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Letter to the Editor

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Intranasal esketamine use in treatment-resistant depression: mechanism of action, clinical adverse effects, contraindications, safe administration protocol, and treatment process

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Dear Editor,

The U.S. Food and Drug Administration (FDA) has increasingly focused on breakthrough molecular mechanisms, rapidly acting medications, and expanded therapeutic indications in the treatment of depression. During this period, psychiatric interventions targeting N-methyl-D-aspartate (NMDA) receptors and intracellular signaling pathways have gained prominence, moving beyond the traditional monoamine (serotonin/norepinephrine) hypothesis. This article reviews the mechanism of action, clinical adverse effects, contraindications, safe administration protocols, and treatment process associated with esketamine, one of these novel therapeutic approaches.

Esketamine monotherapy approval: Previously approved only for use in combination with an oral antidepressant, this rapidly acting NMDA receptor modulator administered as a nasal spray has now received approval for use as monotherapy in adults with treatment-resistant depression. Whereas conventional selective serotonin reuptake inhibitors (SSRIs) typically require 6-8 weeks to achieve a clinically meaningful therapeutic response, newly approved NMDA-targeting therapies may produce rapid symptom relief within days.[1]

Esketamine is a paradigm-shifting molecule in psychiatry that exerts its effects through cellular pathways fundamentally distinct from those of conventional antidepressants. While traditional antidepressants such as SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) primarily aim to increase synaptic concentrations of serotonin, norepinephrine, or dopamine, esketamine directly targets the glutamatergic system, the brain's principal excitatory neurotransmitter network.[2]

Esketamine is the (S)-enantiomer of racemic ketamine and exhibits substantially higher affinity for NMDA receptors. At the cellular level, its therapeutic effects are mediated through the following sequence of events: Esketamine selectively and reversibly antagonizes NMDA (N-methyl-D-aspartate) receptors located on inhibitory gamma-aminobutyric acid (GABA)-ergic interneurons. This blockade reduces inhibitory neuronal activity, resulting in a process known as disinhibition. Consequently, a rapid and robust release of glutamate occurs from pyramidal neurons within the prefrontal cortex. The released glutamate subsequently binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on neighboring neurons. Activation of AMPA receptors increases intracellular sodium influx, leading to neuronal excitation. This AMPA-mediated signaling stimulates the synthesis and release of brain-derived neurotrophic factor (BDNF). BDNF then activates downstream signaling pathways, including the mammalian target of rapamycin (mTOR) pathway.[3]

In brains affected by chronic stress and depression, where synaptic connections have become weakened or diminished, activation of the mTOR pathway promotes the rapid formation of new synaptic connections and dendritic spines within hours. In summary, whereas conventional antidepressants primarily seek to alter neurochemical concentrations in the brain, esketamine appears to facilitate rapid restoration of neural architecture through enhancement of synaptic plasticity.

Despite its rapid antidepressant effects, esketamine requires close clinical monitoring because of its acute central nervous

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system effects.[4] Adverse effects generally begin within 10-15 minutes after administration, peak at approximately 40 minutes, and typically resolve completely within 1.5-2 hours. According to clinical studies, the most commonly reported acute adverse effects include dissociation (the most frequently reported adverse effect), sedation and dizziness, transient increases in blood pressure (typically a temporary rise of approximately 10-20 mmHg in systolic blood pressure and 5-10 mmHg in diastolic blood pressure following administration), cognitive disturbances, and nausea and vomiting. Although ulcerative cystitis has been associated with chronic ketamine misuse, the risk appears to be very low at therapeutic doses; nevertheless, vigilance is warranted during long-term treatment. Esketamine is classified as a controlled substance, and caution should be exercised in individuals with a history of substance use disorders due to its potential to activate reward pathways. Clinicians should remain aware of its potential for misuse and dependence.

Esketamine represents a novel therapeutic approach for the management of treatment-resistant depression (TRD) and patients presenting with acute suicidal ideation. In contrast to conventional antidepressants, which typically exhibit a therapeutic lag of several weeks, esketamine exerts a rapid-onset action within hours of administration. This swift response is mediated by the promotion of neuroplasticity and the accelerated repair of synaptic connectivity, thereby playing a critical role in the immediate suppression of suicidal thoughts.[5] TRD is clinically defined by an inadequate response to at least two distinct lines of traditional antidepressant therapies, such as SSRIs or SNRIs, administered at adequate dosages and durations; in this refractory cohort, esketamine significantly enhances the probability of clinical remission and sustained recovery.[5] Given the profound risk of mortality associated with major depressive disorder, the fast-acting property of esketamine is potentially life-saving. Clinical data indicate that a reduction in suicidal tendencies can be observed as early as 2 to 4 hours post-initial administration.[6] Consequently, supervised clinical or inpatient administration of esketamine serves as a crucial intervention for crisis stabilization and immediate symptomatic relief in severe psychiatric emergencies.[6] However, due to the transient physiological and psychological changes induced by the medication, its use is absolutely contraindicated in certain patient populations. Esketamine is contraindicated in patients for whom transient increases in blood pressure or intracranial pressure could pose a significant or life-threatening risk. Table summarizes conditions in which esketamine use is absolutely contraindicated, as well as other medical conditions that require extreme caution or avoidance during treatment.

Table. Medical conditions in which esketamine use is absolutely contraindicated and conditions requiring extreme caution

Absolute contraindications	Conditions requiring particular caution
Aneurysmal vascular diseases	Uncontrolled hypertension and cardiovascular disorders
Arteriovenous malformations	Patients presenting with active psychotic symptoms
History of intracerebral hemorrhage	A history of manic episodes
Hypersensitivity	A history of hypomanic episodes

(Adapted from McIntyre et al.[11])

Safe administration protocol: Due to its adverse-effect profile, esketamine nasal spray cannot be purchased from a pharmacy and self-administered at home. The safety protocol includes the following steps: The patient self-administers the medication intranasally under the supervision of a psychiatrist or trained nurse in a certified healthcare facility. Following administration, blood pressure is monitored, and the patient remains under observation in the clinic for a minimum of 120 minutes until any dissociative and/or sedative effects have fully resolved. Patients are strictly prohibited from driving motor vehicles or operating heavy machinery requiring sustained attention on the day of treatment. Normal daily activities may generally be resumed the following day. One of the most commonly reported adverse effects of esketamine is nausea and vomiting. To minimize this risk, patients should abstain from consuming solid food for at least 2 hours prior to the start of the treatment session. In addition, the intake of liquids, including water, should be discontinued at least 30 minutes before administration to reduce the likelihood of vomiting and to optimize treatment tolerability. If the patient uses other intranasal medications (e.g., allergy nasal sprays), these should be administered at least 1 hour before esketamine to avoid interference with its absorption through the nasal mucosa. Immediately before treatment, the patient's blood pressure should be assessed. If baseline blood pressure is considered dangerously elevated (e.g., ≥140/90 mmHg), the treatment session should be postponed until adequate blood pressure control has been achieved.[4]

The treatment course consists of two main phases: the Induction (Initiation) Phase and the Maintenance Phase. Each esketamine nasal spray device contains 28 mg of esketamine. Depending on the patient's clinical needs, two devices (56 mg) or three devices (84 mg) are administered per treatment session. The induction phase encompasses Weeks 1-4 and involves treatment twice weekly. Treatment is initiated with 56 mg on the first day. During subsequent sessions, the dose may be maintained at 56 mg or increased to 84 mg, depending on the patient's tolerability and the treating physician's clinical judgment. The primary objective of this phase is to rapidly promote the restoration of synaptic connectivity in the brain and achieve an acute reduction in depressive symptoms.[4] The Optimization and Maintenance Phase encompasses Week 5 onward. Once depressive symptoms have been adequately controlled, the frequency of treatment sessions is gradually reduced: Once weekly (56 mg or 84 mg) on Weeks 5-8, and typically once every two weeks (or once weekly, depending on the patient's clinical status) on Week 9 onward. The duration of maintenance therapy varies according to the patient's clinical response and sustained remission and may continue for several months.

When more than one device is used during a treatment session (56 mg or 84 mg total dose), a 5-minute interval should be observed between administrations of each device. This interval facilitates optimal absorption of the medication through the nasal mucosa. Following administration, the patient is transferred to a comfortable, quiet room with subdued lighting. To facilitate tolerance of transient dissociative experiences, patients may be encouraged to listen

to music or use an eye mask during the observation period. Approximately 2 hours after administration, the patient may be discharged if blood pressure has returned to an acceptable range and all clinically significant sedative and dissociative effects have resolved. Patients are required to arrange for a responsible accompanying person to escort them home following each treatment session.

Esketamine is a pharmaceutical product that has been approved and licensed by the Turkish health authorities, specifically the Turkish Medicines and Medical Devices Agency (TİTCK).[7] However, the current approved indication in Turkiye continues to specify the use of esketamine in combination with an oral antidepressant.[7] Although the U.S. FDA expanded approval in January 2025 to permit the use of esketamine as a standalone (monotherapy) treatment for treatment-resistant depression, this indication expansion has not yet been fully incorporated into Turkish regulatory guidance and prescribing information.[8]

Because esketamine is a specialized ketamine derivative with recognized abuse and misuse potential, it is subject to the red prescription (controlled substance) system in Turkiye. Consequently, patients are not permitted to purchase the medication from a pharmacy for home use or self-administration. Administration of esketamine is restricted to authorized healthcare settings and must be conducted under direct medical supervision. Treatment may be provided only in appropriately equipped psychiatric centers, university hospitals, and selected private hospitals that have received authorization from the Ministry of Health. Concurrently, esketamine nasal spray represents a high-cost biopharmaceutical intervention. Within the framework of the Turkish healthcare system, whether the Social Security Institution (SGK) will incorporate this agent into its comprehensive reimbursement scheme-and under what stringent regulatory criteria, such as a formal medical board consensus report-remains a pivotal subject of debate regarding equitable access to treatment.

In Turkiye, the clinical stabilization of acutely depressed patients presenting to emergency departments with suicidal ideation typically necessitates prolonged hospitalization extending over several weeks. Consequently, the potential of esketamine to mitigate suicidal thoughts within a 2-to-4-hour window post-administration could substantially alleviate the acute clinical burden imposed on emergency departments and psychiatric inpatient units.[9] Furthermore, approximately 30% to 40% of patients diagnosed with major depressive disorder in Turkiye exhibit resistance to conventional pharmacotherapies, specifically SSRIs and SNRIs. Historically, therapeutic options for this treatment-resistant cohort were largely restricted to electroconvulsive therapy (ECT) or the off-label utilization of intravenous ketamine infusions.[10] In this context, esketamine introduces a regulatory-approved and standardized therapeutic alternative formally sanctioned by the Turkish Ministry of Health.

The ongoing clinical and academic debate surrounding esketamine utilization in Turkiye-interpreted through the lens of national major depressive disorder epidemiology, TRD dynamics, and acute suicidal crisis management-underscores the necessity for a meticulous evaluation of this agent's therapeutic potential and clinical risk-benefit profile. In the context of Turkish neuropsychiatry, esketamine emerges as a transformative intervention, particularly for acute crisis stabilization. However, maximizing its clinical efficacy and translational utility is strictly contingent upon several critical parameters: the standardization of clinical infrastructure within medical institutions, stringent patient selection criteria implemented by psychiatric clinicians, and, pivotally, the establishment of sustainable fiscal frameworks and healthcare reimbursement policies designed to mitigate socioeconomic disparities in treatment accessibility.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for the publication of this correspondence and any related clinical details.

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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