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# COMPARING ROUTES OF KETAMINE ADMINISTRATION IN TREATMENT-RESISTANT DEPRESSION: EFFICACY, SAFETY, AND OPTIMIZATION OF DOSING STRATEGIES

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**ABSTRACT**

**Background:** Treatment-resistant depression (TRD) is associated with substantial functional impairment, suicide risk, and health-care costs. Ketamine and its S-enantiomer, esketamine, have emerged as rapid-acting glutamatergic treatment options for TRD.
**Aim:** This review aims to synthesize current evidence on the different ketamine administration routes for TRD, with a focus on acute and maintenance efficacy, dosing strategies, safety, infrastructure needs, and positioning within stepped-care algorithms.
**Methods:** A narrative review of randomized controlled trials, meta-analyses, systematic reviews, and long-term open-label studies was performed. Outcomes were grouped by route and examined for (1) antidepressant response, (2) adverse-event profile, (3) required clinical resources, and (4) integration with other treatments such as electroconvulsive therapy and psychotherapy.
**Results:** Ketamine and esketamine can be administered via intravenous (IV), intranasal (IN), oral, subcutaneous (SC), and intramuscular (IM) routes. IV racemic ketamine shows the strongest and fastest antidepressant effect but demands infusion-suite equipment and monitoring for transient hypertension and dissociation. FDA-approved IN esketamine offers robust long-term data but requires administration under supervised in-clinic administration and blood pressure monitoring. According to the reviewed studies, IV and IN routes remain the best-supported options for achieving a rapid response. Oral, sublingual and extended-release formulations provide easier access and lower cost, but have reduced bioavailability, modest effect sizes, and higher diversion risk. These routes of administration may be useful for maintenance treatment in resource-constrained settings. SC and IM injections achieve ~90 % bioavailability with minimal infrastructure, yet evidence is limited to small series.
**Conclusion:** The optimal ketamine route is context-dependent, and requires balancing efficacy, safety, cost, and health-system capacity. Future research should include direct comparative trials and extended safety monitoring to better define the long-term efficacy, tolerability, and optimal clinical use of different ketamine administration routes.

**KEYWORDS**

Treatment-Resistant Depression, Ketamine, Administration Routes, Acute, Maintenance, Neuroplasticity

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## Introduction

According to the FDA and EMA, treatment-resistant depression (TRD) is a major depressive disorder that has not shown an adequate response after at least 2 antidepressant trials of adequate dose and duration, with adherence confirmed, during the same depressive episode (Fiorillo et al., 2025). TRD is associated with substantial functional impairment, elevated suicide risk, and high health-care costs, underscoring the need for more effective interventions beyond conventional monoaminergic antidepressants, augmentation strategies, and neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT) (Sakopoulos & Todman, 2025; Smith-Apeldoorn et al., 2022; McIntyre et al., 2023). In this context, ketamine and its S-enantiomer esketamine have emerged as rapid-acting antidepressants with a distinct glutamatergic mechanism, producing clinically meaningful symptom reductions within hours to days in many patients with TRD (Sakopoulos & Todman, 2025; Al-Garni et al., 2026). Initially developed as an anesthetic, ketamine's non-competitive N-methyl-D-aspartate (NMDA) receptor antagonism is thought to trigger downstream increases in glutamate transmission, synaptic plasticity, and neural network reorganization, potentially opening a "window" during which adjunctive psychotherapeutic and rehabilitative interventions may be particularly effective (Sakopoulos & Todman, 2025). Over the past decade, multiple formulations and routes of administration have been investigated in both acute and maintenance paradigms for TRD (Sakopoulos & Todman, 2025; Al-Garni et al., 2026; Smith-Apeldoorn et al., 2022). While research

initially centered on intravenous racemic ketamine and intranasal esketamine, it has since expanded to include oral, extended-release, subcutaneous, and intramuscular preparations (Al-Garni et al., 2026; Smith-Apeldoorn et al., 2022; Glue et al., 2024). While randomized controlled trials and meta-analyses demonstrate robust short-term efficacy of intravenous ketamine and modest but significant effects of intranasal esketamine, emerging data suggest that alternative, less resource-intensive routes may sustain antidepressant benefits with acceptable tolerability, albeit on a more limited evidence base (McIntyre et al., 2021; Smith-Apeldoorn et al., 2022; McIntyre et al., 2023). At the same time, concerns about long-term safety, abuse liability, and the infrastructure required for monitoring cardiorespiratory and dissociative adverse effects complicate decisions about how best to integrate ketamine-based treatments into stepped-care algorithms for TRD (McIntyre et al., 2021; Swainson et al., 2022). This review synthesizes current evidence on the efficacy, safety, and practicality of different ketamine administration routes and dosing strategies in TRD, with the aim of clarifying how "optimal" use is likely to be context-dependent - varying according to clinical severity, comorbidities, health-system resources, and patients' preferences and risk profiles (McIntyre et al., 2021).

## 1. Overview of ketamine-based treatments

### 1.1 Molecules, Formulations, and Mechanisms of Action

Ketamine-based treatments for TRD utilize the racemic mixture of ketamine and its more potent S-enantiomer, esketamine (Seshadri et al., 2024). Unlike traditional antidepressants that target monoamine systems, ketamine and esketamine are N-methyl-D-aspartate (NMDA) receptor antagonists (Seshadri et al., 2024; Burcu Kök Kendirlioğlu et al., 2025). Their primary mechanism of action involves blocking these glutamate receptors, which leads to a downstream surge in glutamate release (Sakopoulos & Todman, 2025). This glutamate surge preferentially activates a different type of receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), which in turn triggers signaling pathways involving brain-derived neurotrophic factor (BDNF) and the mammalian target of rapamycin (mTOR) (Sakopoulos & Todman, 2025). This cascade promotes synaptic plasticity, the formation of new neural connections, and helps reverse the stress-induced synaptic deficits associated with depression (McIntyre et al., 2023; Sakopoulos & Todman, 2025). These treatments are available in multiple formulations, each with a distinct pharmacokinetic profile (McIntyre et al., 2021). The bioavailability and onset of action vary significantly by the route of administration:

**Intravenous (IV) Ketamine**: This is the most studied route, offering 100% bioavailability and providing precise dose control (Sakopoulos & Todman, 2025; McIntyre et al., 2021). It is typically used as either a primary or supplemental treatment under direct clinical supervision (McIntyre et al., 2021).

**Intranasal (IN) Esketamine**: The FDA-approved formulation (Spravato®) is co-administered with a conventional antidepressant for TRD (McIntyre et al., 2021; Zaki et al., 2023). It offers a convenient, non-invasive alternative to IV administration but has a lower and more variable bioavailability of approximately 30%-50% (McIntyre et al., 2021; Sakopoulos & Todman, 2025).

**Oral and Sublingual Ketamine**: These non-parenteral forms have limited and variable bioavailability (10%-29%) due to extensive first-pass metabolism (McIntyre et al., 2021; Smith-Apeldoorn et al., 2022; Sakopoulos & Todman, 2025). While less evidence supports their use compared to IV or IN routes, they are being explored for maintenance therapy due to their potential for easier, less supervised administration (McIntyre et al., 2021; Swainson et al., 2022). An extended-release oral ketamine tablet (R-107) has been developed to improve tolerability by maximizing first-pass metabolism and delaying peak concentrations, which may reduce side effects like dissociation (Glue et al., 2024).

**Intramuscular (IM) and Subcutaneous (SC) Ketamine**: These routes have high bioavailability (around 90%) and are sometimes used in outpatient or emergency settings (Smith-Apeldoorn et al., 2022; Sakopoulos & Todman, 2025). However, data supporting their use for maintenance treatment in TRD are scarce (Smith-Apeldoorn et al., 2022).

### 1.2. Acute vs. Maintenance Treatment Phases

The therapeutic application of ketamine is typically divided into two distinct phases: an acute induction phase to achieve rapid symptom relief and a subsequent maintenance phase to sustain the antidepressant effects and prevent relapse (Al-Garni et al., 2026; Smith-Apeldoorn et al., 2022).

#### 1.2.1 Acute Treatment

The hallmark of ketamine therapy is its rapid onset of antidepressant and anti-suicidal effects, often occurring within hours and peaking at 24 hours post-administration (Marcantoni et al., 2020; Sakopoulos &

Todman, 2025). This makes it a valuable intervention for patients with severe TRD and acute suicidal ideation (Seshadri et al., 2024; Sakopoulos & Todman, 2025; Phillips et al., 2019).

An acute treatment course often involves:

- a single sub-anesthetic IV infusion, typically 0.5 mg/kg of body weight administered over 40 minutes (Seshadri et al., 2024; Anand et al., 2023; Sakopoulos & Todman, 2025)
- a short series of repeated infusions, such as six IV infusions administered two or three times a week over a two-to-three-week period (McIntyre et al., 2021; Sakopoulos & Todman, 2025; Phillips et al., 2020)
- an induction phase for intranasal esketamine, which typically involves twice-weekly administration of 56 mg or 84 mg for the first four weeks, co-initiated with a new oral antidepressant (McIntyre et al., 2021; Zaki et al., 2023)

Studies consistently show that single and repeated ketamine administrations produce rapid and significant reductions in depressive symptoms (Ionescu et al., 2019; Sakopoulos & Todman, 2025; Phillips et al., 2020). However, the effects of a single infusion are often transient, with symptoms typically returning within one to two weeks (Smith-Apeldoorn et al., 2022; Marcantoni et al., 2020). This has led to the development of repeated dosing protocols to build upon and prolong the initial response (Smith-Apeldoorn et al., 2022; Phillips et al., 2020).

### 1.2.2 Maintenance Treatment

Given the short-lived effects of acute treatment, maintenance therapy is often necessary to sustain remission and prevent relapse (Smith-Apeldoorn et al., 2022). Maintenance protocols aim to provide ongoing treatment at a reduced frequency after a patient has responded to the initial induction phase (Phillips et al., 2020).

Key aspects of maintenance therapy include:

**Sustained Efficacy**: Long-term studies, particularly for intranasal esketamine, have demonstrated sustained efficacy and safety for up to 4.5 years (McIntyre et al., 2021; Zaki et al., 2023). The SUSTAIN-3 study showed that improvements in depression ratings generally persisted among participants who remained in maintenance treatment, with 46.1% achieving remission at the study's endpoint (Zaki et al., 2023).

**Dosing Schedules**: Maintenance dosing is often individualized based on symptom severity (Zaki et al., 2023). Following an induction phase, intranasal esketamine may be administered weekly or bi-weekly (McIntyre et al., 2021). For IV ketamine, responders from an acute phase of six infusions have shown sustained benefits with once-weekly maintenance infusions (Phillips et al., 2020). Evidence suggests that regular maintenance dosing schedules are superior to variable or as-needed protocols, leading to significantly lower relapse rates (27.3% vs. 45.6%) (Al-Garni et al., 2026).

**Formulation Choice**: While intranasal esketamine has robust data supporting its long-term use, the evidence for long-term IV ketamine is less extensive and comes primarily from open-label trials and case series (McIntyre et al., 2021; Smith-Apeldoorn et al., 2022). Non-parenteral formulations like oral or sublingual ketamine are attractive for maintenance due to their convenience and reduced need for in-clinic monitoring, though high-quality research is still needed to establish optimal dosing strategies (Swainson et al., 2022).

**Integration with Psychotherapy**: The neuroplasticity induced by ketamine is thought to create a "window of opportunity" for psychotherapeutic interventions to be more effective (Sakopoulos & Todman, 2025). Combining ketamine infusions with psychotherapy, known as ketamine-assisted psychotherapy (KAP), has been shown to enhance and prolong the antidepressant response (Al-Garni et al., 2026; Sakopoulos & Todman, 2025). This integrated approach leverages the molecular changes initiated by the drug to facilitate the cognitive and emotional restructuring central to therapy (Sakopoulos & Todman, 2025).

## 2. Intravenous ketamine

### 2.1 Dosing and Acute Efficacy

The standard protocol for IV ketamine involves a sub-anesthetic dose of 0.5 mg/kg, typically based on ideal body weight, infused over a 40- to 45-minute period (Phillips et al., 2020; Shiroma et al., 2020; McIntyre et al., 2021; Anand et al., 2023). However, dosing can be individualized; for instance, in severely affected or multiple treatment-resistant inpatients, doses are often escalated to a range of 0.75-1.0 mg/kg to maximize clinical effect while maintaining tolerability (Vestring et al., 2024). One meta-analysis found that while doses as low as 0.2 mg/kg can be effective, efficacy increases at 0.5 mg/kg, with no clear additional benefit at 1.0 mg/kg (Seshadri et al., 2024).

The primary advantage of IV ketamine is its rapid acute efficacy (Vestring et al., 2024). Clinically significant antidepressant and anti-suicidal effects emerge within hours of the first infusion, with peak

therapeutic benefit typically observed at 24 hours (Phillips et al., 2020; Sakopoulos & Todman, 2025; Marcantoni et al., 2020). Studies consistently report a rapid and robust reduction in scores on depression rating scales, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Beck Depression Inventory (BDI) (Phillips et al., 2020; Vestring et al., 2024).

### 2.2 Single vs. Repeated vs. Maintenance Infusions

The strategy for administering ketamine infusions varies depending on the therapeutic goal, evolving from single doses for acute relief to repeated and maintenance courses for sustained wellness (Phillips et al., 2020).

**Single Infusion:** A single ketamine infusion provides rapid but transient relief from depressive symptoms (Phillips et al., 2020). The antidepressant effects typically last between three and seven days before beginning to wane (Phillips et al., 2020; Sakopoulos & Todman, 2025; McIntyre et al., 2021). While effective for acute crisis management, most patients experience a relapse of symptoms, often within one to two weeks, necessitating further treatment to prolong the benefit (Shiroma et al., 2020; Smith-Apeldoorn et al., 2022).

**Repeated Infusions:** To extend the initial therapeutic effects, repeated infusion protocols are commonly used (Phillips et al., 2020; Marcantoni et al., 2020). These typically involve a series of six infusions administered two or three times per week over a two- to three-week period (Phillips et al., 2020; Marcantoni et al., 2020). This approach has been shown to have cumulative antidepressant effects, with depression severity continuing to decrease with each subsequent infusion (Phillips et al., 2020). Repeated dosing leads to significantly higher response and remission rates compared to a single infusion; one study reported a 59% response rate after a course of six infusions (Phillips et al., 2020). This strategy can extend the median time-to-relapse to approximately six weeks (Shiroma et al., 2020).

**Maintenance Infusions:** Following a successful acute or induction phase, maintenance therapy is implemented to sustain the antidepressant response and prevent relapse (Phillips et al., 2020; Marcantoni et al., 2020). The frequency of maintenance infusions is often individualized, ranging from once a week to once every few months, based on the patient's clinical status (Phillips et al., 2020; Smith-Apeldoorn et al., 2022). Studies have shown that once-weekly infusions are sufficient to maintain the benefits achieved during the acute phase (Phillips et al., 2020). Long-term case series and open-label trials have documented sustained remission for months and even years in patients receiving ongoing maintenance therapy (Smith-Apeldoorn et al., 2022).

### 2.3 Safety and Tolerability

IV ketamine is generally well-tolerated in clinical settings (Vestring et al., 2024; Swainson et al., 2022). The most common side effects are acute, transient, and resolve within a few hours of the infusion (Phillips et al., 2020; Seshadri et al., 2024). These include:

**Psychiatric Effects:** Dissociative symptoms (e.g., feelings of unreality) are common but typically mild and self-limiting (Phillips et al., 2020; Seshadri et al., 2024).

**Cardiovascular Effects:** Modest and temporary elevations in blood pressure and heart rate are frequently observed during the infusion (Phillips et al., 2020; Smith-Apeldoorn et al., 2022).

**Other Common Effects:** Dizziness, headache, and nausea are also reported but are generally mild (Vestring et al., 2024).

Serious adverse events are rare in the context of clinically supervised infusions for depression (Vestring et al., 2024; Dwyer et al., 2021). Long-term concerns associated with recreational ketamine use, such as cognitive impairment, bladder toxicity (cystitis), or addiction, appear to be uncommon with the low doses and controlled administration schedules used for TRD (Smith-Apeldoorn et al., 2022; Swainson et al., 2022). Systematic reviews have found no evidence of increased ketamine craving or misuse in patients treated for depression (Swainson et al., 2022).

### 2.4 Special Populations / Very Resistant Inpatients

IV ketamine has demonstrated efficacy in some of the most difficult-to-treat patient populations.

**Very Resistant Inpatients:** In naturalistic studies of hospitalized patients with multiple treatment resistance (MTR) - defined as having failed an average of seven or more antidepressants over an illness duration of more than 18 years - ketamine has shown clinical benefits (Vestring et al., 2024). In this severely affected cohort, response rates were approximately 29% and remission rates were 15%, with higher doses (0.75–1.0 mg/kg) yielding the most significant symptom reduction (Vestring et al., 2024).

**Patients with Chronic Suicidal Ideation:** While ketamine has potent anti-suicidal effects, outpatients with chronic and severe suicidal ideation may require higher doses than the standard 0.5 mg/kg to achieve a

robust response (Ionescu et al., 2019). One randomized controlled trial in this population found that 0.5 mg/kg was not superior to placebo, suggesting a need for dose escalation (Ionescu et al., 2019).

**Adolescents:** A landmark randomized controlled trial in adolescents (ages 13–17) with TRD found that a single 0.5 mg/kg IV ketamine infusion was well-tolerated and produced a significantly greater reduction in depressive symptoms compared to an active placebo (midazolam) (Dwyer et al., 2021). The therapeutic effects appeared to persist for up to 14 days (Dwyer et al., 2021).

**Other Populations:** Preliminary evidence also supports the safety and effectiveness of IV ketamine in older adults with TRD and in patients with bipolar depression, although more research is needed to establish optimal protocols for these groups (Shiroma et al., 2020; McIntyre et al., 2021; Vestring et al., 2024).

## 3. Intranasal Esketamine

### 3.1 Acute and long-term efficacy

Intranasal esketamine, the S-enantiomer of ketamine, holds a distinct regulatory position as an FDA- and EMA-approved treatment for adults with TRD, administered in conjunction with a conventional oral antidepressant (McIntyre et al., 2021; Zaki et al., 2023), and was later approved for major depression with acute suicidal ideation or behavior (McIntyre et al., 2021).

Its acute efficacy is established through an induction phase, typically involving flexibly dosed 56 mg or 84 mg nasal sprays administered twice weekly for four weeks (McIntyre et al., 2021). Unlike many IV ketamine trials, esketamine was evaluated against a placebo spray co-initiated with a new antidepressant, demonstrating a statistically significant, albeit modest, improvement in MADRS scores (McIntyre et al., 2021). More direct evidence of its potency comes from trials like ESCAPE-TRD, which found esketamine significantly more effective than extended-release quetiapine, with higher remission rates at both 8 weeks (27.1 % vs. 17.6%) and 32 weeks (55% vs. 37%) (McIntyre et al., 2023). A key differentiator for intranasal esketamine is the robust evidence supporting its long-term efficacy and safety, with maintenance data extending up to 4.5 years from studies like SUSTAIN-3 (Zaki et al., 2023). Following induction, treatment frequency is reduced to weekly or bi-weekly individualized dosing to maintain response and prevent relapse, a strategy shown to decrease relapse risk by 51% among stable remitters (McIntyre et al., 2021). Long-term data confirm sustained improvement, with remission rates around 46% and high patient retention, reflecting a remarkably low rate of discontinuation due to lack of efficacy. (4.4%) (Zaki et al., 2023).

### 3.2 Safety, monitoring and regulatory context

The safety profile is well-characterized, with the most common treatment-emergent adverse events being transient and occurring on dosing days; these include dissociation, dizziness, nausea, somnolence, headache, and temporary elevations in blood pressure (Zaki et al., 2023; Seshadri et al., 2024). Crucially, long-term open-label studies have not identified new safety signals, reports of cognitive decline, or evidence of drug-seeking behavior or misuse in the clinical trial context (McIntyre et al., 2021; Zaki et al., 2023). Due to these acute effects and theoretical abuse potential, esketamine is regulated under a strict Risk Evaluation and Mitigation Strategy (REMS) in the United States (McIntyre et al., 2021). This mandates that the nasal spray be self-administered by the patient under the direct supervision of healthcare personnel in a certified clinical setting (Zaki et al., 2023; McIntyre et al., 2021). Following administration, patients must be monitored for at least two hours until sedation and dissociation have subsided and vital signs have stabilized, and they are prohibited from driving until the following day (McIntyre et al., 2021). European approvals similarly require supervised dosing but do not impose a formal REMS; instead, national guidelines recommend clinic-based administration and post-dose observation (McIntyre et al., 2023).

## 4. Non-parenteral and Alternative Routes

### 4.1 Oral and Extended-Release Ketamine

Oral ketamine undergoes extensive first-pass metabolism in the liver, resulting in a low and inconsistent bioavailability estimated at only 10-20% (Glue et al., 2024). While this significantly reduces the amount of parent drug reaching systemic circulation, the subsequent conversion into primary metabolites - specifically norketamine and hydroxynorketamine - may be advantageous. Research suggests these metabolites contribute significantly to the drug's antidepressant potential, effectively providing prolonged therapeutic exposure (Glue et al., 2024). To address these limitations, an extended-release oral tablet (R-107) was developed. The formulation is designed for slow absorption to maximize the first-pass effect and provide a more sustained, lower-level exposure to ketamine and its metabolites (Glue et al., 2024). In a recent phase-2 enrichment-

follow-up trial, patients who first responded to a short course of the drug were then randomized to receive different doses or placebo twice weekly. The 180 mg dose group showed a statistically significant reduction in depression scores compared with placebo (Glue et al., 2024). Importantly, the tablet was well-tolerated, with minimal dissociative side effects and no clinically significant increases in blood pressure, which are common concerns with intravenous ketamine (Glue et al., 2024).

### 4.2 Other Non-parenteral Routes (Oral, Sublingual, Intranasal Racemic)

#### 4.2.1 Compounded Oral and Sublingual (SL) Ketamine

These formulations are frequently used in outpatient settings because they can be prepared by compounding pharmacies from inexpensive generic racemic ketamine (Swainson et al., 2022). Sublingual administration (lozenge or liquid held under the tongue) offers slightly better bioavailability - approximately 25-30 % - than standard oral tablets because part of the dose bypasses hepatic metabolism (McIntyre et al., 2021). Both oral and SL routes, however, show highly variable absorption between individuals, making consistent dosing challenging, and their onset of action is slower, which may limit suitability for acute symptom relief (McIntyre et al., 2021).

#### 4.2.2 Intranasal (IN) Racemic Ketamine

This route involves a nasal spray compounded from racemic ketamine and is distinct from the FDA-approved esketamine nasal spray (Spravato®) (McIntyre et al., 2021). The rich vascular supply of the nasal mucosa allows rapid absorption and bypasses first-pass metabolism, producing a much faster onset of antidepressant effects than oral or SL formulations (McIntyre et al., 2021). Small pilot studies have demonstrated rapid antidepressant effects, but the evidence base is less robust than that for intranasal esketamine, and its use remains off-label and non-standardized (McIntyre et al., 2021).

### 4.3 Additional Concerns with Non-Parenteral Use

#### 4.3.1 Abuse and Diversion Potential

Ketamine is a Schedule III controlled substance with a known potential for abuse (Swainson et al., 2022). Providing take-home oral, SL, or IN prescriptions creates a significant risk of misuse (taking more than prescribed), diversion (giving or selling the medication), or the development of a substance-use disorder (Swainson et al., 2022). While supervised clinical trials have not reported major addiction issues, the risk is higher in less-controlled, real-world settings (Swainson et al., 2022). Tamper-resistant formulations such as the hard R-107 tablet are specifically designed to mitigate these risks (Glue et al., 2024).

#### 4.3.2 Urinary Tract and Bladder Toxicity

Chronic, high-dose recreational ketamine use is linked to severe ketamine-induced cystitis, characterized by urinary pain, incontinence, and irreversible bladder damage (Swainson et al., 2022; McIntyre et al., 2021). This risk appears very low with the intermittent, sub-anesthetic doses used for depression treatment (Swainson et al., 2022), but clinicians should remain vigilant for potential long-term urinary tract issues with unsupervised or frequent use (Swainson et al., 2022).

#### 4.3.3 Psychotomimetic and Dissociative Effects

Feelings of disconnection from reality, perceptual changes, or confused thoughts can still occur with non-parenteral ketamine, especially when doses are increased to overcome low bioavailability (Swainson et al., 2022). Patients must be thoroughly educated about these potential effects, and initial dosing may need to be administered in a supervised setting to ensure safety and tolerability (Swainson et al., 2022).

### 4.4 Subcutaneous and Intramuscular Ketamine

SC injection provides high systemic exposure (≈ 93 % bioavailability) and is logistically simpler than an IV infusion (McIntyre et al., 2021). Small studies of repeated SC injections (e.g., 0.5 mg/kg) over a four-week period have shown the method to be both effective and well-tolerated (Al-Garni et al., 2026). IM injection also yields ≈ 93 % bioavailability with a rapid onset of effect (McIntyre et al., 2021). It is commonly employed in ketamine-assisted psychotherapy (KAP), where a single bolus dose facilitates a therapeutic experience (Swainson et al., 2022) and has been used in clinical settings for acute depression. Evidence for both SC and IM routes comes mainly from smaller studies and case series, lacking the large-scale, controlled data that support IV ketamine or intranasal esketamine (Swainson et al., 2022).

### 5. Comparing Routes: Efficacy, Safety, and Practicality

Ketamine can be delivered by a variety of routes, each with distinct pharmacokinetic properties, efficacy signals, safety considerations, infrastructure requirements, and patterns of clinical access. Table 1. and 2. compare different administration routes: their bioavailability, typical regimen, quantitative efficacy, safety profile, infrastructure cost and access (in a clinical setting).

**Table 1.** Bioavailability, typical regimen and representative efficacy of different administration routes

| Studies | Route | Approx. Bioavailability | Typical Regimen (dose + frequency) | Representative Efficacy* |
|---|---|---|---|---|
| McIntyre et al., 2021; Sakopoulos & Todman, 2025; Phillips et al., 2020; Marcantoni et al., 2020 | **IV racemic ketamine** | ~100 % | 0.5 mg/kg infusion over 40 min; 1-3 × / week (induction) then as needed | Large effect size (SMD ≈ 0.8-1.5); response odds ratio > 7 at 24 h |
| Glue et al., 2024 | **Extended-release oral tablet (R-107)** | Low (≈10-20 % + slow release) | 180 mg PO twice weekly (after responder lead-in) | Mean MADRS reduction 6.1 points vs placebo; relapse ↓ from 70 % to 43 % |
| McIntyre et al., 2021; Sakopoulos & Todman, 2025; Smith-Apeldoorn et al., 2022 | **Standard oral/ compounded SL ketamine** | 10-20 % (PO); 25-30 % (SL) | 0.5-1 mg/kg PO or SL daily or BID (varies) | Modest mood improvement; effect sizes not consistently quantified |
| McIntyre et al., 2021 | **Intranasal racemic ketamine** | ≈45-50 % | 50 mg IN BID (off-label) | limited pooled data |
| Sakopoulos & Todman, 2025; Zaki et al., 2023; McIntyre et al., 2021 | **Intranasal esketamine (FDA-approved)** | ≈45-50 % | 56 mg or 84 mg IN twice weekly (induction) then weekly/bi-weekly | Similar effect size to IV |
| McIntyre et al., 2021; Al-Garni et al., 2026; Smith-Apeldoorn et al., 2022 | **Subcutaneous (SC) ketamine** | ≈90-95 % | 0.5 mg/kg SC twice weekly (maintenance) | limited pooled data |
| McIntyre et al., 2021; Sakopoulos & Todman, 2025; Smith-Apeldoorn et al., 2022 | **Intramuscular (IM) ketamine*** | ≈90-95 % | 0.5-1 mg/kg IM single bolus (KAP) or repeated weekly | limited pooled data |

*Efficacy values are drawn from the most robust available data for each route (randomized trials, meta-analyses, or well-characterized open-label series)

Oral ketamine has the lowest systemic exposure (≈10-20 % bioavailability) because the drug undergoes extensive first-pass metabolism in the liver. Intravenous (IV) infusion provides essentially 100% bioavailability and has the most robust efficacy data. IV administration, however, requires continuous cardiac and hemodynamic monitoring because acute dissociation, hypertension, and tachycardia are common. Subcutaneous (SC) and intramuscular (IM) injections achieve high systemic exposure (≈90-95 %) while eliminating the need for infusion pumps. Because SC and IM injections need only a syringe, a brief observation period, and a trained clinician, they are less resource intensive than IV infusions but still require a medical setting for safe administration. Across all non-parenteral routes, the potential for misuse, diversion, and, with chronic high-dose exposure, bladder toxicity remains a concern; tamper-resistant formulations such as R-107 aim to mitigate diversion risk.

**Table 2.** Main safety concerns, cost and access to different administration routes.

| Studies | Route | Main Safety Concerns | Infrastructure / Cost** | Access (clinical setting) |
|---|---|---|---|---|
| Sakopoulos & Todman, 2025; Shiroma et al., 2020; Phillips et al., 2020 | **IV racemic ketamine** | Transient dissociation, ↑BP/HR, psychotomimetic effects | High - infusion pumps, continuous monitoring, dedicated infusion suite | Limited to specialized infusion centers |
| Glue et al., 2024 | **Extended-release oral tablet (R-107)** | Minimal dissociation, no significant BP rise; tamper-resistant design reduces diversion | Moderate - pharmacy dispensing; periodic clinic visits for safety checks | Potential for home use; broader outpatient access |
| Swainson et al., 2022 | **Standard oral/ compounded SL ketamine** | Variable absorption, higher dose may increase dissociation; higher diversion risk; dizziness, headache, nausea, transient dissociation, modest BP rise | Low - generic tablets or compounding pharmacy; minimal clinic resources | Highly accessible |
| Swainson et al., 2022 | **Intranasal racemic ketamine** | Nasal irritation, transient dissociation; limited safety data | Low-Moderate - nasal spray kit; brief observation | Off-label; access depends on prescriber willingness and compounding |
| Swainson et al., 2022 | **Intranasal esketamine (FDA-approved)** | Transient ↑BP, dissociation; REMS-mandated monitoring | Moderate-High - certified REMS clinic, trained staff | Restricted to certified REMS sites |
| Smith-Apeldoorn et al., 2022 | **Subcutaneous (SC) ketamine** | Brief injection site discomfort; no clinically significant adverse events were reported | Moderate - syringe, brief observation; no infusion equipment | Feasible in outpatient or community clinic |
| Sakopoulos & Todman, 2025; Smith-Apeldoorn et al., 2022 | **Intramuscular (IM) ketamine** | No serious adverse events were reported | Moderate - syringe, short monitoring; feasible in outpatient/ therapy settings | Outpatient psychotherapy settings or urgent care |

**Infrastructure/cost categories are relative: **Low** (pharmacy dispensing, minimal clinical oversight), **Moderate** (basic injection supplies with brief monitoring), **High** (specialized infusion equipment and continuous monitoring).

### 6. Dosing schedules and maintenance strategies

An in-depth analysis of ketamine dosing and maintenance strategies for treatment-resistant depression (TRD) reveals distinct protocols tailored to different administration routes, each comprising an acute induction phase followed by a long-term maintenance phase designed to prevent relapse.

**Table 3.** Administration routes and corresponding acute and maintenance dosing schedules for ketamine-based therapies in TRD

| Studies | Administration Route (Formulation) | Acute (Induction) Schedule - dose, frequency, duration | Maintenance (Continuation) Schedule - dose, frequency, duration |
|---|---|---|---|
| Glue et al., 2024 | **Oral extended-release ketamine tablets (R-107)** | 120 mg once daily for 5 consecutive days | 30 mg, 60 mg, 120 mg or 180 mg taken twice weekly for 12 weeks |
| Anand et al., 2023; Phillips et al., 2020; McIntyre et al., 2021; | **Intravenous (IV) ketamine - standard sub-anesthetic** | 0.5 mg/kg infused over 40 min; schedules reported:<br>6 infusions over 12 days (Mon-Wed-Fri)<br>6 infusions over 3 weeks (2 × weekly)<br>6 infusions over 2 weeks (3 × weekly) | Maintenance regimens are highly variable:<br>Weekly or bi-weekly infusions for up to 1 year (individualized)<br>Once every 1-2 weeks for 8 months<br>Once every 3 weeks (median > 15 months)<br>Weekly after acute phase in some trials |
| Vestring et al., 2024; | **IV ketamine - high-dose protocol (0.75-1 mg/kg)** | 0.5 mg/kg start, rapidly escalated to 0.75-1 mg/kg; given twice weekly for 5 weeks | Average interval ≈ 11 days (≈ weekly) for ≈ 5 maintenance infusions; total maintenance period ranged 7-407 days |
| McIntyre et al., 2021; Zaki et al., 2023 | **Intranasal (IN) esketamine (Spravato®)** | Flexible dose (28, 56 or 84 mg) twice weekly for 4 weeks | After induction, step-down to once weekly for 4 weeks, then weekly or every 2 weeks (or every 4 weeks) based on CGI-S; most participants received weekly/bi-weekly dosing for 1–3 years |
| McIntyre et al., 2021 | **Intranasal racemic ketamine** | Doses of 50 mg (well-tolerated) or 100 mg (limited by sedation) given up to twice weekly in small case series | No standardized maintenance |
| Smith-Apeldoorn et al., 2022 | **Oral racemic ketamine** | Initial observed dose then 2 × daily for 6 weeks (e.g., 1 mg/kg) in some protocols | Long-term use reported up to 3 years with frequencies ranging 2 × weekly to once monthly; dosing typically 1-2 mg/kg |
| Swainson et al., 2022 | **Sublingual (SL) ketamine** | not defined | not defined; limited data |
| Sakopoulos & Todman, 2025; Smith - Apeldoorn et al., 2022 | **Intramuscular (IM) ketamine** | Typical dose 0.5-1 mg/kg; used when IV access unavailable | No explicit maintenance schedule reported; occasional use in acute settings |
| Al-Garni et al., 2026; Smith-Apeldoorn et al., 2022 | **Subcutaneous (SC) ketamine** | Doses comparable to IV (≈0.5 mg/kg) in isolated studies - either flexible (ranging from 0.5 to 0.9 mg/kg) or fixed at 0.5 mg/kg twice weekly for 4 weeks | from once per week up to once every 12 weeks |

*All acute schedules are drawn from the specific study phases described in the source documents; where a study reports multiple acute regimens (e.g., different frequencies), the most commonly used schedule is listed.

**maintenance schedules vary widely across trials; the table captures the range of approaches reported (fixed weekly/bi-weekly, individualized intervals, or “as needed”)

Systematic reviews synthesizing evidence across these modalities have identified key principles for successful long-term maintenance. A crucial finding is that regular, fixed-dosing schedules are significantly more effective at preventing relapse than variable or "as-needed" protocols, with relapse rates of 27.3% for fixed schedules compared to 45.6% for variable regimens (Al-Garni et al., 2026). Furthermore, exploratory analyses have identified several predictors of a more favorable treatment response. These include younger age (<45 years) and a shorter duration of the current depressive episode (<2 years), suggesting that earlier intervention may yield better outcomes and challenging the traditional view of reserving ketamine only for end-stage treatment resistance (Al-Garni et al., 2026). Finally, the integration of psychotherapy has emerged as a powerful adjunct to pharmacotherapy. Concurrent psychotherapy is associated with a significantly lower risk of relapse (Hazard Ratio: 0.72), capitalizing on the window of enhanced neuroplasticity induced by ketamine (Al-Garni et al., 2026). This "convergence" allows therapeutic interventions to more effectively restructure maladaptive cognitive and emotional patterns, thereby consolidating the molecular benefits of ketamine into lasting psychological change (Sakopoulos & Todman, 2025).

## 7. Positioning Ketamine and Esketamine in TRD Algorithms

Ketamine and intranasal esketamine are positioned as rapid-acting interventions for adults with TRD, typically after the failure of at least two conventional antidepressants (McIntyre et al., 2021). Their unique glutamatergic mechanism and rapid onset of action - often within hours to days - differentiate them from all other available pharmacotherapies and place them as key considerations alongside neurostimulation techniques (McIntyre et al., 2023; Sakopoulos & Todman, 2025).

### 7.1 Position Relative to ECT and Other Neuromodulation

Ketamine-based treatments are often considered in the same therapeutic tier as electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (rTMS) for patients with moderate-to-severe TRD (McIntyre et al., 2021). The choice between these modalities is guided by clinical severity, patient preference, contraindications, and accessibility (McIntyre et al., 2021).

#### 7.1.1 Comparison with ECT

**Efficacy:** In a major head-to-head trial involving patients with nonpsychotic TRD, intravenous (IV) ketamine was found to be noninferior to ECT (Anand et al., 2023). The response rate (a decrease of ≥50% in depressive symptoms) was 55.4% in the ketamine group compared to 41.2% in the ECT group (Anand et al., 2023). However, other meta-analyses have suggested that ECT may be superior for achieving remission, indicating that the choice should be individualized (Burcu Kök Kendirlioğlu et al., 2025; Anand et al., 2023).

**Cognitive Side Effects:** Ketamine is generally associated with fewer adverse cognitive effects than ECT (Burcu Kök Kendirlioğlu et al., 2025). The comparative trial noted that ECT was associated with a more significant decrease in memory recall after three weeks of treatment, though this effect recovered during follow-up (Anand et al., 2023).

**Clinical Placement:** Given its favorable side-effect profile and lower stigma, ketamine is an attractive alternative for patients who are hesitant to undergo ECT (Anand et al., 2023). ECT remains a first-line option for severe, catatonic, or psychotic depression, but for nonpsychotic TRD, ketamine presents a viable and non-inferior alternative (Anand et al., 2023).

#### 7.1.2 Use After Neuromodulation Failure

A critical finding for algorithmic placement is that a history of non-response to neurostimulation does not appear to predict a poor response to ketamine (McIntyre et al., 2023; McIntyre et al., 2021). Preliminary evidence indicates that the effectiveness of IV ketamine is not significantly reduced in individuals with TRD who previously failed to respond to ECT or rTMS, making it a logical next-step treatment in these cases (McIntyre et al., 2023; McIntyre et al., 2021).

### 7.2 Combined (Concurrent) Therapeutic Approaches

Combining ketamine with other therapeutic modalities is an emerging strategy aimed at enhancing and prolonging its antidepressant effects.

#### 7.2.1 Ketamine and ECT

While using ketamine as an anesthetic agent during ECT has not been shown to increase the procedure's effectiveness (Burcu Kök Kendirlioğlu et al., 2025), a concurrent protocol where patients receive both treatments on consecutive days has been studied as a potential option for "ultra-TRD" (Burcu Kök Kendirlioğlu et al., 2025). In a retrospective study of patients who had failed to respond to either modality alone, this combined approach resulted in response rates of at least 50% and was recommended as a protocol for the most difficult-to-treat cases (Burcu Kök Kendirlioğlu et al., 2025).

#### 7.2.2 Ketamine-Assisted Psychotherapy (KAP)

This approach leverages the state of heightened neuroplasticity induced by ketamine to enhance the efficacy of psychotherapy (Sakopoulos & Todman, 2025). The dissociative and emotionally open state created by ketamine may help disrupt rigid, negative thought patterns, creating a "therapeutic window" (Sakopoulos & Todman, 2025).

Studies show that combining ketamine infusions with psychotherapy leads to more pronounced and sustained symptom reduction compared to ketamine alone (Sakopoulos & Todman, 2025). Specifically, Cognitive Behavioral Therapy (CBT) has been shown to significantly extend the antidepressant effects of IV ketamine in TRD responders (Sakopoulos & Todman, 2025). This suggests that integrating psychotherapy is a powerful strategy for consolidating ketamine's biological effects into lasting psychological change (Sakopoulos & Todman, 2025; McIntyre et al., 2021).

### 7.3 Sequential Therapeutic Approaches

Most ketamine and esketamine treatment protocols are inherently sequential, involving a distinct acute or induction phase followed by a longer-term maintenance phase to prevent relapse.

A formal sequential strategy used in clinical trials is the "enrichment design" (Glue et al., 2024). In this model, all participants first receive open-label ketamine for a short period (e.g., five days of daily oral extended-release ketamine) (Glue et al., 2024). Only those who show a positive response are then randomized to continue treatment (with different doses or placebo) in a longer double-blind phase (Glue et al., 2024). This approach efficiently identifies patients most likely to benefit before committing them to a lengthy trial and is a model for clinical practice where an initial series of treatments confirms responsiveness before a long-term maintenance plan is established.

## 8. What is “most optimal”? Context-dependant synthesis.

**Table 3.** Key factors that shape the “optimal” ketamine-based strategy for TRD and the trade-offs that must be balanced

| Factor | What matters | Typical trade-off |
|---|---|---|
| **Patient risk profile & comorbidities** | Cardiovascular status (BP/HR spikes with IV or intranasal esketamine)<br>History of psychosis (ketamine’s dissociative effects)<br>Substance-use disorder (misuse potential) | Higher-dose IV/IN routes give faster, larger antidepressant gains but raise hemodynamic and psychotomimetic risks; lower-dose oral or extended-release formulations are safer but may produce a modest response. |
| **Service capacity & infrastructure** | Need for an infusion suite, anesthesia staff (IV ketamine) or REMS-certified clinic (IN esketamine)<br>Ability to monitor patients for 1-2 h post-dose | Intensive settings guarantee safety and limit diversion but limit access; take-home oral tablets are logistically easy and scalable but sacrifice direct supervision. |
| **Cost & reimbursement** | Drug price (generic IV ketamine is cheap; branded IN esketamine is costly)<br>Administration expenses (infusion chair, staff)<br>Insurance coverage | Low drug cost + high procedural cost (IV) versus high drug cost + structured reimbursement (IN); oral formulations are cheapest overall but often lack insurance coverage. |
| **Misuse/ diversion risk** | Potential for recreational use or dose escalation<br>Presence of a REMS program (IN esketamine) vs. unrestricted dispensing (oral) | Supervised IV/IN administration virtually eliminates diversion; take-home oral or sublingual preparations offer convenience but increase misuse risk. |

The most “optimal” route is therefore context-dependent: a patient with uncontrolled hypertension or a substance use disorder history is steered toward low-dose, supervised IV/IN administration (or an alternative neuromodulation such as rTMS); a well-screened, low-risk patient in a resource-limited setting may benefit from an oral extended-release tablet that can be self-administered; and a severely affected, catatonic or psychotic patient may still be best served by ECT, with ketamine reserved for adjunctive or rescue use. Each decision reflects a balance between rapid efficacy, safety, logistical feasibility, cost constraints, and abuse potential (McIntyre et al., 2021).

**9. Gaps, limitations, and future directions**

Current research on ketamine and related agents for treatment-resistant depression is hampered by several critical gaps. First, there is a paucity of direct head-to-toe comparisons across administration routes - intravenous, intranasal, oral, sublingual or intramuscular - making it impossible to delineate relative efficacy, safety, and tolerability profiles (Glue et al., 2024; Swainson et al., 2022; Anand et al., 2023; Al-Garni et al., 2026; McIntyre et al., 2021). Second, long-term safety and neurocognitive outcomes remain poorly characterized; most trials have follow-up periods of weeks to months, and only a few open-label extensions provide limited data, leaving questions about cognitive decline, cardiovascular effects, and abuse potential unanswered (Glue et al., 2024; Vestring et al., 2024; Shiroma et al., 2020; Marcantoni et al., 2020; Swainson et al., 2022; Zaki et al., 2023; Anand et al., 2023; Smith-Apeldoorn et al., 2022; McIntyre et al., 2021). Third, the existing evidence base suffers from methodological limitations such as small sample sizes, heterogeneous TRD definitions, enrichment designs, open-label phases, and lack of active-placebo controls, which restrict generalizability and risk bias (Shiroma et al., 2020; Ionescu et al., 2019; Marcantoni et al., 2020; Seshadri et al., 2024; Sakopoulos & Todman, 2025; Smith-Apeldoorn et al., 2022). Fourth, biomarkers and clinical predictors of route-specific response have not been validated; studies repeatedly note the need for pharmacogenomic, neuroimaging or phenotypic markers to personalize treatment selection (McIntyre et al., 2023; Glue et al., 2024; Marcantoni et al., 2020; Swainson et al., 2022; McIntyre et al., 2021). Future research therefore must (a) conduct well-powered, randomized head-to-head trials of multiple routes; (b) incorporate extended follow-up with comprehensive neurocognitive batteries and safety monitoring; (c) standardize TRD definitions and outcome measures; and (d) systematically evaluate candidate biomarkers and predictors to guide individualized therapy (Shiroma et al., 2020; Zaki et al., 2023; Al-Garni et al., 2026; Seshadri et al., 2024; McIntyre et al., 2021).

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