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Intravenous Esketamine in Adult Treatment-Resistant Depression: A Double-Blind, Double-Randomization, Placebo-Controlled Study

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ABSTRACT

BACKGROUND: The purpose of this study was to assess the efficacy and safety and to explore the dose response of esketamine intravenous (IV) infusion in patients with treatment-resistant depression (TRD).

METHODS: This multicenter, randomized, placebo-controlled trial was conducted in 30 patients with TRD. Patients were randomly assigned 1:1:1 to receive an IV infusion of .20 mg/kg or .40 mg/kg esketamine or placebo over 40 minutes on day 1. The primary end point was change in Montgomery–Åsberg Depression Rating Scale total score from day 1 (baseline) to day 2. Nonresponders who received placebo on day 1 were randomly assigned again 1:1 to IV esketamine .20 mg/kg or .40 mg/kg on day 4. Secondary efficacy and safety measures were also evaluated.

RESULTS: Of the enrolled patients, 97% (29 of 30) completed the study. The least squares mean changes (SE) from baseline to day 2 in Montgomery–Åsberg Depression Rating Scale total score for the esketamine .20 mg/kg and .40 mg/kg dose groups were −16.8 (3.00) and −16.9 (2.61), respectively, and showed significant improvement (one-sided $p = .001$ for both groups) compared with placebo (−3.8 [2.97]). Esketamine showed a rapid (within 2 hours) and robust antidepressant effect. Treatment-emergent adverse events were dose dependent. The most common treatment-emergent adverse events were headache, nausea, and dissociation; the last-mentioned was transient and did not persist beyond 4 hours from the start of the esketamine infusion.

CONCLUSIONS: A rapid onset of robust antidepressant effects was observed in patients with TRD after a 40-minute IV infusion of either .20 mg/kg or .40 mg/kg of esketamine. The lower dose may allow for better tolerability while maintaining efficacy.

Keywords: Efficacy, Esketamine, Intravenous, Safety, TRD, Treatment-resistant depression

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Major depressive disorder (MDD) is a recurrent and disabling psychiatric illness that is projected to be the leading cause of disease burden worldwide by 2030 (1,2). Nearly one third of patients with MDD do not achieve remission from currently available treatments and are considered to have treatment-resistant depression (TRD), which is associated with chronicity, morbidity, and functional disability (3–6). A significant need exists to develop novel treatments for patients with TRD (7–9).

Ketamine is a racemate that comprises the R-(−)-ketamine enantiomer (arketamine) and the S-(+)-ketamine enantiomer (esketamine). Esketamine has a threefold to fourfold higher affinity for *N*-methyl-D-aspartate (NMDA) receptors than arketamine (10–12). The mechanism of action putatively results from noncompetitive binding to NMDA glutamate receptors. The rapid-onset antidepressant effects associated with ketamine and its reported efficacy in patients with depression who had been unresponsive to conventional antidepressant treatments have generated considerable interest among clinicians and researchers (13–20). In addition, most of the studies conducted previously focused on the safety and efficacy of a single intravenous (IV) ketamine infusion (.5 mg/kg) (14,16,19). However, there is evidence that most patients who respond to ketamine relapse within several days or up to 1 week after a single infusion (14,21,22). It is important to identify a strategy for maintaining the antidepressant effects of ketamine. This proof-of-concept trial evaluates, for the first time, the antidepressant efficacy and safety profile of .20 mg/kg and .40 mg/kg IV esketamine compared with IV placebo in patients with TRD.

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METHODS AND MATERIALS

The protocol and informed consent documents were approved by independent ethics committees or institutional review boards. Written informed consent was obtained from all participants at screening.

Participants

Participants included men and women 18–64 years old who met DSM-IV-TR (23) diagnostic criteria for recurrent MDD without psychotic features, based on clinical assessment and confirmed by the Mini-International Neuropsychiatric Interview (24). Based on the conventional definition of TRD (25), patients were required to have had an inadequate response to at least one antidepressant drug in their current depressive episode and an inadequate response to at least one other antidepressant either in their current or in a previous depressive episode, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (4). At screening and on day −1, patients were also required to have a total score of at least 34 on the Inventory of Depressive Symptomatology–Clinician Rated, 30-Item (mild, 12–23; moderate, 24–36; severe, 37–46; very severe, 47–84) (26). Exclusion criteria included any primary DSM-IV-TR diagnosis of active generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa; patients were also excluded if they had been acutely suicidal or homicidal requiring hospitalization in the past 12 months or had a history of previous nonresponse to ketamine or esketamine.

Study Design

This double-blind (DB), double-randomization, placebo-controlled, multicenter study comprised three phases: screening (up to 2 weeks), DB treatment (day 1 to day 7), and posttreatment (4 weeks, comprising an optional open-label phase lasting up to 2 weeks and a follow-up phase making up the remainder). On day 1 (first dose) of the DB treatment phase, patients were randomly assigned 1:1:1 to receive an IV infusion of .20 mg/kg or .40 mg/kg esketamine or placebo (.9% saline solution) over 40 minutes. All patients received the study medication by continuous infusion using an electronic infusion pump, which was managed by an anesthesiologist or other physician experienced with ventilation management in each clinical site. Responders after the single dose were defined as patients experiencing a reduction of >50% in the Montgomery–Åsberg Depression Rating Scale (MADRS) (27) total score on days 2, 3, or 4 (before the second dose) versus day 1 (baseline). On day 4 (second dose) of the DB treatment phase, responders received the same treatment as day 1. For nonresponders, the following rules were applied: 1) patients who received placebo on day 1 were randomly assigned again 1:1 to IV esketamine .20 mg/kg or .40 mg/kg, and 2) patients who received esketamine .20 mg/kg or .40 mg/kg on day 1 received esketamine .40 mg/kg on day 4.

For both randomizations (on day 1 and day 4), central randomization was implemented based on a computer-generated randomization schedule prepared by the sponsor before the study. The randomization was balanced by using randomly permuted blocks and was stratified by study center. On day −1 or day 1 before dosing, the unblinded pharmacist at each study site contacted the randomization center and provided the required subject information. The randomization center assigned a randomization number to the subject and informed the unblinded pharmacist at the site about the assigned treatment. On day 3 or day 4 (before the second dose), the investigator informed the unblinded pharmacist whether the subject was a responder or not. To maintain study blinding, the pharmacist contacted the randomization center for each subject (responders and nonresponders) to obtain a new randomization number. During the study, the subject was assessed by qualified trained site raters who were blinded to the subject's treatment. After completing the DB treatment phase, patients—with clinical input from the physician investigators—could choose to receive up to four optional open-label treatments of IV esketamine .40 mg/kg (or lower) on days 7, 10, 14, and 17. Per protocol, if IV esketamine was not well tolerated on day 1 or day 4, the dose for the open-label treatment could start at .30 mg/kg.

Outcome Measures

The primary end point was change in MADRS total score from day 1 (baseline) to day 2 (24 hours after the first infusion). The typical recall period for the MADRS is 7 days, although the MADRS was also administered for a recall period of 2 hours, 4 hours, 24 hours, and since last assessment. For the 2-hour and 4-hour recall periods, the sleep and appetite items were not assessed. Predose scores for these two items obtained on the same day were carried forward unchanged.

Secondary end points included 1) change in MADRS total score from day 1 (baseline) to day 3 and day 4 (before the second dose) and from day 4 (before the second dose) to day 7; 2) change in MADRS total score from day 1 (baseline) to day 35 (including days 7, 10, 14, 17, 21, 28, and 35); 3) proportion of responders after the single dose on days 2, 3, or 4 compared with placebo; 4) change in the Quick Inventory of Depressive Symptomatology–Self Report, 16-Item score from day 1 (baseline) to day 14; and 5) change from day 1 (baseline) to day 7 on Clinical Global Impression–Severity, Clinical Global Impression–Improvement, Patient Global Impression of Severity, and Patient Global Impression of Change.

Safety assessments included treatment-emergent adverse events (TEAEs), clinical laboratory tests, 12-lead electrocardiogram, vital signs, physical examinations, Columbia Suicide Severity Rating Scale (C-SSRS), Clinician Administered Dissociative States Scale (CADSS), Brief Psychiatric Rating Scale (BPRS), and Massachusetts General Hospital-Cognitive and Physical Functioning Questionnaire (MGH-CPFQ). All TEAEs were followed to satisfactory resolution or to a clinically stable end point.

Statistical Analyses

Between each esketamine group and placebo, a planned sample size of 10 per treatment group was estimated to provide 90% power to detect 1) a difference of 60% in response rate (one-sided Fisher's exact test, .10 significance level), assuming a 20% placebo response rate, and 2) a

difference of 40% in MADRS total score reduction (two-sample *t* test, .10 significance level), assuming SD of 32% (16).

The intent-to-treat analysis set for all efficacy analyses included all randomly assigned patients who received at least one dose of study medication and had baseline and at least one postbaseline efficacy assessment during the DB phase. A mixed-effects model using repeated measures was performed on change in MADRS total score from day 1 (baseline) to day 4 (predose). The model included baseline MADRS total score as a covariate and day, treatment, center, and day-by-treatment interaction as fixed effects as well as a random subject effect. An unstructured variance-covariance matrix was used. The response rate after the single dose in each esketamine group was compared with placebo using a logistic regression model including baseline MADRS total score and treatment.

An analysis of variance or covariance on rank test was used to analyze Clinical Global Impression–Improvement, Patient Global Impression of Change, or change in Clinical Global Impression–Severity or Patient Global Impression of Severity score from day 1 (baseline) to days 2, 3, or 4 (predose). In addition, summary statistics were provided by treatment sequence for 1) change in MADRS total score from day 4 (predose) to days 5, 6, and 7; 2) change in Quick Inventory of Depressive Symptomatology–Self Report, 16-Item score from day 1 (baseline) to days 7 and 14; and 3) Clinical Global Impression–Improvement, Patient Global Impression of Change, or change in Clinical Global Impression–Severity or Patient Global Impression of Severity score on days 5 through 7. All safety analyses were performed on the safety analysis set, which included all randomly assigned patients who received at least one dose of study drug. Safety results were summarized descriptively.

RESULTS

Baseline Characteristics

Of the 42 patients screened, 30 were randomly assigned to three treatment groups (Supplemental Figure S1). There were 29 (97%) patients who completed the DB phase and entered the posttreatment phase; 1 patient withdrew because of a TEAE (dissociative symptoms; detailed in Safety). Of the 29 patients, 26 opted for the optional open-label treatment phase. Three patients declined to participate in the open-label treatment phase because of personal reasons that prevented them from traveling to the clinic.

Patient demographics and baseline psychiatric characteristics were generally balanced across treatment groups (Table 1). The Inventory of Depressive Symptomatology–Clinician Rated, 30-Item scores were in the severe range for 80% of patients and in the very severe range for 20% of patients. In the current episode of depression, 67% of patients had had an inadequate response to at least two antidepressant treatments, and the remaining 33% of patients had had an inadequate response to one antidepressant treatment (and an inadequate response to at least one other antidepressant in a previous depressive episode). The two most common lifetime prior failed antidepressants were venlafaxine and duloxetine, both of which are serotonin-norepinephrine reuptake inhibitors. Other common failed antidepressants included mirtazapine, paroxetine, escitalopram, bupropion, and sertraline. During the DB phase, all 30 patients received two infusions of study medication. During the posttreatment phase, all 26 patients who opted for open-label treatment received at least two doses, and 21 (81%) patients received all four doses. Three patients had dose reductions (one from .40 mg/kg to .30 mg/kg and two from .40 mg/kg to .20 mg/kg) during this phase.

Efficacy

The improvement in depressive symptoms, as measured by reduction in MADRS total score 24 hours after treatment, was significantly greater in both esketamine groups compared with the placebo group (one-sided with .10 significance level, $p = .001$ for both esketamine groups). The least squares mean changes (SE) from day 1 (baseline) were −3.8 (2.97) for placebo, −16.8 (3.00) for esketamine .20 mg/kg, and −16.9 (2.61) for esketamine .40 mg/kg; effect sizes (Cohen's *d*) were −1.54 and −1.70 for the esketamine .20 mg/kg and .40 mg/kg groups, respectively. As illustrated in the plot of mean MADRS total score over time (day 1 predose until day 4 predose) (Figure 1), esketamine showed rapid (within 2 hours) and robust antidepressant effects at each dose tested. Consistent with the primary efficacy result, most secondary efficacy

Table 1. Demographic and Baseline Characteristics

	Placebo (n = 10)	Esketamine .20 mg/kg (n = 9)	Esketamine .40 mg/kg (n = 11)	Total (N = 30)
Age, Years, Mean (SD)	42.7 (10.89)	44.7 (13.38)	41.8 (11.63)	43.0 (11.59)
Sex, F/M, *n* (%)	6/4 (60/40)	5/4 (56/44)	7/4 (64/36)	18/12 (60/40)
Race, White/Other, *n* (%)	10/0 (100/0)	9/0 (100/0)	10/1 (91/9)	29/1 (97/3)
Weight, kg, Mean (SD)	77.9 (20.51)	86.8 (25.69)	78.4 (19.37)	80.8 (21.41)
Body Mass Index, kg/m^2, Mean (SD)	27.8 (5.23)	29.4 (9.94)	27.3 (4.71)	28.1 (6.65)
MADRS Total Score, Mean (SD)	33.9 (4.15)	33.1 (3.55)	33.7 (5.82)	33.6 (4.54)
IDS-C_{30} Category, Severe/Very Severe, *n* (%)	8/2 (80/20)	7/2 (78/22)	9/2 (82/18)	24/6 (80/20)
Lifetime Failed Antidepressants, *n* (%)				
2	2 (20)	5 (56)	1 (9)	8 (27)
3	1 (10)	1 (11)	3 (27)	5 (17)
≥4	7 (70)	3 (33)	7 (64)	17 (57)

F, female; IDS-C_{30}, Inventory of Depressive Symptomatology–Clinician Rated, 30-Item; M, male; MADRS, Montgomery–Åsberg Depression Rating Scale.

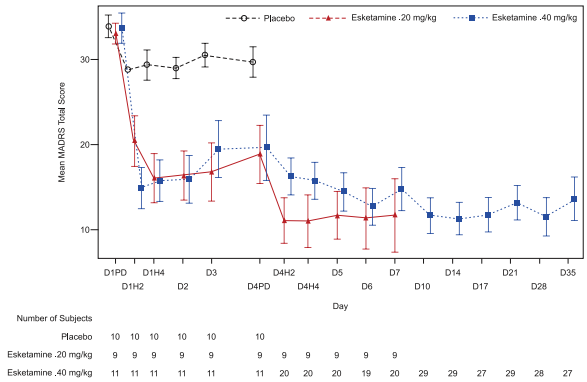

Figure 1. Mean Montgomery–Åsberg Depression Rating Scale (MADRS) total score over time by dose. The x-axis is not proportional to real time to accommodate up to day 35. Error bars represent SE. D, day; H, hour; PD, predose.

outcomes after the first DB dose showed significant differences between the two esketamine groups and the placebo group (Table 2).

There were no responders among placebo patients; the proportions of patients who met responder's criteria were 67% and 64% for the esketamine .20 mg/kg and .40 mg/kg groups, respectively. Nonresponders to the first dose (day 1) of placebo or .20 mg/kg esketamine improved after the second dose on day 4, and the largest improvements on days 5, 6, and 7 versus day 4 (predose) were observed in the groups that switched from placebo to esketamine .20 mg/kg or .40 mg/kg (Supplemental Table S1 and Supplemental Figure S2). Overall, change in MADRS total score from day 1 to day 35 indicated robust and persistent efficacy with esketamine (Supplemental Table S1).

Safety

The overall percentage of patients with TEAEs during the combined DB and posttreatment phases was similar in the placebo (50%) and esketamine .20 mg/kg (50%) treatment sessions but was higher in the esketamine .40 mg/kg (70%) treatment session (Table 3). The three groups in Table 3 are per actual doses in individual treatment sessions and are not mutually exclusive, as the esketamine .40 mg/kg treatment session included all randomly assigned patients and had longer exposure duration to the study drug because all patients who entered the open-label treatment phase per protocol received the .40 mg/kg dose. The most common (reported by ≥10% of patients) TEAEs were as follows: placebo, nausea (20%), headache (20%), and tooth infection (10%); esketamine .20 mg/kg, nausea (25%) and headache (17%); esketamine .40 mg/kg, headache (23%), dissociation (17%), and nausea (10%). During the esketamine-free follow-up phase, the TEAEs reported by at least one patient were headache (11%), nausea (7%), and constipation (7%).

Most TEAEs were mild or moderate. There were two severe TEAEs during the DB phase and one severe TEAE during the posttreatment phase. One of the two severe TEAEs during the DB phase led to the discontinuation of study drug. The patient (who had received placebo on day 1) experienced intolerable dissociative symptoms (reported as visual hallucinations, depersonalization and derealization, and disturbances in logical thinking) with onset during the infusion of .40 mg/kg esketamine on day 4 that lasted for 1 hour. The infusion was interrupted at 28 minutes, and the event resolved without any other intervention. The CADSS score at 40 minutes after the infusion started was 51, but it decreased to 33 at 4 hours postinfusion. The investigator assessed the event as very likely related to the study drug. The other severe TEAE during the DB phase occurred 15 minutes after infusion of esketamine .40 mg/kg on day 1. This TEAE was moderate initially but intensified to severe dissociation at 40 minutes postinfusion and then returned to moderate dissociation and resolved. The CADSS score at 40 minutes postinfusion was 75, but it decreased to 0 at 4 hours postinfusion. The one severe TEAE during the posttreatment phase was also the only serious adverse event of the study. This patient received six doses of esketamine (.20 mg/kg on day 1 and .40 mg/kg on days 4, 7, 10, 14, and 17) and responded on days 10, 14, 17, 28, and 35. At all assessment visits, the patient's CADSS and BPRS scores were 0, and vital signs, electrocardiograms, and clinical laboratory assessments were within normal ranges. On day 23, the patient fell and sustained an injury to his wrist, and later his vehicle collided with a parked car when he drove. Examination the next day (day 24) revealed a fracture in his right wrist, and the patient was found to have a lung tumor with brain metastasis, which had not been known at study entry. The investigator considered these serious adverse events to be unrelated to study medication. The patient was referred for treatment of lung cancer.

No deaths occurred during the study. No clinically significant changes in laboratory tests, electrocardiograms, or physical examinations were observed. The only clinically significant vital sign abnormalities were a case of irregular breathing and a case of transient high blood pressure (both with esketamine .40 mg/kg dosing), which resolved within 2 hours without intervention. During the combined DB and posttreatment phases, the C-SSRS results (Supplemental Table S2) indicated that no patients had treatment-emergent suicidal behavior or suicidal intent. The C-SSRS suicidal ideation scores either improved or were maintained from screening through the open-label treatment portion of the posttreatment phase for all but one patient (received esketamine .40 mg/kg on days 1, 4, 10, and 17), whose C-SSRS scores fluctuated between improvement and worsening at various time points but ultimately approached the baseline level at the last measurement point on day 17. The MGH-CPFQ outcomes (Supplemental Table S3) appeared to indicate that esketamine treatment was associated with improvement of cognitive and physical functioning.

The mean BPRS total score reached a maximum (which was dose related) at 30–40 minutes after the start of infusion of .20 mg/kg or .40 mg/kg esketamine and then diminished and approached the baseline value 2 hours after the start of infusion (Figure 2A). The CADSS results displayed a similar pattern as the BPRS results. The mean CADSS total score was the highest (which was dose related) at 40 minutes after the start of infusion of .20 mg/kg or .40 mg/kg esketamine but returned to the baseline level 4 hours after the start of infusion (Figure 2B). No subjects had dissociative

Table 2. Secondary Efficacy Outcomes After First Double-Blind Dose

	Placebo (n = 10)	Esketamine .20 mg/kg (n = 9)	Esketamine .40 mg/kg (n = 11)
Change in MADRS Total Score, Baseline to Day 3			
LS mean change (SE)	−2.3 (3.38)	−16.3 (3.45)	−13.4 (3.03)
p value (minus placebo)[a]	—	.003	.009
80% CI[a]	—	(−19.9, −8.1)	(−16.7, −5.4)
Change in MADRS Total Score, Baseline to Day 4 (Predose)			
LS mean change (SE)	−3.1 (3.51)	−14.2 (3.59)	−13.2 (3.16)
p value (minus placebo)[a]	—	.014	.018
80% CI[a]	—	(−17.3, −4.9)	(−16.0, −4.1)
Proportion of Responders to First Dose			
Responder, n (%)[b]	0	6 (67)	7 (64)
Odds ratio (vs. placebo)	—	40.2	34.5
p value (vs. placebo)[c]	—	.013	.014
Change in CGI-S Score, Baseline to Day 2			
Mean change (SD)	−.2 (.42)	−1.4 (1.33)	−1.6 (1.21)
p value (minus placebo)[d]	—	.003	.002
Change in CGI-S Score, Baseline to Day 3			
Mean change (SD)	−.2 (.63)	−1.3 (1.50)	−1.4 (1.36)
p value (minus placebo)[d]	—	.013	.012
Change in CGI-S Score, Baseline to Day 4 (Predose)			
Mean change (SD)	−.2 (.63)	−1.6 (1.42)	−1.4 (1.36)
p value (minus placebo)[d]	—	.006	.007
CGI-I Score, Day 2			
Mean (SD)	3.7 (.48)	2.6 (1.24)	2.5 (1.21)
p value (minus placebo)[e]	—	.009	.007
CGI-I Score, Day 3			
Mean (SD)	3.9 (.74)	2.6 (1.01)	2.8 (1.25)
p value (minus placebo)[e]	—	.004	.018
CGI-I Score, Day 4 (Predose)			
Mean (SD)	3.7 (.48)	2.7 (1.00)	2.8 (1.17)
p value (minus placebo)[e]	—	.007	.015
Change in PGI-S Score, Baseline to Day 2			
Mean change (SD)	−.2 (.42)	−.2 (.44)	−.6 (1.12)
p value (minus placebo)[d]	—	.460	.082
Change in PGI-S Score, Baseline to Day 3			
Mean change (SD)	−.2 (.42)	−.7 (.87)	−.4 (.51)
p value (minus placebo)[d]	—	.078	.088
Change in PGI-S Score, Baseline to Day 4 (Predose)			
Mean change (SD)	−.3 (.48)	−.8 (.97)	−.6 (.82)
p value (minus placebo)[d]	—	.151	.132
PGI-C Score, Day 2			
Mean (SD)	3.9 (.32)	3.2 (.67)	3.2 (.87)
p value (minus placebo)[e]	—	.004	.006
PGI-C Score, Day 3			
Mean (SD)	3.9 (.57)	3.0 (.71)	3.6 (1.43)
p value (minus placebo)[e]	—	.013	.115
PGI-C Score, Day 4 (Predose)			
Mean (SD)	3.9 (.57)	3.1 (.78)	3.3 (.91)
p value (minus placebo)[e]	—	.012	.020

CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; CI, confidence interval; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity.

[a]p values (one-sided with level of significance of 10%) and CIs (two-sided) are based on the mixed-effect model using repeated measures with baseline score as a covariate and day, treatment, center, and day-by-treatment interaction as fixed effects as well as a random patient effect.

[b]Responders were defined as patients who had a reduction in MADRS total score of >50% from baseline on days 2, 3, or 4 (predose).

[c]p values (one-sided with level of significance of 10%) are based on the logistic regression model with treatment and baseline MADRS.

[d]p values (one-sided with level of significance of 10%) are based on the analysis of covariance on rank test with original baseline score as a covariate and with treatment and center effects.

[e]p values (one-sided with level of significance of 10%) are based on the analysis of variance on rank test with treatment and center.

symptoms that persisted beyond 4 hours after drug administration.

DISCUSSION

The primary efficacy end point was reached in demonstrating improvement in depressive symptoms, as measured by change in MADRS total score from day 1 to day 2. The results were statistically significant and clinically meaningful for both esketamine dose groups, .20 mg/kg and .40 mg/kg, versus placebo, as demonstrated by the high effect size. No clear dose response was observed between the two doses.

Robust onset of efficacy for both esketamine dose groups was evident 2 hours after infusion (the earliest time point measured), as assessed by the MADRS total score. These results stand in sharp contrast to the time course of response typically seen with conventional oral treatments for MDD, which are reported for efficacy end points at 4–12 weeks postdose (28). The strong efficacy signal found in this trial was also reflected by the responder analysis, which showed 67% (esketamine .20 mg/kg) and 64% (esketamine .40 mg/kg) of the patients with TRD responding, whereas no patient in this study responded to placebo infusion. These response rates were achieved within 3 days of a single esketamine dose. In contrast, approved oral combinations of antipsychotics and monoaminergic antidepressants for TRD or inadequately responsive MDD have response rates of approximately 37%–56% after 6–12 weeks (28). Finally, response rates by MADRS with IV esketamine in the present study appear to be similar to the rates observed with IV ketamine in published studies (13,16,18,21). Although differences in study design limit direct comparisons, the results support the hypothesized similar efficacy of esketamine to racemic ketamine, based on the higher affinity of esketamine for the NMDA receptor. With esketamine being three to four times more potent than arketamine at NMDA receptors (10–12), .20 mg/kg and .40 mg/kg esketamine correspond to a racemic ketamine dose equivalent of approximately .31 mg/kg and .62 mg/kg (11), respectively. Moreover, because the metabolism of esketamine tends to be higher in the absence of arketamine (29,30), the .40 mg/kg

Table 3. TEAEs for Combined Double-Blind and Open-Label Phases by Dose

Patients reporting, *n* (%)[a]	Placebo[b] (*n* = 10)	Esketamine .20 mg/kg[c] (*n* = 12)	Esketamine .40 mg/kg[d] (*n* = 30)
Patients With at Least One TEAE	5 (50)	6 (50)	21 (70)
Patients With Drug-Related TEAEs[e]	3 (30)	3 (25)	20 (67)
Patients With TEAEs Leading to Death	0	0	0
Patients With Drug-Related SAEs	0	0	0
Discontinuation of Study Agent Because of TEAEs[f]	0	0	0
TEAEs Reported by at Least 5% of Patients[g]			
Dissociation	0	1 (8)	5 (17)
Dizziness	0	1 (8)	1 (3)
Dry mouth	0	1 (8)	2 (7)
Headache	2 (20)	2 (17)	7 (23)
Nasopharyngitis	0	0	2 (7)
Nausea	2 (20)	3 (25)	3 (10)
Oropharyngeal pain	0	1 (8)	1 (3)
Paresthesia	0	0	2 (7)
Rash	0	1 (8)	0
Thrombophlebitis	0	1 (8)	0
Tooth infection	1 (10)	0	0
Vertigo	0	0	2 (7)
Vomiting	0	1 (8)	1 (3)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]Percentages are calculated with the number of patients in each group as denominator. Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.

[b]Placebo includes 10 patients in the placebo group from day 1 (baseline) to day 4 (predose).

[c]Esketamine .20 mg/kg includes nine patients in the esketamine .20 mg/kg group from day 1 (baseline) to day 4 (predose) and three nonresponders to placebo from day 1 (baseline) to day 4 (predose) who were then randomly assigned to esketamine .20 mg/kg treatment during the second randomization.

[d]Esketamine .40 mg/kg includes all randomly assigned patients.

[e]Study drug relationships of "possible," "probable," and "very likely" are included in this category.

[f]Action taken of "drug withdrawn" is included in this category but "drug interrupted" is not.

[g]Reported dictionary version: Medical Dictionary for Regulatory Activities 15.1; http://www.meddra.org/how-to-use/support-documentation/english.

esketamine dose was selected as comparable to .5 mg/kg ketamine, whereas the .20 mg/kg dose was selected to test the efficacy of a lower dose. However, doses lower than those assessed herein warrant testing to establish a minimum effective dose.

Similar to ketamine, esketamine led to transient dissociative and psychotic symptoms. According to CADSS severity categories (16,31), the peak mean CADSS total scores at 40 minutes postinfusion on day 1 for the esketamine .20 mg/kg and .40 mg/kg groups would be categorized as high. However, symptoms subsided to baseline levels within 4 hours. The CADSS scores showed evidence of dose dependence on each DB dosing day. A similar pattern was observed for psychotic-like effects measured using BPRS total scores. These results are similar to results of IV ketamine studies (13,14,16–18).

When used in high dosages or as a drug of abuse, ketamine has also been associated with short-lasting, completely reversible or long-lasting cognitive impairment. Cognitive assessments of healthy volunteers showed that subanesthetic infusion of ketamine leads to transient, dose-dependent cognitive effects (32). In a 1-year study of recreational users, infrequent ketamine use (less than four times a week but at least once a month) of presumably high dosages was not associated with long-term cognitive impairment, but frequent use (more than four times a week) was associated with impaired short-term and long-term memory (33). The patients with TRD in the present study endorsed subjective symptoms reflecting cognitive impairment at baseline (evidenced by the mean baseline MGH-CPFQ scores), which was expected because "diminished ability to think or concentrate, or indecisiveness" is one of the core DSM-IV-TR criteria for MDD (23). After the first dose on day 1, an improvement in the MGH-CPFQ score was observed in patients who were assigned to both esketamine treatment arms. After the second dose on day 4, the largest MGH-CPFQ improvements were observed in patients who switched from placebo to esketamine .20 mg/kg or .40 mg/kg, whereas patients previously treated with esketamine on day 1 maintained their favorable rating. Further studies with formal cognitive testing are needed to evaluate the long-term risks and benefits of novel treatment paradigms targeted to the NMDA receptor.

Our study has some limitations. One design limitation was that no CADSS assessment was obtained between the 40-minute and the 4-hour postdose time points, so we could not establish the precise time course of either the peak dissociative symptoms or of their resolution. Based on the ketamine literature, we anticipate that these side effects would have resolved by the 2-hour time point, but the data acquired here do not allow that inference. Another potential limitation was that the 0% response rate to placebo was lower than the hypothesized 20% response rate estimated for the power analysis. Relatively few data have been published that provide placebo response rates after only one treatment day; most studies instead have assessed such rates following ≥1 week of placebo administration. Nevertheless, even for a TRD sample and assessments after 1 day, the rate observed in this study appears remarkably low. In addition, although the modest sample size of 30 subjects is greater than that for randomized controlled and open-label studies of racemic ketamine (18,34), the small sample size limits the interpretations that can be drawn and the generalizability of the sample to the broader population of patients with TRD. Finally, the use of only two doses limits the assessment of the full dose range and the optimal dosing, and the lowest effective dose remains to be established (especially doses <.20 mg/kg, which will be explored in future studies). However, this proof-of-concept study is the first randomized controlled trial investigating IV esketamine in the treatment of TRD, and it provides valuable information for further investigation.

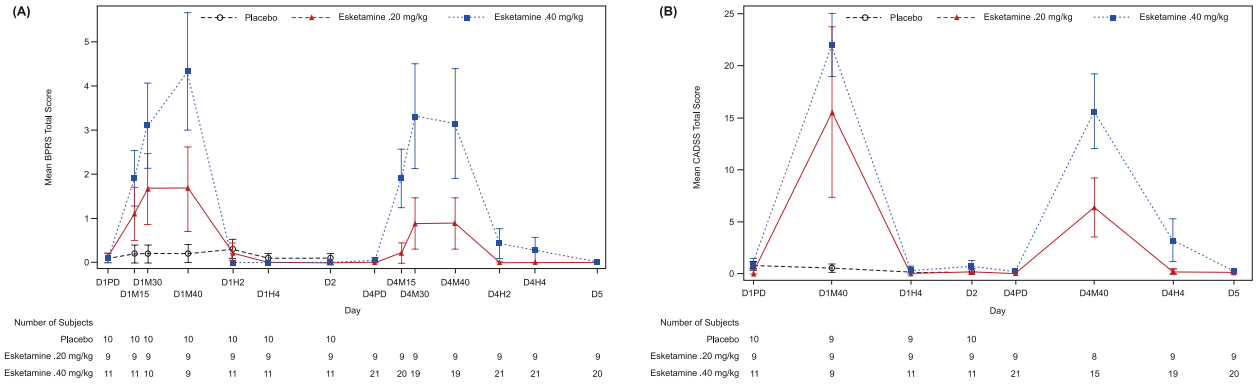

Figure 2. **(A)** Mean plot of Brief Psychiatric Rating Scale (BPRS) total score over time in the double-blind phase by dose. **(B)** Mean plot of Clinician Administered Dissociative States Scale (CADSS) total score over time in the double-blind phase by dose. Error bars represent SE. D, day; H, hour; M, minute; PD, predose.

In conclusion, although the sample size was limited, approximately 67% of patients with TRD who were treated with low-dose IV esketamine experienced rapid (within hours), robust, and persistent improvement of depressive symptoms, with limited adverse effects. The outcome measures reflecting improvement in depressive symptoms did not differ significantly between the two doses of IV esketamine tested here, suggesting that the lower dose of esketamine may allow for better tolerability while maintaining efficacy. Additional studies are required to assess if alternative formulations of esketamine can be developed to avoid the inconvenience of IV infusion and how best to develop a treatment paradigm that enables a sustained long-term response.

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Esketamine is not approved for the treatment of major depressive disorder.

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ClinicalTrials.gov: A Study of the Efficacy of Intravenous Esketamine in Adult Patients With Treatment-Resistant Depression; https://clinicaltrials.gov/ct2/show/NCT01640080; NCT01640080.

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REFERENCES

1. World Health Organization (2008): The Global Burden of Disease: 2004 Update. Geneva, Switzerland: World Health Organization.
2. Collins PY, Patel V, Joestl SS, March D, Insel TR, Daar AS, *et al*. (2011): Grand challenges in global mental health. Nature 475:27–30.
3. Gaynes BN, Warden D, Trivedi MH, Wisniewski SR, Fava M, Rush AJ (2009): What did STAR*D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr Serv 60: 1439–1445.
4. Fava M, Davidson KG (1996): Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 19:179–200.
5. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al*. (2006): Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 163:1905–1917.
6. Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, *et al*. (2006): Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: Implications for clinical practice. Am J Psychiatry 163:28–40.
7. Lapidus KA, Soleimani L, Murrough JW (2013): Novel glutamatergic drugs for the treatment of mood disorders. Neuropsychiatr Dis Treat 9:1101–1112.
8. Murrough JW, Charney DS (2012): Is there anything really novel on the antidepressant horizon? Curr Psychiatry Rep 14:643–649.
9. Murrough JW (2012): Ketamine as a novel antidepressant: From synapse to behavior. Clin Pharmacol Ther 91:303–309.
10. Kohrs R, Durieux ME (1998): Ketamine: Teaching an old drug new tricks. Anesth Analg 87:1186–1193.
11. Oye I, Paulsen O, Maurset A (1992): Effects of ketamine on sensory perception: Evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 260:1209–1213.
12. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997): Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 7: 25–38.

13. Murrough JW, Iosifescu DV, Chang LC, Al Jurdi RK, Green CE, Perez AM, *et al*. (2013): Antidepressant efficacy of ketamine in treatment-resistant major depression: A two-site randomized controlled trial. Am J Psychiatry 170:1134–1142.
14. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al*. (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63:856–864.
15. Mathew SJ, Shah A, Lapidus K, Clark C, Jarun N, Ostermeyer B, *et al*. (2012): Ketamine for treatment-resistant unipolar depression: Current evidence. CNS Drugs 26:189–204.
16. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS (2010): Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial. Int J Neuropsychopharmacol 13: 71–82.
17. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, *et al*. (2010): Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 67:139–145.
18. Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, aan het Rot M, *et al*. (2013): Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 74:250–256.
19. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, *et al*. (2000): Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354.
20. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, *et al*. (2010): Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 71:1605–1611.
21. Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, *et al*. (2012): Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: Results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 37:1526–1533.
22. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception II: Implications for major psychiatric disorders. Biol Psychiatry 54:515–528.
23. American Psychiatric Association (2000): Diagnostic and Statistical Manual of Mental Disorders, 4th ed, text rev. Washington, DC: American Psychiatric Association.
24. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, *et al*. (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59(suppl 20):22–33; quiz 34–57.
25. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G (2006): A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. Depress Anxiety 23:364–372.
26. Trivedi MH, Rush AJ, Ibrahim HM, Carmody TJ, Biggs MM, Suppes T, *et al*. (2004): The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: A psychometric evaluation. Psychol Med 34:73–82.
27. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389.
28. Spielmans GI, Berman MI, Linardatos E, Rosenlicht NZ, Perry A, Tsai AC (2013): Adjunctive atypical antipsychotic treatment for major depressive disorder: A meta-analysis of depression, quality of life, and safety outcomes. PLoS Med 10:e1001403.
29. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K (1993): Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using a stereoselective analytical method. Br J Anaesth 70:666–671.
30. Persson J, Hasselstrom J, Maurset A, Oye I, Svensson JO, Almqvist O, *et al*. (2002): Pharmacokinetics and non-analgesic effects of S- and R-ketamines in healthy volunteers with normal and reduced metabolic capacity. Eur J Clin Pharmacol 57:869–875.
31. Petrakis IL, Limoncelli D, Gueorguieva R, Jatlow P, Boutros NN, Trevisan L, *et al*. (2004): Altered NMDA glutamate receptor antagonist response in individuals with a family vulnerability to alcoholism. Am J Psychiatry 161:1776–1782.
32. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al*. (1994): Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 51:199–214.
33. Morgan CJ, Muetzelfeldt L, Curran HV (2010): Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. Addiction 105:121–133.
34. Lapidus KA, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, *et al*. (2014): A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 76:970–976.