RESCUING THE RESISTANT: KETAMINE AND ESKETAMINE

IN MODERN DEPRESSION THERAPY

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ANCC ACCREDITED NCPD HOURS: 1.5hrs

TARGET AUDIENCE: RN/APRN

NEED ASSESSMENT

Major depressive disorder (MDD) is one of the most common and disabling mental health conditions worldwide. Unfortunately, about 30% to 40% of people with MDD do not get better even after trying two or more antidepressants. This is known as treatment-resistant depression (TRD), and it creates serious challenges for both patients and healthcare providers. Traditional antidepressants often take weeks to work and may not fully relieve symptoms, especially in people with TRD or those at risk of suicide who need fast and effective help. In recent years, ketamine and esketamine have gained attention as new and promising treatments for TRD. These medications work differently from standard antidepressants by targeting the brain's glutamate system, and they can relieve symptoms within hours. Esketamine, in particular, is now FDA-approved as a nasal spray for TRD. However, many healthcare professionals, including nurses, nurse practitioners, physician assistants, and psychiatrists, are not fully trained or familiar with how to use these treatments safely. There are still questions about choosing the right patients, how to give the treatment, how to monitor for side effects like high blood pressure or dissociation, and how to follow required safety rules like the REMS program. Some providers are also unsure how to manage risks like misuse or dependence. As ketamine clinics continue to grow and esketamine becomes more available, providers need to understand these treatments clearly. This continuing education article is designed to fill those knowledge gaps by explaining how ketamine and esketamine work, how to use them safely and effectively, what

responsibilities healthcare professionals have, and what ethical and legal guidelines must be followed in real-world practice.

OBJECTIVES

Upon completion of this continuing education activity, the RN/APRN will be able to:

- **Describe the pathophysiology and diagnostic criteria of treatment-resistant depression (TRD)** and explain the limitations of traditional antidepressant therapies in this population.
- **Explain the pharmacological mechanisms of action of ketamine and esketamine**, including their effects on glutamatergic neurotransmission and synaptic plasticity.
- **Identify appropriate candidates for ketamine/esketamine treatment** by applying current clinical guidelines, contraindications, and risk assessment strategies.
- **Demonstrate knowledge of safe administration protocols for ketamine and esketamine**, including dosing regimens, monitoring parameters, and the FDA-mandated Risk Evaluation and Mitigation Strategy (REMS) requirements for esketamine.
- **Evaluate the potential adverse effects, safety concerns, and misuse risks** associated with ketamine/esketamine therapy, and develop strategies for effective monitoring and management.
- **Outline the roles and responsibilities of RN/APRNs** in the interdisciplinary management of patients receiving ketamine/esketamine, including patient education, informed consent, and coordination of follow-up care.
- **Discuss ethical, regulatory, and clinical considerations** in the use of ketamine and esketamine for TRD in diverse clinical settings.

GOAL

The goal of this continuing education activity is to empower healthcare professionals, particularly advanced practice providers, with up-to-date, evidence-based knowledge and practical clinical strategies to safely and effectively incorporate ketamine and esketamine into the treatment of patients with treatment-resistant depression (TRD). By enhancing competence in patient selection, administration protocols, safety monitoring, and interdisciplinary care, this activity aims to improve therapeutic outcomes, reduce risks, and support high-quality, patient-centred management of TRD in diverse clinical settings.

INTRODUCTION

Treatment-resistant depression (TRD) poses a critical and complex challenge in modern psychiatric care, affecting nearly one-third of individuals diagnosed with major depressive disorder (MDD). Despite advances in pharmacotherapy, many patients fail to achieve remission with traditional monoaminergic antidepressants, leading to persistent functional impairment, increased healthcare utilization, and elevated risk of suicide. The urgent need for faster-acting and mechanistically novel treatments has driven the exploration of alternative therapeutic pathways beyond serotonin, norepinephrine, and dopamine.

In recent years, ketamine and its S-enantiomer, esketamine, have emerged as transformative agents in the management of TRD. These glutamate-modulating agents offer rapid antidepressant effects, often within hours, marking a paradigm shift in how clinicians approach severe and treatment-refractory depression. Esketamine, approved by the U.S. Food and Drug Administration (FDA) as a nasal spray, has gained increasing adoption in clinical practice under the framework of a strict Risk Evaluation and Mitigation Strategy (REMS) program. Meanwhile, intravenous ketamine, though used off-label, has demonstrated robust evidence supporting its use in specialized settings.

As the landscape of depression treatment evolves, healthcare professionals must stay informed about the safe, ethical, and effective integration of these agents into clinical care. This continuing education activity is designed to equip advanced practice providers with the foundational knowledge and clinical tools needed to optimize outcomes, minimize risks, and uphold high standards of care in patients with TRD.

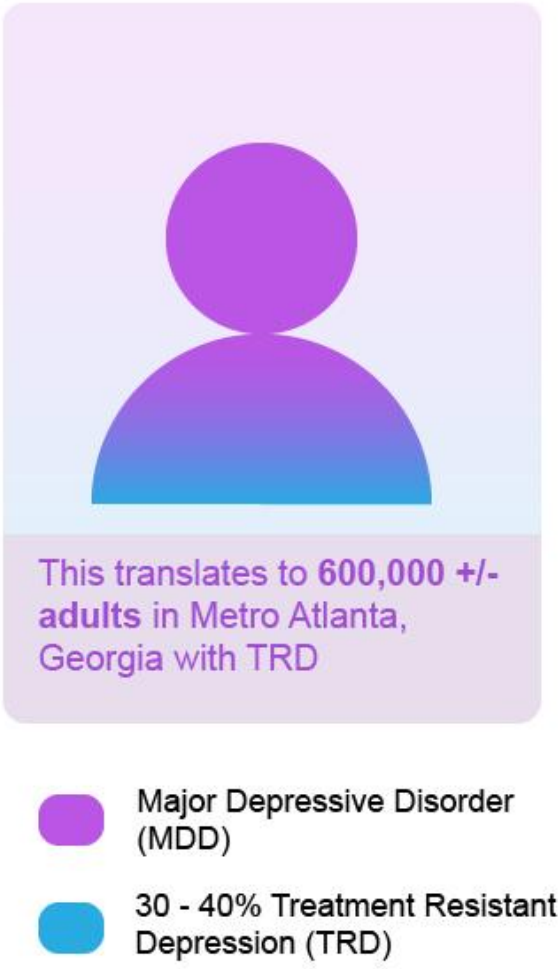
TREATMENT-RESISTANT DEPRESSION (TRD)

DEFINITION

Treatment-resistant depression (TRD) refers to a major depressive disorder (MDD) that does not respond adequately to at least two different antidepressant treatments of adequate dose and duration, from different pharmacological classes. While there is no universally agreed-upon definition, most clinical guidelines consider TRD present when a patient fails to achieve remission despite multiple therapeutic trials, including both pharmacologic and non-pharmacologic interventions.

TRD represents a significant clinical and public health concern, often associated with

prolonged suffering, increased risk of suicide, higher rates of comorbidities, and functional impairment across occupational, social, and physical domains.

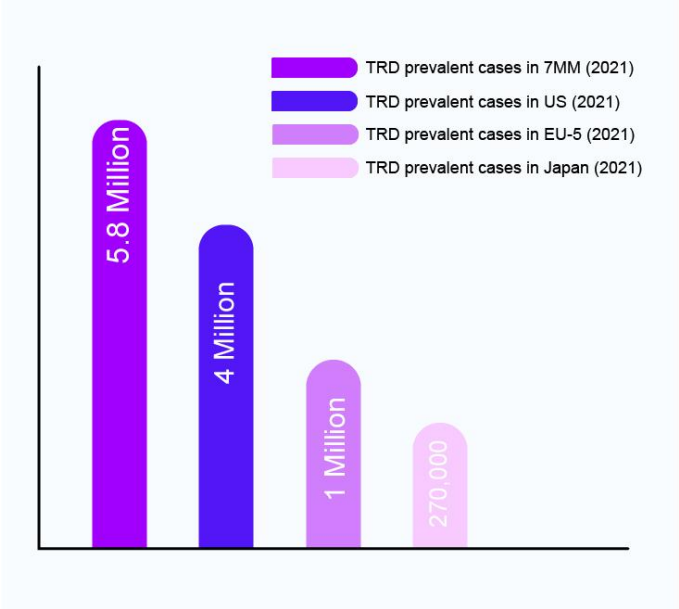


EPIDEMIOLOGY

Major depressive disorder affects approximately 280 million people globally, with lifetime prevalence rates ranging from 10% to 20%. Among those diagnosed with MDD, it is estimated that **30% to 40%** will not respond adequately to at least two trials of antidepressants, meeting criteria for TRD.

Key epidemiological observations include:

- **Higher prevalence of TRD** in females, individuals with early-onset depression, and those with comorbid psychiatric or medical conditions.
- **Increased healthcare burden**: Patients with TRD utilize more medical resources, including hospitalizations, emergency visits, and outpatient care.
- **Elevated suicide risk**: Individuals with TRD have a notably higher risk of suicide compared to treatment-responsive patients.



EPIDEMIOLOGICAL INSIGHTS ACROSS THE 7MM

Treatment-resistant depression (TRD) presents a significant public health burden across the seven major markets (7MM) comprising the United States, Germany,

France, Spain, Italy, the United Kingdom, and Japan. A comparative analysis of peer-reviewed literature, national health databases, and expert clinical opinions reveals a marked geographic variation in TRD prevalence within these regions.

As of 2021, an estimated 5.8 million individuals across the 7MM were affected by TRD. The United States accounted for the largest share of these cases, reflecting both a high baseline prevalence of major depressive disorder and increased recognition of treatment resistance in clinical practice. The EU5 countries (Germany, France, Italy, Spain, and the UK) collectively accounted for over 1.5 million prevalent cases. Within this group, Germany reported the highest number of TRD cases (~560,000 in 2021), a figure projected to slightly decline to ~550,000 by 2032 due to demographic shifts, including a declining population. In contrast, Italy exhibited the lowest TRD prevalence (~127,000 cases in 2021), with a modest projected increase to ~130,000 by 2032.

Japan, representing the Asian segment of the 7MM, reported approximately 270,000 TRD cases in 2021. These figures highlight the global reach of TRD and underscore the pressing need for innovative treatment strategies and clinician education tailored to regional epidemiologic and healthcare system contexts.

PATHOPHYSIOLOGY OF TRD

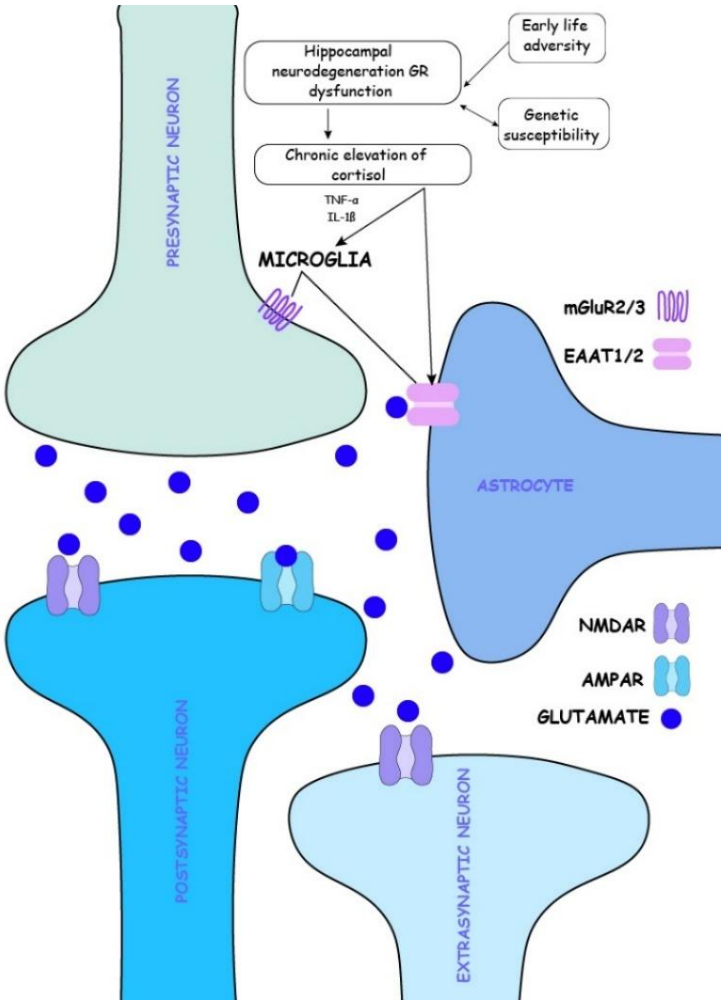
The pathophysiology of TRD is multifactorial and incompletely understood. Traditional antidepressants target monoaminergic pathways, particularly serotonin (5-HT), norepinephrine (NE), and dopamine (DA), yet this approach appears insufficient in a subset of patients with TRD. Proposed mechanisms underlying TRD include:

GLUTAMATERGIC DYSREGULATION IN TRD

Emerging neuroscientific research underscores the critical involvement of the glutamatergic system, particularly glutamate, the brain's principal excitatory neurotransmitter, in the pathophysiology of treatment-resistant depression (TRD). Unlike traditional monoaminergic theories, which focus on serotonin, norepinephrine, and dopamine imbalances, the glutamatergic hypothesis highlights dysregulation at the level of **N-methyl-D-aspartate (NMDA) receptors** and downstream signalling pathways.

In TRD, dysfunction in NMDA receptor activity and impaired synaptic plasticity, especially within the prefrontal cortex and limbic regions, are thought to contribute to

persistent depressive symptoms, anhedonia, and cognitive disturbances. These alterations disrupt neuroplastic mechanisms necessary for emotional regulation and resilience, offering a mechanistic rationale for the observed inefficacy of conventional antidepressants in this population. This evolving understanding of glutamatergic dysregulation has paved the way for novel interventions such as **ketamine and esketamine**, which target this system to induce rapid antidepressant effects through mechanisms distinct from traditional therapies.



- **Neuroinflammation**

  Patients with TRD often show increased levels of inflammatory markers such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). These pro-inflammatory cytokines may interfere with neurotransmitter systems and reduce the effectiveness of antidepressant treatments.

- **HPA Axis Dysregulation**

  Chronic stress and depression are associated with abnormal activity of the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels. This hormonal imbalance can damage brain areas involved in mood regulation, such as the hippocampus, and impair neurogenesis.

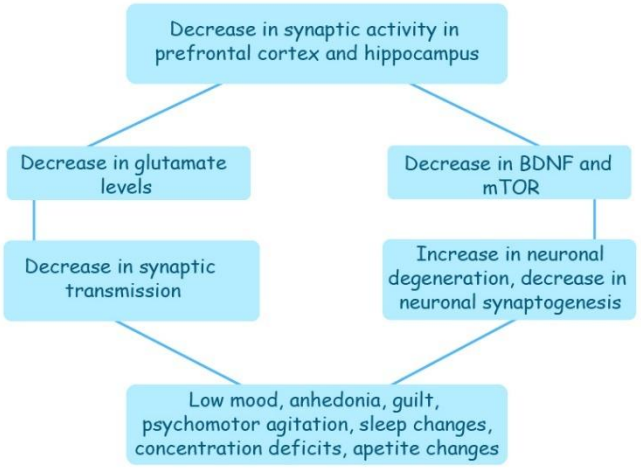
- **Neurotrophic Impairment**

  Lower levels of brain-derived neurotrophic factor (BDNF), a protein essential for neuron growth and survival, have been found in individuals with TRD. This reduction may weaken neural connections and the brain's ability to adapt to stress and emotional challenges.

- **Genetic and Epigenetic Factors**

  Variations in genes that regulate neurotransmitter function, receptor sensitivity, and neuroplasticity can influence how individuals respond to antidepressants. Epigenetic changes, alterations in gene expression without

DNA sequence changes, may also play a role in TRD.



DIAGNOSTIC CRITERIA

While TRD is not a standalone diagnosis in DSM-5, it is operationally defined based on treatment history. Commonly accepted diagnostic criteria include:

1. **Confirmed diagnosis of Major Depressive Disorder (MDD)**, based on DSM-5 criteria.
2. **Failure to respond to at least two antidepressant trials** from different pharmacological classes.
3. **Adequate dose and duration of each antidepressant trial**, typically defined as:
   - **Dose**: Within or above the therapeutic range.
   - **Duration**: At least 4–6 weeks per trial.
4. **Objective assessment tools** such as the Antidepressant Treatment History Form (ATHF) or the Maudsley Staging Method (MSM) are often used to evaluate treatment resistance severity.

Exclusion of pseudo-resistance is essential, as nonadherence, incorrect diagnosis (e.g., bipolar depression), subtherapeutic dosing, or comorbidities (e.g., substance use, personality disorders) may falsely suggest TRD.

LIMITATIONS OF TRADITIONAL ANTIDEPRESSANTS IN TRD

Traditional antidepressants, including SSRIs, SNRIs, tricyclics, and MAOIs, are limited in TRD due to several factors:

- **Delayed onset of action**: Therapeutic effects typically take 4–6 weeks, which can be problematic in patients with severe symptoms or suicidality.
- **Monoaminergic plateau**: Many patients do not achieve full remission, even with augmentation or switching strategies within the monoaminergic class.
- **Adverse effects**: Poor tolerability may contribute to treatment discontinuation or inadequate adherence.
- **Lack of efficacy in certain biological subtypes**: Patients with significant neuroinflammatory or glutamatergic dysfunction may not respond to monoaminergic modulation alone.

Treatment-Resistant Depression (TRD) represent a complex and multifactorial con-

dition marked by inadequate response to standard antidepressant therapies. Its underlying pathophysiology extends beyond traditional monoamine imbalances to include glutamatergic dysfunction, neuroinflammat - ion, HPA axis dysregulation, neurotrophic deficits, and genetic influences, each contributing to the persistence and severity of depressive symptoms. Traditional antidepressants often fail to address these diverse mechanisms, highlighting the need for innovative, mechanism-based interventions. A clear understanding of TRD's diagnostic criteria and pathobiological underpinnings is essential for identifying appropriate candidates for novel therapies such as ketamine and esketamine, and for improving outcomes in this difficult-to-treat population.

PHARMACOLOGICAL MECHANISMS OF KETAMINE AND ESKETAMINE

Ketamine and esketamine represent a paradigm shift in the treatment of major depressive disorder (MDD), particularly in cases of **treatment-resistant depression (TRD)**. Unlike conventional antidepressants, which primarily target monoaminergic systems (serotonin, norepinephrine, and dopamine), ketamine and esketamine exert their effects through the **glutamatergic system**, resulting in rapid and robust antidepressant responses.

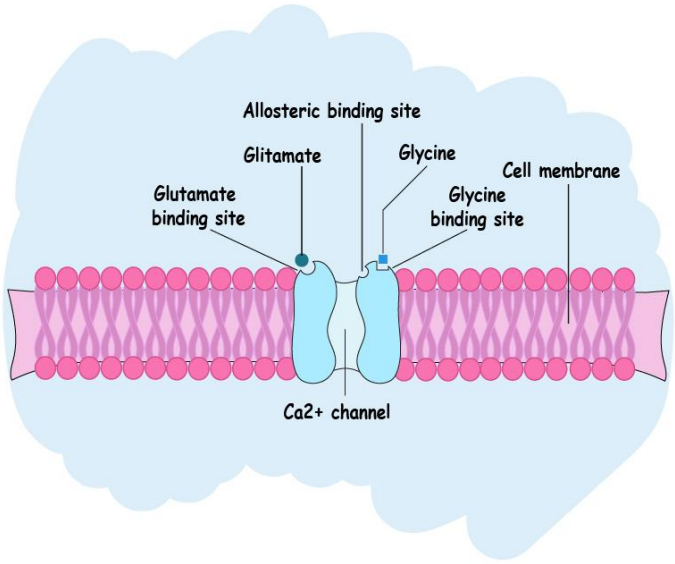
A 2024 systematic review found substantial antidepressant effects for ketamine, though with variability in individual response.

1. NMDA Receptor Antagonism

The primary mechanism of both ketamine and esketamine involves **noncompetitive antagonism of the N-methyl-D-aspartate (NMDA) receptor**, a subtype of glutamate receptor. By blocking NMDA receptors located on **GABAergic interneurons**, ketamine reduces the inhibitory tone these interneurons exert on excitatory glutamatergic neurons.

Result: This leads to a **transient burst of glutamate release** in the prefrontal cortex.

Significance: This glutamate surge initiates downstream signalling cascades that are crucial for the antidepressant effect.



2. Activation of AMPA Receptors

The surge in extracellular glutamate stimulates **α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors**, another type of glutamate receptor. AMPA receptor activation is essential for the **rapid antidepressant action**. It shifts the balance of glutamatergic signalling away from NMDA and toward AMPA meditated neurotransmission. This **AMPA-to-NMDA throughput shift** is thought to be a key driver of synaptic potentiation and mood improvement.

Another comprehensive overview of reviews (OoR) published in 2024 synthesized 26 studies and reaffirmed the rapid efficacy of ketamine and esketamine for both unipolar and bipolar depression, as well as their anti-suicidal effects

3. mTOR Pathway Activation and Synaptogenesis

AMPA receptor activation triggers **intracellular signalling cascades**, most notably the **mammalian target of rapamycin (mTOR) pathway**.

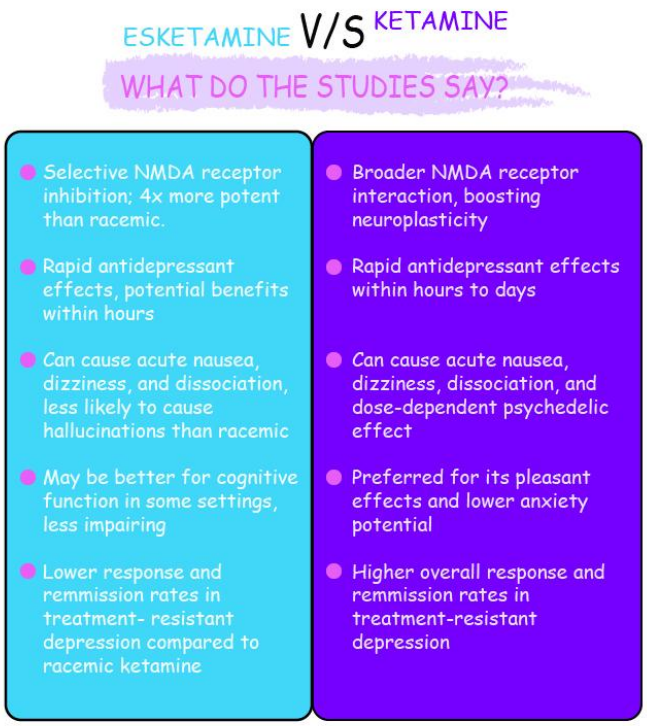
- The mTOR pathway promotes **increased expression of brain-derived neurotrophic factor (BDNF)** and initiates **synaptogenesis** (formation of new synapses).
- This synaptic remodelling primarily occurs in regions such as the **prefrontal cortex and hippocampus**, which are involved in emotion regulation and cognition.
- The enhancement of **synaptic connectivity and plasticity** is believed to reverse the structural and functional deficits seen in chronic depression.

4. Additional Mechanisms and Neurobiological Effects

- **Esketamine**, the S-enantiomer of ketamine, has a **higher affinity for the NMDA receptor** and may offer **greater potency** and **fewer psychotomimetic effects** compared to racemic ketamine.
- Both agents also influence **monoaminergic systems**, **opioid receptors**, and **anti-inflammatory pathways**, although these roles are secondary.

- **Reduction of pro-inflammatory cytokines** and **normalization of the HPA axis** may also contribute to sustained mood improvement.

A 2022 pilot study evaluated intranasal esketamine in patients with both TRD and PTSD, showing that two-thirds achieved response and one-third achieved remission after six months, with notable reductions in suicidality and PTSD symptoms when combined with trauma-focused therapy



CLINICAL IMPLICATIONS

The rapid onset of action(within hours) differentiate ketamine and esketamine from traditional antidepressants that typically require weeks for full effects

These agents are particularly beneficial in avute suicidal ideation and TRD, where fast symptom itself is critical

Their mechanistically novel approach addresses key deficits in synaptic function and neuroplasticity that monoaminergic agents fails to target

IDENTIFYING APPROPRIATE CANDIDATES FOR KETAMINE AND ESKETAMINE THERAPY IN TREATMENT-RESISTANT DEPRESSION

Precision in patient selection is a cornerstone of effective and safe implementation of ketamine and esketamine therapy in clinical practice. Both agents have emerged as valuable options for individuals with treatment-resistant depression (TRD), yet their use necessitates adherence to stringent clinical criteria, risk stratification, and regulatory compliance to optimize outcomes and minimize adverse effects.

EVIDENCE-BASED INCLUSION CRITERIA

The **primary indication** for ketamine and esketamine is **major depressive disorder (MDD) with inadequate response to at least two different antidepressant regimens of adequate dose and duration**, defining TRD. Esketamine, specifically, has received FDA approval for:

- **Treatment-resistant depression**, in conjunction with an oral antidepressant.
- **Major depressive disorder with acute suicidal ideation or behaviour**, offering a time-sensitive intervention for high-risk patients.

Candidates for ketamine/esketamine therapy should meet the following clinical criteria:

- Documented diagnosis of MDD per **DSM-5** criteria.
- History of **nonresponse or intolerance** to two or more antidepressants from different pharmacologic classes.
- No prior history of **psychotic spectrum disorders**, given potential for psychotomimetic side effects.
- Capability and willingness to comply with **supervised administration protocols**, particularly in REMS-certified centres for esketamine.

EXCLUSION CRITERIA AND SAFETY PRECAUTIONS

Given the neuropsychiatric and hemodynamic effects of these agents, certain patients are at elevated risk and are generally excluded unless risk is mitigated:

- **Uncontrolled hypertension** or significant cardiovascular disease (e.g., recent MI, aneurysm, unstable angina).
- **Current or past diagnosis of psychosis**, schizophrenia, or bipolar I disorder.
- **Active substance use disorder**, particularly involving dissociative, hallucinogenic, or sedative-hypnotic substances.
- **Pregnancy or lactation**, due to unknown foetal and neonatal risk profiles.
- **Intracranial pathology**, such as elevated intracranial pressure or recent stroke.
- Inability to comply with monitoring requirements or absence of access to a **REMS-certified treatment setting** (for esketamine).

RISK ASSESSMENT STRATEGIES

Before initiation, a structured and multidisciplinary risk–benefit assessment is essential. Best practices include:

- **Structured psychiatric evaluation** to confirm TRD diagnosis and assess treatment history.
- **Standardized symptom rating tools** (e.g., MADRS, PHQ-9) for baseline and ongoing assessment.
- **Cardiovascular screening**, including blood pressure monitoring and cardiac history review.
- **Suicide risk assessment** using validated tools (e.g., C-SSRS), particularly in patients receiving esketamine for suicidal ideation.
- **Informed consent process**, emphasizing treatment expectations, potential side effects, and safety monitoring.

ALIGNMENT WITH CLINICAL GUIDELINES

Professional societies and regulatory bodies, including the **American Psychiatric Association (APA)** and the **FDA Risk Evaluation and Mitigation Strategy (REMS) program**, recommend strict adherence to treatment protocols:

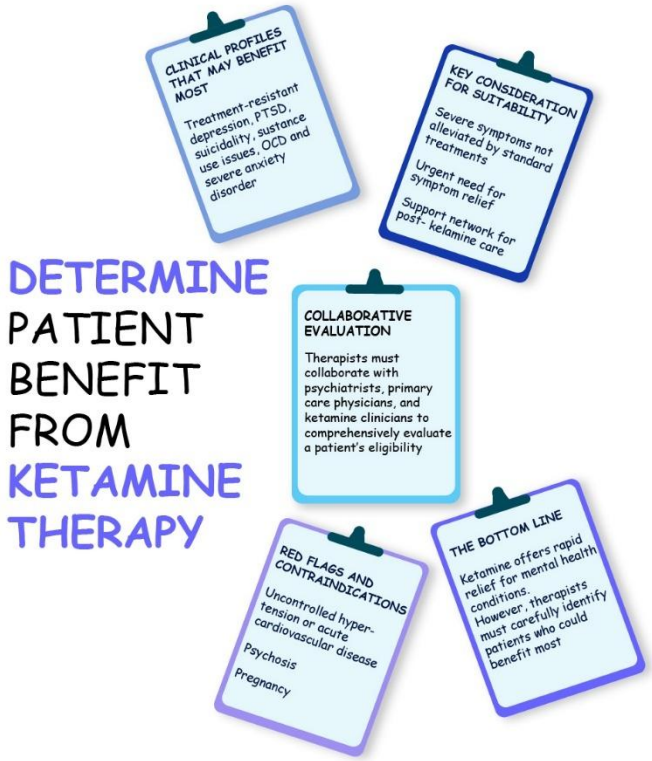
- **Esketamine must be administered in certified healthcare settings** under observation, with vital sign monitoring pre- and post-dose.
- **Ketamine, when used off-label**, should be delivered through specialized clinics with trained staff, emergency preparedness, and ethical oversight.
- **Treatment sessions must incorporate monitoring for dissociative symptoms, BP changes, and sedation**, with at least two hours of observation.

CLINICAL INTEGRATION AND MULTIDISCIPLINARY COORDINATION

The decision to initiate ketamine or esketamine should involve collaborative input from:

- **Psychiatrists or prescribing APRNs**, who oversee diagnosis and prescribing.
- **Nurses and clinical pharmacists**, responsible for administration, patient education, and adverse effect monitoring.
- **Case managers and social workers**, ensuring adherence, follow-up, and support.

This multidisciplinary approach fosters **personalized treatment planning**, optimizes clinical response, and ensures compliance with legal and ethical standards of care.



SAFE ADMINISTRATION PROTOCOLS FOR KETAMINE AND ESKETAMINE IN TREATMENT-RESISTANT DEPRESSION

The therapeutic use of **ketamine and esketamine** for treatment-resistant depression (TRD) necessitates adherence to **rigorous safety protocols**, structured dosing strategies, and regulatory requirements to minimize risks and optimize patient outcomes. The administration of these agents must be performed in controlled clinical settings, supported by vigilant monitoring and multidisciplinary oversight.

1. Clinical Setting and Oversight

- **Controlled Environment**: Both ketamine and esketamine must be administered in a certified medical facility (e.g., hospital, clinic, or specialized infusion center) equipped to manage potential adverse effects.
  - Esketamine (Spravato) is only available through a **Risk Evaluation and Mitigation Strategy (REMS)** program in the U.S., requiring administration in REMS-certified facilities.
- **Multidisciplinary Team**: Administration should involve psychiatrists, anaesthesiologists, or trained clinicians, with support from nurses and emergency response personnel.
- **Pre-Administration Screening**:
  - Comprehensive medical and psychiatric history to identify contraindications (e.g., uncontrolled hypertension, history of psychosis, substance abuse).
  - Baseline assessments, including vital signs, mental status, and risk of suicidality.
  - Exclusion of patients with active substance use disorders or recent use of monoamine oxidase inhibitors (MAOIs).

2. Dosing Strategies

- **Ketamine (Intravenous, IV)**:

- **Standard Dose**: 0.5 mg/kg body weight, infused over 40 minutes, typically administered 2–3 times per week for 2–4 weeks during the induction phase.
- **Maintenance Phase**: Doses may be tapered to once weekly or biweekly, based on clinical response.
- **Titration**: Adjustments are made based on patient response and tolerability, with doses ranging from 0.25–1.0 mg/kg in some protocols.

▪ **Esketamine (Intranasal)**:

- **Induction Phase**: 56 mg (initial dose) or 84 mg, administered twice weekly for 4 weeks.
- **Maintenance Phase**: 56–84 mg weekly or biweekly, depending on response.
- **Administration**: Self-administered under direct supervision of a healthcare provider, with a 5-minute rest between nasal sprays to minimize side effects.

▪ **Individualization**:

Dosing must account for patient-specific factors (e.g., weight, comorbidities, and prior response to treatment).

3. Monitoring During Administration

▪ **Intra-Administration**:

- Continuous monitoring of vital signs (blood pressure, heart rate, oxygen saturation) due to risks of hypertension, tachycardia, or respiratory depression.
- Observation for dissociative symptoms, sedation, or psychotomimetic effects (e.g., hallucinations).
- For esketamine, patients must remain under observation for **at least 2 hours** post-administration to monitor for side effects and ensure stabilization.

▪ **Post-Administration**:

- Patients must not drive or operate machinery for at least 24 hours due to potential psychomotor impairment.
- Assessment of mental status and suicidal ideation before discharge.
- For esketamine, compliance with REMS mandates post-dose monitoring and documentation.

PARAMETER	KETAMINE (IV)	ESKATAMINE (INTRANASAL)
Blood Pressure & Heart Rate	Baseline, every 15 mins during infusion, and post-dose until stable.	Pre-dose, 40 mins post-dose, and until return to baseline.
Mental Status	Baseline psychiatric evaluation; monitor for dissociation, agitation, and sedation.	Use of standardized tools to assess dissociation (e.g., CADSS).
Sedation Scale	Document sedation using tools (e.g., RASS) throughout administration.	Assess sedation at intervals and post-dose.
Suicide Risk	Regular assessment using tools (e.g., C-SSRS), especially in suicidal ideation cases.	Mandatory pre- and post-dose suicide screening.
Respiratory Rate /O2 Sat	Continuous during infusion; oxygen and resuscitation equipment on hand.	Spot checks pre/post-dose. Rarely causes respiratory depression.
Recovery Time	Monitor 1-2 hours post-infusion until alert and hemodynamically stable.	Observe for ≥2 hours post -dose in a REMS-certified facility.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR ESKETAMINE: DETAILED OVERVIEW

The U.S. Food and Drug Administration (FDA) mandates that **esketamine** (Spravato), approved for treatment-resistant depression (TRD) and major depressive disorder with acute suicidal ideation or behaviour, be administered under a **Risk Evaluation and Mitigation Strategy (REMS)** program. The REMS is designed to mitigate serious risks, including **sedation**, **dissociation**, **abuse/misuse**, and **suicidal thoughts/behaviours**, while ensuring safe and controlled administration. Below is a detailed breakdown of the REMS requirements as outlined, with additional context for clarity.

1. Prescriber Certification

Prescribers must be certified under the Spravato REMS Program to prescribe esketamine. Certification ensures that prescribers are equipped to manage the unique risks associated with the drug.

❖ **Enrollment**:

- Prescribers must enrol in the Spravato REMS Program by completing the **Prescriber Enrolment Form** and agreeing to comply with REMS requirements.
- Enrolment is typically done through the Spravato REMS website or authorized channels provided by the manufacturer (Janssen Pharmaceuticals).

❖ **Demonstrated Understanding**:

- **Risk of Sedation and Dissociation**:
  - Sedation can range from mild drowsiness to significant impairment, requiring post-dose monitoring for at least 2 hours.
  - Dissociation (e.g., feeling disconnected from reality, perceptual distortions) is common and may be distressing. Prescribers must understand how to identify, manage, and reassure patients experiencing these effects.
- **Risk of Abuse and Misuse**:
  - Esketamine, a Schedule III controlled substance, has a potential for abuse due to its ketamine-derived psychoactive properties.
  - Prescribers must recognize signs of misuse (e.g., seeking higher doses or unauthorized access) and implement strategies to prevent diversion.
- **Proper Patient Selection**:

- Prescribers must evaluate patients for suitability, excluding those with contraindications such as:
  - History of psychosis or active substance use disorders.
  - Uncontrolled hypertension or recent cardiovascular events.
  - Hypersensitivity to esketamine or ketamine.
- Patients must have a confirmed diagnosis of TRD or MDD with acute suicidality, supported by prior treatment failures (e.g., inadequate response to at least two antidepressants).

- **Monitoring Requirements**:
  - Prescribers must ensure patients are monitored during and after administration for vital signs (blood pressure, heart rate, oxygen saturation) and mental status (dissociation, sedation, suicidal ideation).
  - They must document compliance with REMS protocols, including post-dose observation and patient outcomes.

❖ **Training**:

- Prescribers complete mandatory training on REMS protocols, esketamine's pharmacology, and risk management.
- Training includes guidance on patient counselling, informed consent, and coordination with certified healthcare settings.

2. Healthcare Setting Certification

Healthcare facilities administering esketamine must be REMS-certified to ensure a controlled environment capable of managing risks.

❖ **Certification Process**:

- Facilities (e.g., clinics, hospitals, or outpatient centres) must enrol in the Spravato REMS Program by submitting a **Healthcare Setting Enrolment Form**.
- Certification requires designation of an authorized representative to oversee compliance with REMS requirements.

❖ **Capabilities for Continuous Monitoring**:

- Facilities must have equipment and trained staff to monitor:
  - **Vital Signs**: Blood pressure, heart rate, and oxygen saturation, as esketamine can cause transient hypertension or, rarely, respiratory depression.
  - **Mental Status**: Assessment for dissociation, sedation, or

psychotomimetic effects (e.g., hallucinations).

- Monitoring is continuous during administration and for at least **2 hours post-dose**, as mandated by the REMS program.
- Facilities must have protocols for managing adverse events, including access to emergency interventions (e.g., antihypertensive medications, airway support).

❖ **Post-Dose Observation**:

- Patients must remain in the facility for at least **2 hours** after administration to ensure stabilization of vital signs and resolution of sedation or dissociation.
- Staff must assess patients for readiness to leave, confirming no significant impairment or suicidal ideation.
- Patients are discharged only with a responsible caregiver or transportation arranged, as they are prohibited from driving or operating machinery until the next day.

❖ **No Take-Home Use**:

- Esketamine is administered exclusively in a certified healthcare setting under direct supervision.
- Patients are not permitted to take esketamine home, reducing the risk of misuse or diversion.
- The intranasal device is self-administered by the patient but only under the guidance of a healthcare provider, with doses (56 mg or 84 mg) delivered in a controlled manner.

❖ **Documentation**:

- Facilities must maintain records of each administration, including dose, monitoring outcomes, adverse events, and post-dose observation periods.
- Compliance with REMS is subject to audits by the FDA or the manufacturer.

3. Pharmacy Certification

Pharmacies dispensing esketamine must be REMS-certified to ensure controlled distribution and prevent unauthorized access.

❖ **Certification Requirements**:

- Pharmacies must enrol in the Spravato REMS Program and designate an authorized representative to oversee compliance.
- Only REMS-certified pharmacies can dispense esketamine, and they are restricted to supplying it directly to REMS-certified healthcare settings.

❖ **Dispensing Restrictions**:

- Esketamine is not dispensed to patients or retail pharmacies.
- Pharmacies ship esketamine directly to certified healthcare

facilities for use during supervised administration sessions.

- Each shipment is tracked to ensure accountability and prevent diversion.

❖ **Inventory Control**:

- Certified pharmacies must maintain strict inventory records, documenting receipt, storage, and distribution of esketamine.
- Secure storage is required to prevent theft or unauthorized access, given esketamine's Schedule III status.

4. Patient Education and Consent

Patients must receive comprehensive counselling and provide informed consent before starting esketamine treatment, ensuring they understand the risks, requirements, and responsibilities.

❖ **Counselling on Risks and Side Effects**:

- **Potential Side Effects**:
  - **Sedation**: Patients may feel drowsy or impaired, requiring a 2-hour observation period.
  - **Dissociation**: Perceptual changes or feelings of detachment are common but typically resolve within hours. Patients are reassured that these effects are transient and monitored.
  - **Other Side Effects**: Nausea, dizziness, increased blood pressure, or headache may occur.
- **Post-Treatment Recovery Time**:
  - Patients are informed that they cannot drive, operate machinery, or engage in activities requiring full alertness until the next day (at least 24 hours post-dose).
  - They must arrange transportation home with a caregiver or service.
- **Risks of Long-Term Use**:
  - **Dependency and Abuse Potential**: Patients are educated about esketamine's Schedule III status and the risk of psychological dependence or misuse, particularly if they have a history of substance abuse.
  - **Bladder Toxicity**: Chronic use may lead to urinary tract issues (e.g., cystitis), as seen with ketamine. Patients are advised to report symptoms like frequent urination or pain.
  - **Cognitive Effects**: Limited data suggest potential cognitive impacts with prolonged use; patients are informed of the need for periodic assessments.

❖ **Informed Consent**:

- Patients must sign a **Patient Enrollment Form** to participate in the REMS program, acknowledging they understand the risks, monitoring requirements, and restrictions (e.g., no take-home use, no driving post-dose).
- Consent includes agreement to comply with follow-up appointments and report adverse effects promptly.

❖ **Ongoing Education**:

- Patients receive repeated counseling at each session to reinforce awareness of side effects, restrictions, and the importance of adherence to the treatment schedule.
- Educational materials (e.g., brochures, videos) provided by the REMS program or manufacturer are used to support understanding.

❖ **Transportation Arrangements**:

- Patients are required to confirm transportation plans before each session, ensuring they have a responsible caregiver or service to take them home.
- Facilities verify these arrangements before discharging patients.

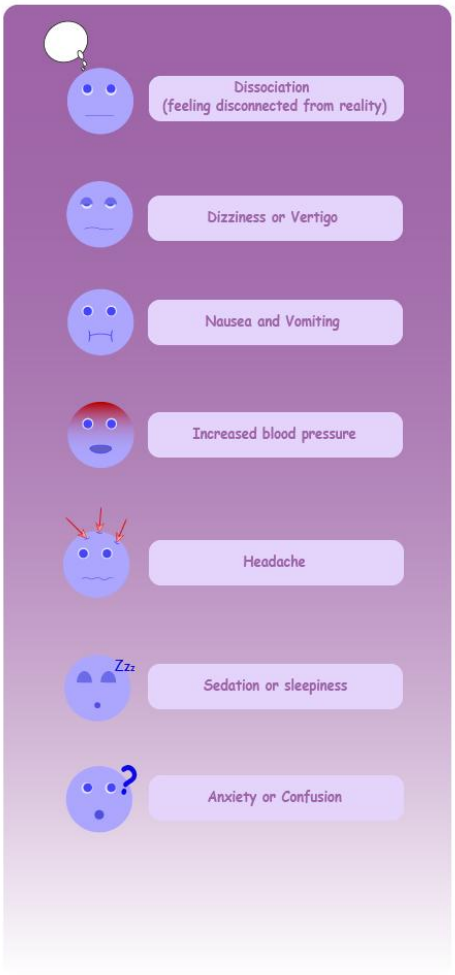
The Spravato REMS Program is a robust framework ensuring the safe use of esketamine for TRD by enforcing strict controls on prescribing, administration, and dispensing. Prescriber certification guarantees expertise in risk management, healthcare setting certification ensures a controlled environment with continuous monitoring, pharmacy certification prevents unauthorized access, and patient education/consent empowers informed participation. These measures collectively minimize risks like sedation, dissociation, and abuse while enabling access to a critical treatment for patients with TRD.

ADVERSE EFFECTS, SAFETY CONCERNS, AND RISK MANAGEMENT OF KETAMINE/ESKETAMINE THERAPY

Ketamine and esketamine offer hope for patients with treatment-resistant depression (TRD), but they come with potential side effects and safety issues that need careful management. Understanding these risks helps ensure safe and effective use.

1. Common adverse effects

Patients may experience temporary side effects, especially during or shortly after treatment:



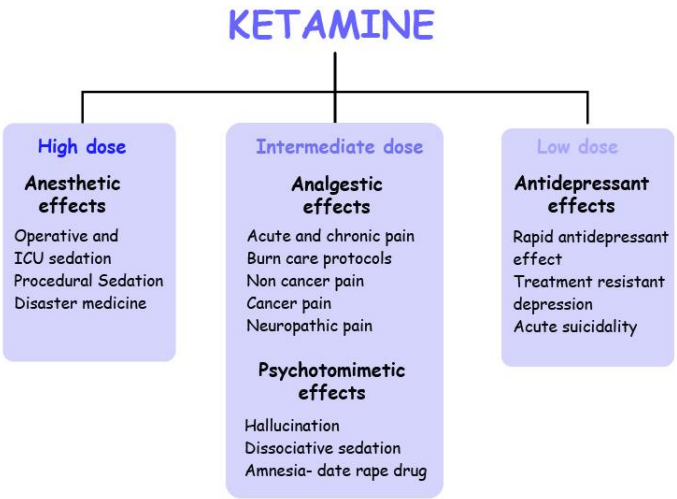
These effects usually wear off within a few hours, but patients must be monitored during this time.

2. Safety Concerns

- **Cardiovascular Effects**: Both drugs can raise blood pressure and heart rate, so they should be used carefully in patients with heart conditions.
- **Mental Health Risks**: Some patients may experience hallucinations, agitation, or worsening mood. Suicide risk must be closely monitored.
- **Driving Impairment**: Patients should not drive or operate heavy machinery until the next day after receiving treatment.
- **Long-Term Use**: Repeated use may lead to problems like memory issues or bladder irritation (mostly with high-dose or recreational use).

3. Risk of Misuse and Dependence

- **Abuse Potential**: Ketamine is a known substance of abuse. Although esketamine has a lower risk, both drugs require careful use.
- **REMS Program**: To reduce misuse, esketamine can only be given in certified clinics under the FDA's **Risk Evaluation and Mitigation Strategy (REMS)** program.



4. Monitoring and Management Strategies

STRATEGY	PURPOSE
Pre-treatment screening	Identify heart issues, substance abuse history, or psychiatric instability.
Vital sign monitoring	Track blood pressure and heart rate before and after treatment.
Mental health assessment	Monitor mood, thoughts of self-harm, or dissociative symptoms.
Post-dose observation	Patients stay in the clinic for at least 2 hours.
Follow-up appointments	Assess long-term effects and overall response to treatment.
Patient education	Inform about side effects, safety rules, and the importance of support.

While ketamine and esketamine can be life-changing for people with TRD, they must be used with caution. Careful monitoring, patient education, and safety planning are essential to minimize risks and ensure the best possible outcomes.

APRNS' ROLES IN INTERDISCIPLINARY MANAGEMENT OF KETAMINE/ESKETAMINE THERAPY

Advanced Practice Registered Nurses (APRNs), including Nurse Practitioners and Clinical Nurse Specialists, play a vital role in ensuring the safe, ethical, and effective use of ketamine and esketamine in patients with treatment-resistant depression (TRD). Their responsibilities span across clinical, educational, ethical, and collaborative domains, and are essential for optimal patient outcomes.

1. Patient Assessment and Selection

- **Conduct comprehensive psychiatric and medical evaluations** to assess candidacy for ketamine/esketamine therapy.
- **Screen for contraindications** such as uncontrolled hypertension, active substance use disorder, or psychosis.
- **Evaluate baseline mental status**, suicide risk, and functional impairment.
- Participate in interdisciplinary case reviews to confirm appropriateness of therapy.

2. Patient Education and Informed Consent

- Provide clear, evidence-based education to patients and families regarding:
  - Mechanism of action of ketamine/esketamine
  - Expected benefits and potential risks
  - Dosing protocol and monitoring requirements
  - REMS program regulations and clinic-based administration
- Facilitate **informed consent discussions**, ensuring patients understand:
  - The off-label or approved use (depending on the agent)

- Risk of side effects, including dissociation and hypertension
- Safety precautions (e.g., no driving post-treatment)

3. Safe Administration and Monitoring

- Participate in or oversee **intranasal esketamine administration** in REMS-certified settings or **intravenous/intramuscular ketamine** infusions (as per institutional protocol).
- Monitor **vital signs** and **mental status** pre-, during, and post-treatment.
- Respond to emergent symptoms such as hypertensive episodes, dissociation, or panic.
- Document therapeutic response and adverse events in collaboration with the interdisciplinary team.

4. Coordination of Interdisciplinary Care

- Collaborate with psychiatrists, psychologists, primary care providers, pharmacists, and social workers to:
  - Develop individualized treatment plans
  - Optimize co-prescribed psychotropic medications
  - Address comorbidities and psychosocial needs
- Coordinate **post-treatment follow-up care**, ensuring continuity of care and reassessment of depressive symptoms and functioning.
- Facilitate referrals to psychotherapy or additional mental health services as needed.

5. Risk Management and Advocacy

- Reinforce adherence to safety protocols and REMS requirements.
- Monitor for **signs of misuse, tolerance, or psychological dependence**.
- Advocate for **access to care**, including insurance approvals and treatment adherence support.
- Promote patient-centred care and uphold ethical standards in vulnerable populations.

APRNs are integral to the multidisciplinary team managing ketamine/esketamine therapy. Their clinical expertise, holistic approach, and emphasis on patient advocacy uniquely positioned them to guide safe treatment delivery, patient engagement, and long-term recovery planning.

ETHICAL, REGULATORY, AND CLINICAL CONSIDERATIONS IN THE USE OF KETAMINE AND ESKETAMINE FOR TRD

The use of ketamine and esketamine in the treatment of TRD presents unique challenges that intersect clinical practice, ethics, and regulatory oversight. As these therapies

become more widely adopted, healthcare providers especially APRNs, must navigate a landscape that requires clinical precision, ethical sensitivity, and regulatory compliance to ensure patient safety and optimal outcomes.

1. Ethical Considerations

A. Informed Consent and Shared Decision-Making

- **Comprehensive Information**: APRNs must provide clear, accessible information about the potential risks, benefits, and alternatives of ketamine and esketamine. This includes:
  - **Risks**: Dissociation, sedation, hypertension, potential for abuse, and limited long-term safety data.
  - **Benefits**: Rapid antidepressant effects, often within hours or days, compared to traditional antidepressants.
  - **Alternatives**: Other TRD treatments (e.g., SSRIs, ECT, TMS) and their comparative efficacy and risks.
- **Transparency for Off-Label Use and Novelty**:
  - **Ketamine**: As an off-label treatment for TRD, APRNs must disclose its non-FDA-approved status for this indication, emphasizing the evidence base and gaps in long-term data.
  - **Esketamine**: As an FDA-approved nasal spray, its novel administration and strict REMS protocols should be explained, including the need for supervised administration.
- **Shared Decision-Making**:
  - Engage patients in a collaborative process, addressing:
    - **Rapid-Acting Effects**: Highlight the potential for quick symptom relief, which may be life-saving in severe cases, but clarify that effects may not be sustained without maintenance therapy.
    - **Temporary Dissociative Experiences**: Explain these as common, short-lived side effects (e.g., feeling detached or "out of body") and reassure patients about monitoring to ensure safety.
    - **Limited Long-Term Efficacy Data**: Acknowledge uncertainty about prolonged use, including risks like cognitive impairment or bladder toxicity, to foster realistic expectations.
  - Use decision aids or plain-language materials to enhance understanding, especially for patients with mental health challenges that may affect comprehension.

- **Ethical Imperative**: Respect patient autonomy by ensuring consent is voluntary, informed, and revisited as treatment progresses, particularly if new risks or side effects emerge.

B. Equity and Access

- **Barriers to Access**:
  - **Cost**: Ketamine infusions and esketamine treatments are expensive, often costing hundreds of dollars per session. Insurance coverage varies, with esketamine more likely to be covered than off-label ketamine.
  - **Geographic Availability**: Certified REMS facilities for esketamine and ketamine clinics are concentrated in urban areas, limiting access for rural or underserved populations.
  - **Systemic Inequities**: Marginalized groups (e.g., low-income, minority, or uninsured patients) may face additional barriers due to financial constraints or a lack of culturally competent care.
- **Ethical Advocacy**:
  - APRNs should advocate for policies that expand insurance coverage and subsidize costs for TRD treatments.
  - Collaborate with community organizations to improve outreach and education about ketamine/esketamine for underserved populations.
  - Support telehealth or mobile clinic initiatives to bridge geographic gaps, where feasible, while ensuring compliance with REMS and safety protocols.
- **Ethical Imperative**: Promote justice by addressing disparities and ensuring that socioeconomic or geographic factors do not dictate access to potentially life-saving treatments.

C. Potential for Misuse and Dependence

- **Risks of Psychoactive Properties**:
  - Ketamine's dissociative and euphoric effects contribute to its history of recreational abuse ("Special K"). Esketamine, while more regulated, carries similar risks.
  - Unregulated or poorly monitored use (e.g., in non-certified settings) increases the potential for overuse, dependence, or diversion.
- **Ethical Stewardship**:
  - **Careful Patient Selection**: Screen patients for substance use disorders, history of addiction, or psychiatric conditions that may increase misuse risk. Exclude those with active substance abuse.
  - **Regular Monitoring**: Implement structured follow-ups to assess for signs of dependence, such as craving or escalating dose requests. Use validated

tools (e.g., substance use screening questionnaires) to guide assessments.

- **Clear Treatment Boundaries**: Establish protocols for treatment frequency and duration, avoiding ad hoc or patient-driven escalations. For example, limit ketamine infusions to evidence-based intervals (e.g., weekly or biweekly during induction).
- **Secure Handling**: Ensure compliance with DEA regulations for controlled substances, including locked storage and meticulous record-keeping to prevent diversion.

- **Ethical Imperative**: Balance therapeutic benefits with harm prevention, prioritizing patient safety and public health by minimizing misuse risks.

PRACTICAL GUIDANCE FOR APRNS

- **Informed Consent Process**:
  - Use a checklist to ensure all risks, benefits, and alternatives are covered.
  - Document discussions and patient understanding in the medical record.
  - Revisit consent before each treatment phase, especially for off-label ketamine.
- **Equity Advocacy**:
  - Partner with local health departments or advocacy groups to identify resources for underserved patients.
  - Educate patients about financial assistance programs for esketamine (e.g., manufacturer savings programs).
- **Misuse Prevention**:
  - Develop or adopt standardized protocols for patient screening and monitoring.
  - Train staff on recognizing signs of dependence and diversion.
  - Engage pharmacists or addiction specialists for complex cases.

The regulatory landscape for ketamine and esketamine in treating treatment-resistant depression (TRD) is complex, requiring strict adherence to federal, state, and institutional guidelines. Below is a concise overview of the specified regulatory considerations, tailored for APRNs to ensure compliance and patient safety.

2. Regulatory Considerations

A. REMS Program for Esketamine

- **FDA Mandate**: Esketamine (Spravato), approved for TRD, is subject to a Risk Evaluation and Mitigation Strategy (REMS) due to risks of sedation, dissociation, abuse, and suicidal ideation.
- **Key Requirements**:
  - **Certified Healthcare Setting**: Esketamine must be administered in a REMS-certified facility (e.g., clinic

or hospital) equipped to monitor patients and manage adverse effects.

- **Post-Administration Monitoring**: Patients must be observed for at least 2 hours after each dose to assess for sedation, dissociation, hypertension, or other side effects. Monitoring includes vital signs and mental status checks.
- **REMS Certification**:
  - Providers (including APRNs) must complete REMS training and enroll in the program to prescribe or administer esketamine.
  - Pharmacies dispensing esketa -mine must be REMS-certified and comply with distribution protocols.
- **Documentation and Registry**: Providers must document each administration, monitoring period, and patient outcomes. Patients are enrolled in a REMS registry to track safety data.

- **APRN Responsibilities**:
  - Verify facility and personal REMS certification before initiating treatment.
  - Ensure compliance with monitoring protocols, including availability of emergency equipment (e.g., oxygen, blood pressure monitors).
  - Maintain accurate records for audits by the FDA or REMS program.

B. Off-Label Use of Ketamine

- **Regulatory Status**: Intravenous (IV) or intramuscular (IM) ketamine is not FDA-approved for TRD but is widely used off-label based on clinical evidence of efficacy.
- **Key Requirements**:
  - **Robust Documentation**: APRNs must document:
    - Clinical rationale for ketamine use (e.g., failure of other TRD treatments).
    - Evidence supporting off-label use (e.g., citing studies or guidelines).
    - Patient-specific factors justifying treatment (e.g., severity of depression, suicide risk).
  - **Adherence to Institutional Policies**: Follow facility-specific protocols for off-label ketamine use, which may include:
    - Approval from a pharmacy and therapeutics committee.

    - Oversight by a psychiatrist or medical director.
    - Standardized dosing and monitoring guidelines.
  - **Comprehensive Informed Consent**:
    - Clearly explain ketamine's off-label status and investigational nature for TRD.
    - Disclose risks (e.g., dissociation, hypertension, potential long-term effects like bladder toxicity), benefits, and alternatives.
    - Document patient understanding and agreement, ideally using a signed consent form.
- **APRN Responsibilities**:
  - Stay informed about state and institutional regulations governing off-label prescribing.
  - Use evidence-based protocols (e.g., American Psychiatric Association guidelines) to guide dosing and administration.
  - Ensure monitoring for at least 2 hours post-administration, similar to esketamine, to manage acute risks.

C. Licensing and Scope of Practice

- **State Regulations**:
  - APRNs must confirm that their state's Nurse Practice Act permits prescribing and administering controlled substances like ketamine (Schedule III) and esketamine.
  - Some states require collaborative agreements with physicians or specific certifications for controlled substance prescribing.
  - Verify procedural privileges for administering IV/IM ketamine, as this may require additional training or credentialing.
- **Institutional Policies**:
  - Facilities may impose stricter requirements, such as limiting ketamine/esketamine administration to specific roles (e.g., psychiatric APRNs) or requiring physician oversight.
  - APRNs must ensure alignment with hospital or clinic policies, including privileging processes for performing procedures like IV infusions.
- **DEA Compliance**:
  - APRNs with DEA registration must adhere to regulations for handling Schedule III substances, including secure storage, accurate record-keeping, and preventing diversion.
  - Regularly audit controlled substance logs to ensure compliance.
- **APRN Responsibilities**:

- Review the state board of nursing guidelines and consult legal or regulatory experts if unclear about the scope.
- Complete required training for ketamine/esketamine administration and maintain active licensure and certifications.
- Collaborate with institutional leadership to clarify privileges and ensure compliance with policies.

PRACTICAL GUIDANCE FOR APRNS

- **REMS Compliance**:
  - Enrol in the esketamine REMS program via the FDA or manufacturer portal (e.g., https://www.spravatorems.com).
  - Use checklists to ensure all REMS steps (certification, monitoring, documentation) are completed for each patient.
- **Off-Label Ketamine**:
  - Develop or adopt standardized consent forms for off-label ketamine, covering risks, benefits, and investigational status.
  - Reference peer-reviewed studies or guidelines (e.g., APA's 2017 ketamine consensus statement) in documentation to justify use.
- **Scope of Practice**:
  - Maintain an updated file of state regulations, DEA registration, and institutional privileges for quick reference.
  - Engage in continuing education on controlled substance management and TRD therapies to stay within scope.

3. Clinical Considerations in Diverse Settings

A. Inpatient Psychiatric Facilities

- May serve as appropriate settings for **initial administration**, especially for patients with suicidal ideation or severe depression.
- Need for **close medical and psychiatric monitoring**.

B. Outpatient Mental Health Clinics

- Increasingly used for **ongoing esketamine administration** under REMS.
- Require robust protocols for **screening, monitoring, and emergency preparedness**.

C. Ketamine Clinics

- Often operate independently and vary widely in **oversight and adherence to guidelines**.
- APRNs should ensure these clinics adhere to **evidence-based protocols**, ethical practices, and have medical oversight.

D. Rural and Underserved Areas

- Limited access may necessitate **telehealth integration**, collaborative care models, or centralized administration centres.

The administration of ketamine and esketamine for TRD requires a balanced approach that integrates **clinical evidence, ethical responsibility, and regulatory compliance**. APRNs and other providers must advocate for safe and equitable care delivery while navigating the complexities of rapidly evolving psychiatric treatment paradigms. Maintaining transparency, promoting access, and adhering to professional standards is essential for maximizing therapeutic benefit and minimizing harm in all clinical contexts.

CONCLUSION

The emergence of ketamine and esketamine as novel therapeutic options has transformed the clinical landscape for individuals suffering from treatment-resistant depression (TRD), a population historically underserved by conventional antidepressant therapies. By targeting the glutamatergic system and enhancing synaptic plasticity, these agents offer a rapid and mechanistically distinct approach to alleviating depressive symptoms, particularly in patients who have failed to respond to multiple prior treatments.

However, the integration of ketamine and esketamine into clinical practice requires more than pharmacologic knowledge. Advanced Practice Registered Nurses (APRNs) and other healthcare providers must possess a comprehensive understanding of TRD pathophysiology, patient selection criteria, pharmacologic mechanisms of action, safe administration protocols, adverse effect monitoring, and the ethical and regulatory frameworks guiding treatment.

Through evidence-based guidelines, vigilant safety practices, and interdisciplinary collaboration, APRNs play a central role in optimizing outcomes, enhancing patient safety, and expanding access to these groundbreaking interventions. As the field evolves, continued education, ethical vigilance, and regulatory adherence will be critical in ensuring that ketamine and esketamine are applied judiciously and equitably to improve the lives of those affected by severe, refractory depression.

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Bobo, W. V., Vande Voort, J. L., Croarkin, P. E., Leung, J. G., Tye, S. J., & Frye, M. A. (2016). Ketamine for treatment-resistant unipolar and bipolar major depression: Critical review and implications for clinical practice. *Depression and Anxiety, 33*(8), 698–710. https://doi.org/10.1002/da.22502

Coyle, C. M., & Laws, K. R. (2015). The use of ketamine as an antidepressant: A systematic review and meta-analysis. *Human Psychopharmacology: Clinical and Experimental, 30*(3), 152–163. https://doi.org/10.1002/hup.2462

Daly, E. J., Trivedi, M. H., Janik, A., Li, H., Zhang, Y., Li, X., ... & 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

DelveInsight. (2023). *Treatment-Resistant Depression (TRD) - Market Insight, Epidemiology, and Market Forecast - 2032*. Retrieved from https://www.delveinsight.com/

FDA. (2019). *Spravato (esketamine) REMS*. U.S. Food and Drug Administration. Retrieved from https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

Frontiers in Psychiatry. (2024). *Efficacy and safety of ketamine and esketamine for unipolar and bipolar depression: An overview of reviews*. *Frontiers in Psychiatry*.

Journal of Evidence-Based Review in Psychiatry. (2024). *The role of ketamine in treatment-resistant depression*. *Journal of Evidence-Based Review in Psychiatry*.

Murrough, J. W., Abdallah, C. G., & Mathew, S. J. (2017). Targeting glutamate signalling in depression: Progress and prospects. *Nature Reviews Drug Discovery, 16*(7), 472–486. https://doi.org/10.1038/nrd.2017.16

National Institute for Health and Care Excellence (NICE). (2022). *Esketamine for treatment-resistant depression in adults (TA777)*. Retrieved from https://www.nice.org.uk/guidance/ta777

Nature Translational Psychiatry. (2024). *Personalized use of ketamine and esketamine for*

treatment-resistant depression. Nature Translational Psychiatry.

Papakostas, G. I. (2015). Managing treatment-resistant depression: The role of adjunctive therapy. *Journal of Clinical Psychiatry, 76*(6), e857–e864. https://doi.org/10.4088/JCP.14r09307

PubMed Central (PMC). (2020). *Comparative efficacy of racemic ketamine and esketamine for depression: A systematic review and meta-analysis* (PMC7704936). *PubMed Central.*

PubMed Central (PMC). (2023). *Esketamine for treatment-resistant depression: A review of clinical studies* (PMC9922941). *PubMed Central.*

PubMed Central (PMC). (2024). *Ketamine and esketamine in clinical trials: FDA-approved and emerging uses in depression* (PMC11739757). *PubMed Central.*

Sanacora, G., Frye, M. A., McDonald, W., Mathew, S. J., Turner, M. S., Schatzberg, A. F., ... & Zarate, C. A. (2017). A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry, 74*(4), 399–405. https://doi.org/10.1001/jamapsychiatry.2017.0080

Zarate, C. A., Singh, J. B., Carlson, P. J., Brutsche, N. E., Ameli, R., Luckenbaugh, D. A., ... & Manji, H. K. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Archives of General Psychiatry, 63*(8), 856–864. https://doi.org/10.1001/archpsyc.63.8.856