



## Esketamine for Treatment-Resistant Depression — First FDA-Approved Antidepressant in a New Class

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**T**reating major depressive disorder remains an important challenge worldwide. The disorder impairs productivity, social functioning, and overall health, reducing life expectancy and burden-

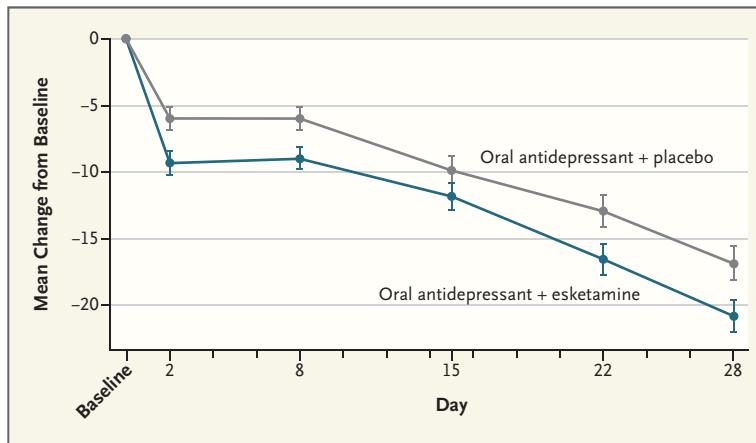
ing health care systems.<sup>1</sup> Although many treatments exist, at least a third of patients do not have a response after two or more trials of antidepressant drugs and are considered to have treatment-resistant depression.<sup>2</sup> Such patients have an increased risk of suicide relative to both the general population and patients with nonresistant major depressive disorder; at least a third of them attempt suicide.<sup>3</sup> The Food and Drug Administration (FDA) has approved only one drug for treatment-resistant depression: a fixed-dose combination of olanzapine and fluoxetine. Most antidepressants take several weeks to begin working. Additional safe and effective medications for treatment-resistant de-

pression, especially ones with a more rapid onset of action, are needed.

The FDA recently approved the S-enantiomer of ketamine, esketamine, a rapidly acting drug shown to be effective in patients with treatment-resistant depression. Ketamine, a noncompetitive antagonist of glutamate receptors of the N-methyl-D-aspartate (NMDA) type, was approved in 1970 as an anesthetic. Ketamine subsequently gained notoriety as a drug of abuse (“Special K”) owing to its dissociative effects. Subsequently, researchers presented preliminary evidence suggesting that ketamine has rapid (within several hours) antidepressant effects<sup>4</sup> — an attractive property, given the need

for urgent relief of depressive and suicidal crises and faster restoration of social and occupational functioning. The longer depressive episodes last, the greater the burdens and costs for patients, their families, society, and the health care system.

Esketamine’s efficacy and safety in treatment-resistant depression were evaluated in three 4-week, placebo-controlled, parallel-group studies (Studies 3001 and 3002 in adults 18 to 65 years of age; Study 3005 in patients 65 years or older) and one longer-term randomized withdrawal study (Study 3003). Long-term safety was also evaluated in a 12-month open-label safety study (Study 3004). Because of the seriousness of treatment-resistant depression and the ethical need for patients to receive a potentially effective treatment, all patients in the 4-week studies started a new oral antidepressant at the time of ran-



**Change in Depression Severity from Baseline in Esketamine Study 3002.**

Depression severity was assessed with the Montgomery-Åsberg Depression Rating Scale. Data are the least squares mean changes ( $\pm$ SE).

domization, which was maintained throughout the studies. Depression severity was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS; scores range from 0 to 60, with higher scores indicating more severe depression).

Study 3002, in which patients were randomly assigned to receive placebo or esketamine (56 mg or 84 mg, at the discretion of the investigator, given intranasally twice weekly), showed a statistically significant effect of esketamine as compared with placebo on the change in MADRS score from baseline to day 28. Moreover, the treatment effect was apparent at day 2 (time of first assessment) — an unusually rapid onset (see graph).

In Study 3003, patients with treatment-resistant depression who had had a response after at least 16 weeks of esketamine treatment were randomly assigned to continue receiving intranasal esketamine (56 mg or 84 mg weekly or biweekly depending on clinical response) or switch to intranasal placebo, with all patients continuing to receive a background

oral antidepressant. The study separately randomly assigned patients who had a remission (as indicated by MADRS scores  $\leq 12$ ) and those who had a response (those with MADRS reductions of 50% or more from baseline but who did not meet remission criteria). In both these groups, the time to depressive relapse was significantly longer in patients who continued esketamine treatment than among patients who switched to placebo. The study provides important evidence that esketamine is effective beyond 1 month in patients who have an initial response. Participants were treated for at least 16 weeks, with median follow-up of 3 months and maximum follow-up of more than 20 months.

For antidepressants, the FDA has generally required two positive, short-term, adequate, and well-controlled studies to meet the regulatory standard for “substantial evidence of effectiveness.” Randomized withdrawal studies are typically conducted after approval to support supplemental indications for maintenance treatment of depression. For esketa-

mine, the FDA requested a randomized withdrawal study before the new drug application was submitted, to answer crucial questions about the duration of effect and determine the appropriate maintenance-dosing interval (i.e., weekly or every other week). These questions were particularly important given esketamine’s pharmacokinetic and pharmacodynamic profile — with rapid effects but also rapid metabolism — and the unknown potential for loss of effect with long-term use. Together, Studies 3002 and 3003 support esketamine’s efficacy, durability of effect, dosing interval, and safety.

Two short-term studies, Study 3001 and Study 3005, failed to demonstrate a statistically significant treatment effect (see table). In Study 3001, two fixed doses of esketamine (56 mg and 84 mg) were compared. The higher dose did not have a statistically significant treatment effect as compared with placebo. The effect of the lower dose, although nominally significant, could not be formally evaluated owing to a prespecified testing sequence that required stopping after the higher dose failed. The timing of the treatment effect for both esketamine groups was similar to that found in Study 3002, with an apparent onset of response at day 2. Although Study 3005 (patients 65 years or older) showed no significant effect, we at the FDA were reassured that Study 3002 provided no evidence of a waning treatment effect with increasing age.

Our experience has been that approximately 50% of short-term, randomized, controlled trials for approved antidepressants may still fail to show a statistically significant effect.<sup>5</sup> For esketamine, the

Results of Short-Term Studies of Esketamine.*					
Study and Treatment Group	No. of Patients	Primary Efficacy Measure: MADRS Total Score			
		Baseline Score	Least Squares Mean Change from Baseline (95% CI)	Least Squares Mean Difference from Placebo (95% CI)	One-Sided P Value†
<b>3001</b>					
ESK, 56 mg	115	37.4±4.8	-18.9 (-21.4 to -16.4)	-4.1 (-7.7 to -0.6)	0.013
ESK, 84 mg	114	37.8±5.6	-18.2 (-20.9 to -15.6)	-3.2 (-6.9 to 0.5)	0.044
Placebo	113	37.5±6.2	-14.9 (-17.4 to -12.4)	—	—
<b>3002</b>					
ESK, 56 or 84 mg	114	37.0±5.7	-20.8 (-23.3 to -18.4)	-4.0 (-7.3 to -0.6)	0.010
Placebo	109	37.3±5.7	-16.8 (-19.3 to -14.4)	—	—
<b>3005</b>					
ESK, 28, 56, or 84 mg	72	35.5±5.9	-10.1 (-13.1 to -7.1)	-3.6 (-7.2 to 0.07)	0.029
Placebo	65	34.8±6.4	-6.5 (-9.4 to -3.6)	—	—

\* In Study 3001, the lower dose could not be tested for statistical significance because the higher dose failed. CI denotes confidence interval, ESK esketamine, and MADRS Montgomery-Åsberg Depression Rating Scale (scores range from 0 to 60, with higher scores indicating more severe depression). Data are from the Food and Drug Administration. Plus-minus values are means ±SD.

† One-sided P values are compared with P=0.025.

positive short-term trial and the positive randomized withdrawal trial provided substantial evidence of effectiveness.

A major safety concern is esketamine's abuse potential. Contributing to this concern are ketamine's "club drug" reputation and recognition of the diversion and misuse of prescription drugs. People who take esketamine may experience immediate and acutely impairing dissociation and sedation, effects that are thought to contribute to abuse. Esketamine also transiently increases blood pressure, with some increases of more than 40 mm Hg. This effect peaks about 40 minutes after administration. Prescribers will need to monitor patients' blood pressure for at least 2 hours after administration.

Balancing these potential risks with the benefits of an effective drug for a serious disease for

which there is substantial unmet need, the FDA approved esketamine with a Risk Evaluation and Mitigation Strategy (REMS). The intent of the REMS is to mitigate the risk of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, while providing access to this effective treatment for treatment-resistant depression. Esketamine will be dispensed and administered to patients only in a medically supervised health care setting where they can be monitored for adverse reactions for at least 2 hours; pharmacies that dispense esketamine must ensure that the drug is dispensed only to clinics and hospitals that are certified in the REMS.

In requiring a REMS as a condition of approval, FDA officials were mindful of the possible impact on patients' access to treatment. Participants in the Febru-

ary 12, 2019, Joint Meeting of the FDA Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee expressed this concern. Although a clear majority of the committee strongly supported approval of esketamine, they noted that patients with treatment-resistant depression in underserved areas might have to travel long distances to receive it, which could affect access and adherence. Further postmarketing experience and additional studies of esketamine, including evaluation of longer dosing intervals, may lead to new approaches that enhance access.

We also considered the patient perspective when deciding on approval. We reviewed data from functional outcome measures in the clinical trials and feedback from patient advocacy groups and individual testimony; a general

theme was the serious need for additional management options for treatment-resistant depression.

Esketamine represents a novel treatment for a severe and life-threatening condition, and its rapid onset of effect is a key benefit. The studies provide evidence of clinically meaningful efficacy when esketamine is used in combination with a newly initiated oral antidepressant. With implementation of a REMS to ensure safe use and minimize abuse poten-

tial, the benefit–risk balance is favorable, and the drug represents an important addition to the treatment options for patients with treatment-resistant depression.

Disclosure forms provided by the authors are available at NEJM.org.

From the Food and Drug Administration, Silver Spring, MD.

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 An audio interview with Dr. Roy Perlis is available at NEJM.org

## “Meaningful Use” of Cost-Measurement Systems — Incentives for Health Care Providers

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The U.S. Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009 authorized an estimated \$20 billion to \$40 billion in incentives for health care providers to both adopt and “meaningfully use” certified electronic health record (EHR) systems. One of the stated main goals of the law, encompassed by the E in the acronym, was the improvement in providers’ efficiency.<sup>1</sup> However, empirical studies have failed to document systematic improvements in provider efficiencies after the adoption of EHRs and the attestation of their meaningful use.<sup>2,3</sup> These findings are not very surprising, given that the meaningful use criteria that providers had to meet to qualify for the financial incentives did not include explicit efficiency measures. (In contrast, the Act did provide in-

centives for providers to record and report results on specific quality metrics, which, unsurprisingly, led to improvement in the measured areas.<sup>2</sup>)

Lawmakers could build on the HITECH Act by introducing additional criteria that prompt and guide providers in improving operational efficiency. Fundamental to efficiency improvements is reliable high-quality information on the resources that are used in providing services to patients. Legislation could require providers to first produce high-quality cost data and then integrate those data with clinical and operational data from their EHR systems.

In fact, providers have increasingly been implementing internal cost-measurement systems that enable them to produce detailed cost data at the level of the individual clinical service item.<sup>4</sup> Policymak-

ers could extend the certification for health information technology products currently used under the HITECH Act to such cost-measurement systems. Following the EHR meaningful-use policy, lawmakers could introduce incentives that progress from the production of cost information to the engagement of clinicians to use it for decision making.

In order to assess the potential usefulness of provider cost-measurement systems for efficiency improvements, in 2014 we conducted a survey of users of the two most widely adopted systems. These systems share the same underlying accounting methods, are licensed by health information technology companies, and have a user base of about 500 to 1000 hospitals each.

Under the HITECH Act, financial incentives are tied to the