower risk of relapse compared with those switched to placebo [42]. In open-label safety studies, patients maintained symptom reduction over 12 months of intermittent dosing, with no new safety concerns emerging [43]. Long-term efficacy has also been linked to improved functional outcomes and quality of life, aligning with sustained reductions in depressive symptom severity [44].

6. Regional practice pattrens

Esketamine nasal spray has been incorporated into clinical practice with significant regional variations. Regulatory frameworks, healthcare infrastructure, cost considerations, and cultural attitudes toward mental health all shape how esketamine is prescribed and monitored.

United States

The U.S. Food and Drug Administration (FDA) approved esketamine in 2019 for adults with TRD, to be used in conjunction with an oral antidepressant [45].

REMS Program: Esketamine can only be administered in certified healthcare settings under the Risk Evaluation and Mitigation Strategy (REMS) program. Patients must be monitored for at least 2 hours post-administration for blood pressure changes and dissociation [46].

Dosing Regimen: Twice weekly during the induction phase (first 4 weeks), followed by weekly or biweekly maintenance dosing.

Clinical Practice: It is often used in outpatient clinics with trained staff, but its uptake is constrained by high cost (up to USD 6,000 per month) and logistical challenges [47].

Europe

The European Medicines Agency (EMA) approved esketamine in 2019 with similar indications. However, European practice emphasizes treatment within hospital or specialized centers.

Guidelines: The EMA requires initiation under psychiatric supervision, with ongoing monitoring [48].

Accessibility: Coverage depends on national health insurance systems. For example, in the Netherlands and Germany, esketamine is reimbursed under certain conditions, while in southern Europe, reimbursement is more restricted [49].

Japan: Esketamine nasal spray was approved in 2022, with usage limited to specialized psychiatric centers. Japanese guidelines emphasize careful patient selection and emphasize post-dose observation due to safety concerns [50].

India: As of 2025, esketamine is not yet widely approved. Ketamine infusions are sometimes used off-label for TRD in major hospitals, but high costs and regulatory hurdles limit availability [51].

China and Southeast Asia: Limited access due to regulatory delays and cost barriers. Research is ongoing, but widespread clinical adoption remains limited [52].

7. Safety and tolerability profile

In the TRANSFORM-1 study, the most commonly reported side effects where nausea, dissociation, dizziness, and headache. In the TRANSFORM-2 study, patients primarly reported nausea, dizziness, dissociation, dysgeusia [53-54].

In the TRANSFORM -3 study, the incidence of the reported advers effects in the esketamine +anti-depressant therapy group was 70.8% Vs. 60% in the esketamine +placebo group and were primarily dizziness, nausea, transient incease in blood pressure, fatigue, headache and dissociation [55].

8. Challenges and future directions

Intranasal esketamine has shown rapid antidepressant effects in treatment-resistant depression (TRD), offering a novel mechanism targeting glutamatergic pathways. Future directions include pragmatic long-term studies, comparative trials with other rapid-acting therapies, and implementation strategies to improve accessibility and cost-effectiveness [56-57].

9. Conclusion

In conclusion,esketamine nasal spray, an (NMDA) receptor antagonist, combined with an SSRI/SNRI, presents a promoting treatment option for patients with TRD.The treatment was well tolerated, with the majority of adverse events being transient and mild-to-moderate in intensity.TRD measures by both clinician and patient -rated evaluation of depression symptoms. Intranasal esketamine represents an important advancement in managing treatment-resistant depression, demonstrating rapid symptom relief where conventional antidepressants have failed. Despite its promise, uncertainties regarding long-term safety, durability of response, monitoring requirements, and access barriers limit its widespread application.

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