Intranasal esketamine

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Treatment-resistant depression (TRD) is a common clinical struggle that practicing clinicians address on a daily basis. Major depressive disorder affects nearly 1 in 5 Americans at some point in their life and, by definition, impairs social and occupational functioning. Historic treatments have focused on the monoamine theories of depression—modulating the monoamines serotonin, norepinephrine, and/or dopamine. Limitations of currently available antidepressants include delayed onset of effect and low remission rates. To further complicate the matter, numerous studies have shown that with each subsequent antidepressant trial, patients have a decreasing likelihood of responding to subsequent antidepressant treatment options. For example, in the classic STAR*D trial, by the time a patient had not responded to the first 2 antidepressant options, the chance that they would respond to a third or fourth antidepressant had decreased to approximately 15% per antidepressant treatment course.[1]

To address the need for new treatments for patients with TRD, on March 5, 2019 the FDA-approved intranasal esketamine (brand name: Spravato) (***Table 1***[2]) following the evaluation of its efficacy through short-term clinical trials and a longer-term maintenance-of-effect trial. Intranasal esketamine is indicated, in conjunction with an oral antidepressant, for adult patients with TRD.[2] Esketamine is a CIII controlled substance, and concerns about abuse, misuse, and diversion have been taken into account within the Risk Evaluation and Mitigation Strategy (REMS) drug safety program. The

Table 1

Fast facts about intranasal esketamine

Brand name: Spravato
Class: *N*-methyl-D-aspartate receptor antagonist
Indication: Adjunctive therapy for adults with treatment-resistant depression
Approval date: March 5, 2019
Availability date: March 18, 2019
Manufacturer: Janssen Pharmaceuticals, Inc., Titusville, NJ
Dosing forms: 28 mg per intranasal device
Recommended dosage for treatment-resistant depression • **Induction phase**. Weeks 1 to 4: Day 1 starting dose 56 mg (2 devices). Subsequent doses 56 or 84 mg (2 or 3 devices) twice weekly • **Maintenance phase**. Weeks 5 to 8: Once weekly, either 56 or 84 mg per session. Weeks 9 and after: Weekly or bi-weekly at 56 mg or 84 mg per session • **Long-term treatment**. Weekly, bi-weekly, or once monthly at 56 or 84 mg per session

Source: Reference 2

This glutamatergic agent is approved as an adjunctive therapy for patients with treatment-resistant depression

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Disclosures

Dr. Mattingly receives grant/research support from Akili, Alkermes, Allergan, Boehringer, Janssen, Medgenics, NLS-1 Pharma AG, Otsuka, Reckitt Benckiser, Roche, Sage, Sunovion, Supernus, and Takeda; is a consultant to Akili, Alkermes, Allergan, Axsome, Ironshore, Intracellular, Janssen, Lundbeck, Otsuka, Neos, Purdue, Rhodes, Sage, Shire, Sunovion, Takeda, and Teva; and is a speaker for Alkermes, Allergan, Janssen, Lundbeck, Otsuka, Sunovion, and Takeda. Dr. Anderson receives grant/research support from Akili, Alkermes, Allergan, Boehringer, Janssen, Medgenics, NLS-1 Pharma AG, Otsuka, Reckitt Benckiser, Roche, Sage, Sunovion, Supernus, and Takeda.

agent is only available through a restricted distribution—the REMS will mandate that REMS certified pharmacies dispense directly to a REMS certified treatment program. Intranasal esketamine will not be sampled or dispensed directly to patients.

How it works

Modern research has looked beyond the monoamine system to explore the neuromodulatory effects of glutamate and gamma-aminobutyric acid (GABA).[3] The yin and yang of glutamate and GABA revolves around neural excitation vs neural inhibition at a local synaptic level. The primary effects of the glutamate and GABA systems (***Table 2***, ***page 33***) can be broken down into several key areas of understanding.

Glutamate modulates ionotropic *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and a family of nonionic metabotropic receptors, or mGluRs. Glutamate stimulation of NMDA or AMPA receptors increases Ca^{2+} ion influx and enhances neural firing. Conversely, GABA stimulation increases Cl^- ion influx, which inhibits neural firing. Antagonizing glutamate receptors inhibits neural firing. *N*-methyl-D-aspartate receptors localized on the GABA interneuron modulate GABAergic activity. Antagonism of the NMDA receptor on GABA interneurons decreases GABA activity. Decreased activity of the GABA interneuron promotes intrasynaptic glutamate release and enhances glutamate stimulation of postsynaptic AMPA receptors. Glutamate stimulation of AMPA receptors then stimulates a cascade of intrasynaptic signaling that promotes the release of brain-derived neurotrophic factor (BDNF) and increased production of neuronal membrane proteins with subsequent neural plasticity.

Esketamine, the S-enantiomer of ketamine, has a higher affinity for the NMDA receptor than the R-enantiomer and has been developed as an intranasal adjunctive treatment for TRD. Esketamine blocks NMDA receptors on GABA interneurons. This allows for increased pulsatile release of glutamate into the synapse. Intrasynaptic glutamate then stimulates postsynaptic AMPA receptors. Glutamate stimulation of postsynaptic AMPA receptors results in an intracellular cascade that activates the enzymes tropomyosin receptor kinase B (TrkB) and mammalian target of rapamycin (mTOR). TrkB stimulation results in increased production and release of BDNF. mTor stimulation increases neuronal membrane protein formation with subsequent increased neural plasticity. Taken together, preclinical models show that esketamine's inhibition of the NMDA receptor on the GABA interneuron results in a cascade of increased BDNF release and synaptogenesis with increased neuroplasticity (***Table 3***, ***page 34***).

Clinical Point

Esketamine's inhibition of the NMDA receptor on the GABA interneuron results in BDNF release and synaptogenesis

Clinical implications

Treatment-resistant depression affects nearly one-third of patients currently receiving standard antidepressant treatment. Major depressive disorder is currently the second leading cause of disability for working adults within the United States and one of the largest causes of disability worldwide. The esketamine nasal spray could be beneficial for patients who have experienced TRD with standard monoamine antidepressants.

Supporting evidence

Clinical trials examining intranasal esketamine include both short- and long-term studies of patients with TRD.

Esketamine was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week) phase III study in adult patients age 18 to 65 with TRD (they had not responded to at least 2 different antidepressants of adequate dose and duration).[4] After discontinuing prior antidepressant treatments, all patients were started on a newly initiated antidepressant and were also randomized to concomitant

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intranasal esketamine or intranasal placebo as follows:

- 114 patients were randomized to the intranasal esketamine plus newly initiated oral antidepressant arm
- 109 patients were randomized to the placebo nasal spray plus newly initiated oral antidepressant arm
- The mean baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score for each group was 37 (ie, moderately to severely depressed).

Newly started antidepressants included escitalopram, sertraline, duloxetine, or extended-release venlafaxine. Esketamine intranasal spray was initiated at 56 mg and could be titrated up to 84 mg at the second dose, based on investigator discretion. The mean age was 47; 62% of the patients were female, 93% were White, and 5% were black. The newly initiated oral antidepressant was a selective serotonin reuptake inhibitor in 32% of patients and an serotonin-norepinephrine reuptake inhibitor in 68% of patients. The time course of response for this 4-week, short-term treatment study is illustrated in ***Figure 1***[2] (***page 35***). While the primary efficacy measure was improvement of MADRS score at Week 4, the majority of the placebo-active drug separation occurred 24 hours after the initial 56 mg dose of esketamine. Between 24 hours and Day 28, intranasal esketamine showed continued separation from antidepressant plus placebo nasal spray. Investigators could increase both placebo nasal spray or esketamine, with 67% of patients receiving 84 mg twice weekly at Day 28.

A long-term, double-blind multicenter maintenance-of-effect trial examined adults age 18 to 65 with TRD.[5-6] Patients in this study were responders in 1 of 2 short-term studies or in an open-label direct enrollment study. Stable remission was defined as a MADRS total score <12 for at least 3 of the last 4 weeks of the study, and stable response was defined as a MADRS reduction of >50% but not in remission.

Table 2

Key facts: Glutamate and GABA

Glutamate modulates ionotropic NMDA and AMPA receptors and a family of non-ionic metabotropic receptors
Glutamate stimulation of NMDA or AMPA increases $Ca2^{+}$ influx and stimulates neural firing
GABA stimulation increases Cl^{-} influx, which inhibits neural firing
Antagonizing glutamate activation decreases neuronal firing
Decreased stimulation of GABA interneuron shuts off the brake on glutamate release and allows increased stimulation of post-synaptic AMPA receptor

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA: gamma-aminobutyric acid; NMDA: *N*-methyl-D-aspartate

After 16 weeks of intranasal esketamine plus an oral antidepressant, stable remitters and stable responders were then randomized separately to continue intranasal esketamine or switch to placebo nasal spray, with both groups continuing on their concomitant oral antidepressant. The primary study endpoint was time to relapse. Relapse was defined as a MADRS total score >22 for more than 2 consecutive weeks, hospitalization for worsening of depression, or any other clinically relevant event. The median age was 48, 66% were female, 90% were White and 4% were black. Patients in stable response or stable remission experienced a significantly longer time to relapse compared with patients who continued their oral antidepressant but were switched to placebo intranasal spray. In this remission response study, patients could receive intranasal treatment weekly or bi-weekly based on symptom severity (***Figure 2***,[2] ***page 36***).

Impact on driving. Two studies examined the impact of esketamine on driving performance. One examined adults with major depressive disorder and the other examined healthy participants. The effects

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In a long-term, maintenance-of-effect trial, patients receiving esketamine experienced a significantly longer time to relapse

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The most common adverse events in patients treated with esketamine were dissociation, dizziness, nausea, sedation, and vertigo

Table 3

Actions of esketamine

Inhibits the NMDA receptor on the GABA interneuron
Causes decreased stimulation of GABA interneuron
Allows increased pulsatile release of glutamate
Glutamate then stimulates post-synaptic AMPA receptors
AMPA stimulation turns on TrkB and mTOR enzymes • TrkB stimulation increases BDNF release • mTOR stimulation increases neural plasticity

AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF: brain-derived neurotrophic factor; GABA: gamma-aminobutyric acid; mTOR: mammalian target of rapamycin; NMDA: *N*-methyl-D-aspartate; TrkB: tropomyosin receptor kinase B

of a single 84-mg dose of esketamine nasal spray on a patient's ability to drive was assessed in 23 healthy adults. In this study, mirtazapine was used as an active control. Driving performance was assessed at 8 hours after treatment with esketamine nasal spray or mirtazapine. Driving performance 8 hours after esketamine nasal spray was similar to placebo and active control. Two participants discontinued the driving task after receiving esketamine due to post-dose adverse reactions. One reported pressure behind the eyes and paresthesia of the hands and feet. The other reported headache and light sensitivity with anxiety.

A second study evaluated the effects of repeated esketamine administration on driving performance in 25 adults with major depressive disorder. In this study, an ethanol-containing beverage was used as an active control. After administration of a single 84-mg dose of intranasal esketamine, driving performance was the same as a placebo at 18 hours. In the multiple dose phase, standard driving performance was similar for esketamine nasal spray and placebo at 6 hours postdose on Days 11, 18, and 25.

Pharmacologic profile

Adverse events. The most common adverse events in patients treated with esketamine nasal spray were dissociation (41%), dizziness (29%), nausea (28%), sedation (23%), and vertigo (23%).[2] The majority of these effects were short-term and resolved during the 2-hour observation period.

In addition to spontaneously reported events, sedation and dissociation were further monitored with specific scales. Sedation was measured with the Modified Observer's Alertness and Sedation Scale. Using this scale, 50% of patients receiving 56 mg and 61% of patients receiving 84 mg of esketamine met criteria for sedation.

Similarly, dissociation/perceptional changes were measured with spontaneously reported events and also with the Clinician Administered Dissociative State Scale. On this scale, 61% of patients receiving the 56-mg dose, and 69% of patients receiving the 84-mg dose met criteria for dissociation/perceptional changes after dose administration.

Increases in blod pressure. Esketamine intranasal spray was associated with a 7 to 9 mm Hg increase in systolic blood pressure and a 4 to 6 mm Hg increase in diastolic blood pressure, both of which peaked 40 minutes post-dose.

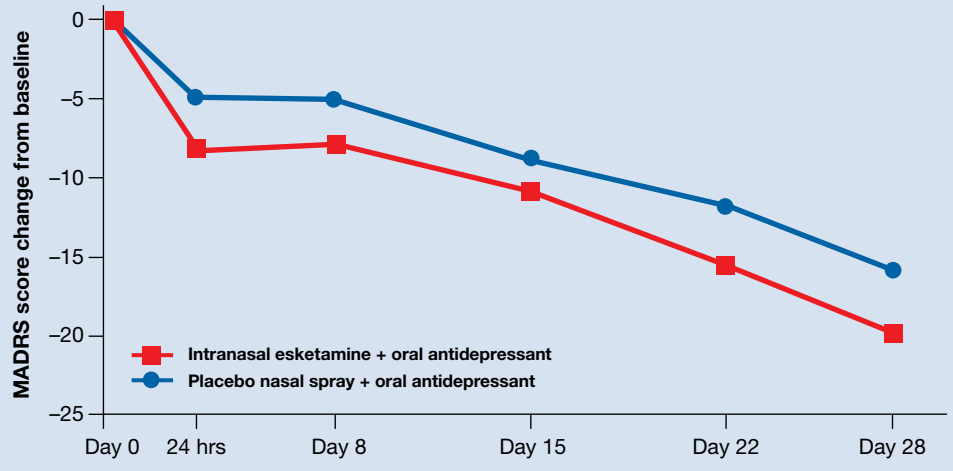
Nausea and vomiting. Intranasal esketamine was associated with a 27% rate of nausea at 56 mg, and 32% at 84 mg, with a 6% rate of vomiting at 56 mg and 12% at 84 mg.

Pharmacokinetics

Esketamine exposure increases from 28 to 84 mg in a fairly dose-proportional range. No accumulation of esketamine was observed in the plasma following twice-weekly administration. Bioavailability is approximately 48% following nasal administration. The Tmax for esketamine plasma concentration is 20 to 40 minutes after the last nasal spray. Protein binding of esketamine is approximately 43% to 45%. The

Figure 1

Short-term response for patients who received intranasal esketamine



MADRS: Montgomery-Åsberg Depression Rating Scale

Source: Reference 2

brain-to-plasma ratio of noresketamine is 4 to 6 times lower than that of esketamine. The half-life of esketamine ranged from 7 to 12 hours. The mean half-life of noresketamine was approximately 8 hours. Esketamine is primarily metabolized to a noresketamine metabolite via cytochrome P450 (CYP) enzymes, 2B6 and 3A4. Noresketamine is metabolized by CYP-dependent pathways and certain metabolites undergo glucuronidation. Drug interaction studies demonstrate that intranasal esketamine had very little effect on pharmacokinetic interactions with other medications.

Potential drug interactions

Central nervous system depressants. Concomitant use of esketamine and other CNS depressants (ie, benzodiazepines, opioids, alcohol) may increase sedation. Patients receiving esketamine with concomitant use of other CNS depressants should be closely monitored for sedation.

Psychostimulants. Concomitant use of esketamine and psychostimulants (ie, amphetamines, methylphenidates, modafinil, and armodafinil) may increase blood pressure. Patients receiving esketamine with concomitant use of psychostimulants should be closely monitored for elevations in blood pressure.

Monoamine oxidase inhibitors. Concomitant use of esketamine with monoamine oxidase inhibitors may increase blood pressure. Closely monitor blood pressure with concomitant use of esketamine and monoamine oxidase inhibitors.

Use in special populations. Because of concerns of increased sedation, intranasal esketamine should be administered cautiously in patients receiving other CNS depressants, such as benzodiazepines. In patients with psychosis or a prior history of psychosis, esketamine should be used with increased caution and the risk/benefit ratio should be carefully considered.

Because of potential teratogenicity, esketamine is not recommended in women who are pregnant, may become pregnant, or who are currently nursing.

Intranasal esketamine was examined in a phase III trial of 194 patients age ≥65. At the end of 4 weeks, there was no statistically significant difference in groups on the

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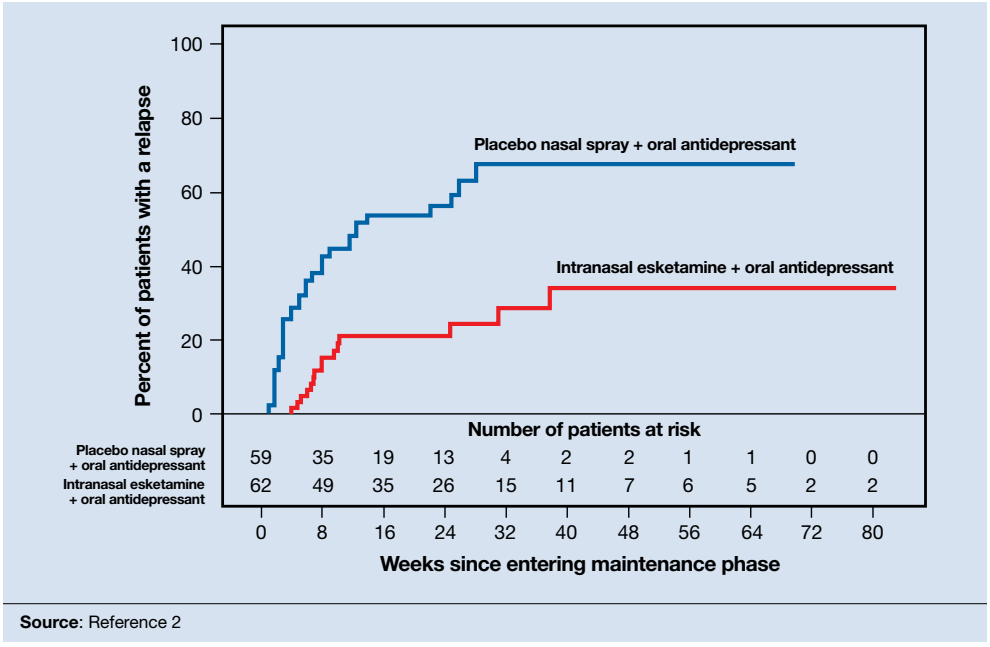
Intranasal esketamine should be administered cautiously in patients receiving other CNS depressants, such as benzodiazepines

Figure 2

Relapse prevention for patients who responded to intranasal esketamine



Source: Reference 2

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Esketamine will be administered through a REMS program only at certified treatment centers

MADRS, the primary efficacy endpoint. There were no overall differences in the safety profile in patients >65 years compared with younger patients; however, the mean esketamine Cmax and area under the curve were higher in older patients compared with younger adults. The mean esketamine half-life was longer in patients with moderate hepatic impairment.

Abuse liability

Esketamine is a CIII controlled substance and concerns about abuse, misuse, and diversion have been taken into account within the REMS drug safety program.[2] Patients with a prior history of substance abuse or misuse should be considered with regard to the risk/benefit ratio.

The REMS drug safety program

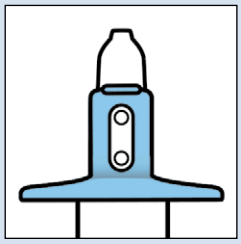
Due to the nature of its usually transient adverse effects, including sedation, dissociation, hypertension, and nausea, intranasal esketamine will be administered through a REMS drug safety program at certified REMS treatment centers. Certified REMS treatment centers will receive training on how to safely and effectively counsel and monitor patients. Prior to treatment, patients will receive blood pressure monitoring and anticipated adverse effects will be discussed. Patients will be instructed to not eat solid food for 2 hours pre-dose and to not drink anything for 30 minutes prior.

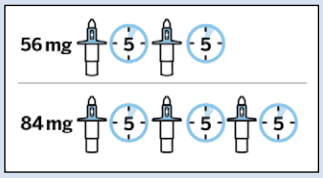
A treatment session consists of nasal administration and a minimum 2-hour post-administration observation period. Blood pressure must be assessed prior to administration and if elevated, (ie, systolic blood pressure >140 mm Hg, diastolic >90 mm Hg), clinicians should consider the risk of short-term increases in blood pressure that may occur. Do not administer if increases in blood pressure or intracranial pressure pose a serious risk.

After each intranasal administration the patient will be observed for 5 minutes before the second nasal inhaler is utilized and for another 5 minutes when the patient

Figure 3

Administering intranasal esketamine: Wait 5 minutes between each device





- After the patient self-administers the first device, take the device from patient.
- **Check that the indicator shows no green dots**. If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm the device is empty.

Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device**.
- If liquid drips out, dab nose with a tissue.

Do not blow nose.

IMPORTANT: Ensure that the patient waits 5 minutes after each device to allow medication to absorb.

Source: Reference 2

is receiving 84 mg (ie, each inhaler equals 28 mg). After administering, blood pressure should be reassessed at approximately 40 minutes, which corresponds to the Cmax of intranasal esketamine, and periodically thereafter as warranted.

The patient will then be monitored in a quiet environment for a minimum of 2 hours to make sure that dissociative phenomenon, sedation, and hypertensive reactions have normalized prior to discharge from a certified REMS treatment center.

Dosing and administration

Each intranasal device is primed for 2 infusions (1 in each nostril) for a total dose of 28 mg of esketamine. Combinations of devices can be used to adjust the dose as appropriate for individual patients. The recommended starting dose is 56 mg (ie, 2 devices, with a 5-minute gap between devices). The dose can be increased to 84 mg (ie, 3 intranasal devices spaced at 5-minute intervals) by the second dose based on clinical judgment.

The patient will be instructed to recline the head to a 45° angle, clear his or her nostrils prior to the first treatment, and then self-administer a dose to each nostril while holding the reciprocal nostril closed and inhaling. This process is then repeated every 5 minutes for each subsequent device, with a maximum total dose of 3 devices, or 84 mg (***Figure 3***[2]). The patient will then be monitored for blood pressure, heart rate, and signs of psychologic or physiologic changes for the next 2 hours. Patients may not drive a car or operate any type of motor equipment until the following day after receiving a normal night's sleep. Patients will be released from the REMS treatment center after 2 hours if both psychological and physical adverse effects have normalized.

Missed treatment sessions. If a patient misses a treatment session and there is worsening of depressive symptoms, consider returning the patient to the previous dosing schedule (ie, every 2 weeks to once weekly, or weekly to twice weekly).

continued

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Each intranasal esketamine device is primed for 2 infusions for a total dose of 28 mg

Related Resource

- Sullivan MG. FDA approves intranasal esketamine for refractory major depressive disorder. Clinical Psychiatry News. https://www.mdedge.com/psychiatry/article/195712/depression/fda-approves-intranasal-esketamine-refractory-major-depressive. Published March 5, 2019.

Drug Brand Names

Armodafinil • Nuvigil	Mirtazapine • Remeron
Duloxetine • Cymbalta	Modafinil • Provigil
Escitalopram • Lexapro	Sertraline • Zoloft
Esketamine • Spravato	Venlafaxine • Effexor

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Intranasal esketamine is contraindicated for patients with aneurysmal vascular disease

Contraindications for intranasal esketamine include:

- aneurysmal vascular disease, including thoracic and abdominal aortic, intracranial, and peripheral arterial vessels, or arterial venous malformations
- history of intracerebral hemorrhage
- hypersensitivity to esketamine, ketamine, or any of the excipients.

Clinical considerations

Intranasal esketamine represents a unique delivery system for the first glutamatergic treatment approved for patients with TRD.

Why Rx? Treatment-resistant depression is found in nearly 1 out of 3 patients with currently available monoaminergic antidepressant treatment options. Patients with TRD are at increased risk of physical and psychological impairment, subsequent worsening of their condition, and social and occupational disability.

References

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6. Wajs E, Aluisio L, Morrison R, et al. Long-term safety of esketamine nasal spray plus oral antidepressants in patients with treatment-resistant depression: phase III open-label safety and efficacy study. Poster presented at the 2018 American Society of Clinical Psychopharmacology Annual Meeting; May 2018; Miami, Florida.

Bottom Line

Intranasal esketamine is the first glutamatergic treatment option FDA-approved for patients with treatment-resistant depression who have not responded to standard antidepressant treatment options. In short-term trials, intranasal esketamine significantly improved depressive symptoms as quickly as 24 hours after treatment, with significant improvement maintained through 4 weeks of ongoing administration. In addition, intranasal esketamine was shown to significantly decrease time to relapse for patients who had achieved stable remission or stable response.