Article

Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site Randomized Controlled Trial

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Objective: Ketamine, a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant effects, but small study groups and inadequate control conditions in prior studies have precluded a definitive conclusion. The authors evaluated the rapid antidepressant efficacy of ketamine in a large group of patients with treatment-resistant major depression.

Method: This was a two-site, parallel-arm, randomized controlled trial of a single infusion of ketamine compared to an active placebo control condition, the anesthetic midazolam. Patients with treatment-resistant major depression experiencing a major depressive episode were randomly assigned under double-blind conditions to receive a single intravenous infusion of ketamine or midazolam in a 2:1 ratio (N=73). The primary outcome was change in depression severity 24 hours after drug administration, as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: The ketamine group had greater improvement in the MADRS score than the midazolam group 24 hours after treatment. After adjustment for baseline scores and site, the MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71). The likelihood of response at 24 hours was greater with ketamine than with midazolam (odds ratio, 2.18; 95% CI, 1.21 to 4.14), with response rates of 64% and 28%, respectively.

Conclusions: Ketamine demonstrated rapid antidepressant effects in an optimized study design, further supporting NMDA receptor modulation as a novel mechanism for accelerated improvement in severe and chronic forms of depression. More information on response durability and safety is required before implementation in clinical practice.

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Major depressive disorder is among the most disabling illnesses worldwide (1). A substantial proportion of patients do not achieve a clinically meaningful benefit despite multiple antidepressant trials and augmentation strategies (2, 3). Treatment-resistant major depression, defined as an insufficient response to at least two adequate antidepressant treatments, is associated with low rates of improvement with currently available antidepressant treatments (3, 4), and an intervention for refractory cases is thus an important unmet clinical need. Treatments that exert rapid antidepressant effects are a complementary unmet need, as the usual lag time to therapeutic effect is 4–12 weeks if patients show a response (2). Modulation of monoamine neurotransmitter systems (e.g., norepinephrine, dopamine, or serotonin) is the pharmacological mechanism underlying almost all current antidepressant agents, likely accounting for their similar efficacy and therapeutic time course (5). Therefore, engaging novel molecular targets outside of the monoamine system will likely be required in order to engender a clinically meaningful advance in depression therapeutics (6, 7).

Converging evidence from in vivo brain imaging studies, postmortem investigations, and gene expression studies implicates abnormalities in glutamatergic signaling in the pathophysiology of major depressive disorder (8–10). Ketamine—a glutamate *N*-methyl-D-aspartate (NMDA) receptor antagonist—was associated with rapid antidepressant effects in patients with major depressive disorder (including treatment-resistant major depression) in several small studies and case reports (11–15). Antidepressant activity was observed within hours of a single subanesthetic intravenous infusion, representing a potential paradigm shift in therapeutic approaches for major depressive disorder. Methodological limitations of prior studies, however, including small study groups and the use of a crossover design with an inert placebo control condition (11, 12), precluded definitive conclusions regarding ketamine's antidepressant efficacy. Identifying an appropriate control

This article is featured in this month's AJP Audio, is an article that provides Clinical Guidance (p. 1142), and is discussed in an Editorial by Dr. Rush (p. 1079)

condition for testing the rapid antidepressant effects of ketamine has been particularly challenging since transient psychoactive effects associated with ketamine have the potential to undermine the integrity of the study blind.

We designed the present study to test the rapid antidepressant efficacy of ketamine in a relatively large group of subjects with treatment-resistant major depression, using an active placebo control condition (i.e., the anesthetic benzodiazepine midazolam) to optimize blinding and mitigate the influence of nonspecific factors on antidepressant outcome. We hypothesized that ketamine would be superior to midazolam in improving depressive symptoms 24 hours following a single infusion. The primary outcome at 24 hours was chosen to reflect a potential rapid antidepressant effect while avoiding any overlap with the expected transient psychoactive effects of ketamine or midazolam.

Method

Study Design and Patients

The study enrolled patients at two academic sites, Baylor College of Medicine and Icahn School of Medicine at Mount Sinai, between November 2010 and August 2012. Patients were eligible to participate if they were 21 to 80 years of age, had a primary diagnosis of major depressive disorder as assessed with the Structured Clinical Interview for DSM-IV—Patient Edition (16), and had an inadequate response to at least three therapeutic trials of an antidepressant according to the criteria of the Antidepressant Treatment History Form (17). The form was completed by a study psychiatrist using all available information from the patient report, information provided by a family member or caretaker, pharmacy records, and medical records. Additional study inclusion criteria included a history of at least one previous major depressive episode prior to the current episode (recurrent major depressive disorder) or the combination of a chronic major depressive episode (at least 2 years' duration) and a score of 32 or greater on the Inventory of Depressive Symptomatology—Clinician Rated (18) at screening and within 24 hours of infusion. Patients were excluded if they had a lifetime history of a psychotic illness or bipolar disorder, alcohol or substance abuse in the previous 2 years, unstable medical illness, serious and imminent suicidal or homicidal risk, or a score less than 27 on the Mini-Mental State Examination (19) or if they were taking contraindicated medications. Each patient had a physical examination, routine hematologic and biochemical tests, urine toxicology measurements, and an electrocardiogram (ECG) to detect unstable medical illness or substance use.

The institutional review boards at both participating sites approved the study. After complete description of the study to the subjects, written informed consent was obtained.

Study Procedures

The study patients were free of concomitant antidepressants and other psychotropic medications for the duration of the study with the exception of a stable dose of a nonbenzodiazepine hypnotic (e.g., zolpidem, 10 mg nightly). The protocol required patients to be drug free prior to the infusion, for at least 4 weeks for patients who were taking fluoxetine and for at least 1 week for those taking other medications.

Randomly assigned in a 2:1 ratio, the patients received a single intravenous infusion of ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg) infused over 40 minutes. Selection of midazolam—a short-acting benzodiazepine and anesthetic agent—as the control condition was based in part on pharmacokinetic characteristics similar to those of ketamine: fast onset of action and short elimination half-life (20). We sought to provide an anesthetic agent as a control condition that would mimic ketamine in terms of the time course of nonspecific behavioral effects (e.g., sedation, disorientation). The selected midazolam dose of 0.045 mg/kg is considered equipotent to 0.5 mg/kg of ketamine (21). The study research pharmacist prepared sealed envelopes that contained the drug identity; all other study personnel, including investigators, anesthesiologists, raters, patients, and data analysts, were masked to treatment assignment.

Following admission to a clinical research unit and an overnight fast, an indwelling catheter was placed in the antecubital vein of the nondominant arm, and pulse, blood pressure, digital pulse oximetry, and ECG monitoring were instituted, according to procedures previously described (13, 22). A trained rater conducted symptom ratings during the infusion and for 240 minutes following the start of the infusion. Patients were discharged from the research unit 24 hours after the infusion and received outpatient evaluations 48 hours, 72 hours, and 7 days postinfusion. The patients were instructed to abstain from psychotropic medications and to abstain from substances of abuse and alcohol while at home. Nonresponders were considered patients with less than 50% improvement from baseline in the score on the Montgomery-Åsberg Depression Rating Scale (MADRS) (23). As directed by the protocol, we stopped following the nonresponders 7 days after the infusion. Responders were followed biweekly until relapse or for an additional 4 weeks, whichever came sooner.

Outcomes

The primary outcome was reduction in depression severity as assessed on the clinician-administered MADRS (23) 24 hours following infusion. Trained raters, who were not involved in the infusion-day procedures and who were unaware of treatment-group assignment and infusion-related side effects, performed clinical assessments for the primary outcome at 24 hours and subsequent evaluations. The raters were experienced research staff extensively trained in the use of the instruments, and the MADRS rating conventions were pilot tested in prior ketamine studies in treatment-resistant major depression (13, 22). The two primary raters at each site achieved a high level of interrater reliability, 0.988.

Prior studies suggest that the peak antidepressant effects of ketamine occur within 24 hours of administration (12, 13). We selected the 24-hour change in depression severity as the primary endpoint for the current study because the interval after infusion was considered long enough that acute sedating and other side effects were not likely to be contributory. The interval was sufficiently short such that the individuals who showed substantial mood improvement were unlikely to have already relapsed. Secondary outcomes included the MADRS response rate (defined as a reduction in the baseline score by 50% or more), change in score on the Quick Inventory of Depressive Symptomatology—Self-Report (24), scores on the Clinical Global Impression (CGI) severity and improvement measures (25), and durability of benefit for up to 7 days following infusion.

We recorded general adverse events, dissociative states, and psychotomimetic side effects at regular intervals throughout the study, using the Patient Rated Inventory of Side Effects (26), the Clinician-Administered Dissociative States Scale (27), and the Brief Psychiatric Rating Scale positive symptom subscale (28), respectively.

Statistical Analysis

Power estimates for continuous MADRS scores and dichotomous response outcomes each assumed a two-tailed alpha level

TABLE 1. Characteristics of Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]

Characteristic	Ketamine (N=47)		Midazolam (N=25)	
	N	%	N	%
Female sex	26	55	11	44
White	37	79	23	92
Hispanic ethnicity	7	15	3	12
Recurrent major depressive disorder	28	60	16	64
Chronic index episode (lasting ≥2 years)	33	70	16	64
Prior suicide attempt	14	30	9	36
Prior psychiatric hospitalization	23	49	13	52
Melancholic features	31	66	16	64
Atypical features	4	9	6	24
Unemployed	27	57	15	60
Married or cohabiting	19	40	10	40
	Mean	SD	Mean	SD
Number of major depressive episodes	3.7	3.7	4.0	3.4
Duration of index episode (months)	146.6	158.3	109.2	139.0
Previous antidepressant failures	5.1	2.0	5.0	1.8
Age (years)	46.9	12.8	42.7	11.6
Education (years)	16.5	2.3	16.2	2.3
Age at first major depressive episode (years)	22.2	9.9	19.8	9.8
Duration of major depressive disorder (years)	24.2	12.5	19.7	14.8
Body mass index (kg/m^2)	29.4	7.5	27.0	6.1
Scores on clinical measures				
30-item Inventory of Depressive Symptomatology—Clinician Rated[b]	48	9	48	10
Montgomery-Åsberg Depression Rating Scale[c]	32.6	6.1	31.1	5.6
16-item Quick Inventory of Depressive Symptomatology—Self-Report[d]	16.6	4.1	16.3	4.5

[a] Modified intention-to-treat group.
[b] Scores range from 0 to 84, with higher scores indicating a greater severity of symptoms.
[c] Scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.
[d] Scores range from 0 to 27, with higher scores indicating a greater severity of symptoms.

of 0.05. Conservative effect size estimates, Cohen's d=0.71 for MADRS scores and response rates of 60% versus 15% for ketamine and midazolam, respectively, were derived from previous reports (11, 12). A planned study group of 72 patients randomly assigned in a 2:1 ratio (ketamine versus midazolam) provided 80% and 96% power to detect a change in MADRS scores and response rates, respectively, at 24 hours as a function of treatment.

Modified intention-to-treat analyses included all randomly assigned patients with baseline measurement and at least one postbaseline measurement. Sensitivity analyses evaluated the robustness of conclusions in relation to missing data. We used general linear modeling (with the Proc Mixed function of SAS version 9.3 [SAS Institute, Cary, N.C.]) to examine MADRS scores at 24 hours as a function of treatment after controlling for baseline MADRS score and site. Exact logistic regression (Proc Logistic function, SAS version 9.3) evaluated response as a function of treatment group after adjustment for site.

Secondary analyses of scores on the Quick Inventory of Depressive Symptomatology and CGI severity and improvement scales employed general linear modeling and ordinal logistic regression (Proc Logistic, SAS), respectively, to evaluate treatment after adjustment for baseline measurements and site. Among the responders, general linear mixed modeling was used to evaluate the trajectory of change in the follow-up MADRS scores as a function of time, treatment, and the interaction of time and treatment. All statistical tests used a threshold of $p \leq 0.05$ for significance. Safety and tolerability were analyzed with the use of descriptive statistics.

Results

Study Participants

Of 116 patients who completed informed consent procedures, 73 met all eligibility criteria and were randomly assigned to the study medications. Of these 73, all but one patient (assigned to the ketamine group) received a study medication and completed 24-hour assessments (as shown in Figure SF1 in the data supplement accompanying the online version of this article). Sixty-seven patients completed all assessments through postinfusion day 7.

The ketamine and midazolam groups were well matched with respect to demographic and clinical characteristics. The patients were chronically depressed, had had relatively early illness onsets, and had moderate-to-severe symptom severity (Table 1).

Primary Outcome

Patients in the ketamine group had significantly greater improvement in the MADRS score at 24 hours than the midazolam group (Table 2). After adjustment for baseline scores and site, the mean MADRS score was lower in the ketamine group than in the midazolam group by 7.95 points (95% confidence interval [CI], 3.20 to 12.71), corresponding to a Cohen's d of 0.81. MADRS scores at 24 hours did not differ as a function of site ($F=0.63$, $df=1, 70$, $p=0.43$).

Secondary Outcomes

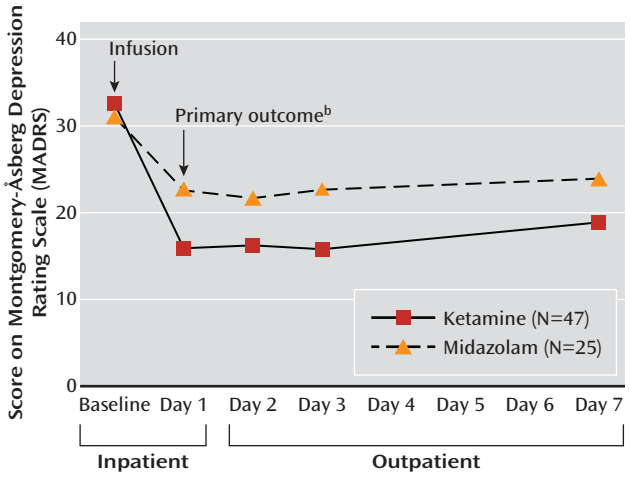
Additional 24-hour outcomes. Consistent with the primary outcome, the likelihood of treatment response at 24 hours was greater for the ketamine group than for the midazolam group (odds ratio, 2.18; 95% CI, 1.21 to 4.14; $p \leq 0.006$); the response rates were 64% and 28%, respectively. This represents a number needed to treat of 2.8. After adjustment for baseline scores and site, the mean score on the Quick Inventory of Depressive Symptomatology—Self-Report was lower in the ketamine group than in the midazolam group by 3.40 points (95% CI, 0.78 to 6.01; $p \leq 0.02$), corresponding to a Cohen's d of 0.63 (Table 2). Responder status at 24 hours did not differ as a function of site (exact p=0.19). Ketamine also improved the odds of being rated as improved or much improved on the CGI improvement measure (odds ratio,

TABLE 2. Clinical Status at 24 Hours of Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]

Clinical Measure	Ketamine (N=47)		Midazolam (N=25)	
	Mean	95% CI	Mean	95% CI
Montgomery-Åsberg Depression Rating Scale (MADRS) score[b]	14.77	11.73–17.80	22.72	18.85–26.59
Quick Inventory of Depressive Symptomatology—Self Report score[c]	8.38	6.71–10.05	11.78	9.63–13.92
	N	%	N	%
Response: ≥50% decrease in MADRS score[d]	30	64	7	28
Clinical Global Impression Scale				
Improvement rating of 2 (much improved) or 1 (very much improved)[e]	29	62	6	24
Severity rating of 2 (minimally ill) or 1 (not at all ill)[f]	25	53	2	8

[a] Modified intention-to-treat group.
[b] Significantly lower score in the ketamine group (t=3.34, df=68, p≤0.001).
[c] Significantly lower score in the ketamine group (t=6.69, df=68, p≤0.01).
[d] Significantly higher proportion in the ketamine group (p≤0.006, exact logistic regression).
[e] Significantly higher proportion in the ketamine group (p≤0.004, ordinal logistic regression).
[f] Significantly higher proportion in the ketamine group (p≤0.001, ordinal logistic regression).

FIGURE 1. Change in Depression Severity Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]



[a] Modified intention-to-treat group. MADRS scores range from 0 to 60, with higher scores indicating a greater severity of symptoms.
[b] Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (p≤0.002).

2.31; 95% CI, 1.25 to 4.66; p≤0.004) and the odds of being rated as minimally or not at all ill on the CGI severity measure (odds ratio, 4.08; 95% CI, 1.76 to 13.51, p≤0.001) (Table 2).

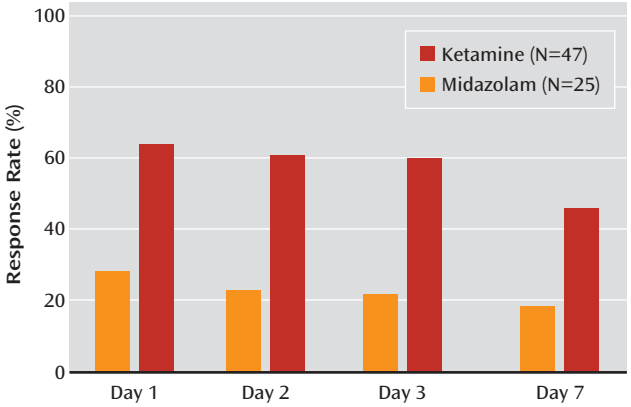
Durability of drug effect. General linear mixed modeling was used to evaluate MADRS scores at 1, 2, 3, and 7 days after infusion as a function of treatment, time, and the interaction of treatment and time, after adjustment for site. While the analyses demonstrated main effects for time (F=7.62, df=1, 202, p≤0.006) and treatment (F=5.93, df=1, 202, p≤0.02), they failed to identify differential change over time as a function of treatment (F=0.31, df=1, 202, p≤0.58). When the analysis controlled for treatment, both groups demonstrated a small worsening in MADRS scores for every additional day postinfusion (b=0.0004; 95% CI, 0.00009 to 0.00062). When the scores were collapsed across time, patients in the ketamine group had lower MADRS scores (mean, 16.93; 95% CI, 14.03 to 19.82) than patients in the midazolam group (mean, 23.19; 95% CI, 19.03 to 27.34 (t=2.44, df=202, p≤0.02; Figure 1). The MADRS scores at day 7 did not differ as a function of site (F=1.81, df=1, 66, p=0.18).

Similarly, when the probability of treatment response was modeled as a function of time, treatment group, and the interaction of treatment and time, there was a main effect of time (F=8.04, df=1, 202, p≤0.006) and a main effect of treatment (F=6.61, df=1, 202, p≤0.02), but we failed to identify differential trajectories of change over time as a function of treatment (F=0.12, df=1, 202, p≤0.73). The effects of time and treatment corresponded to an increase in the probability of being a nonresponder over time and an increase in the probability of being a responder as a function of assignment to ketamine (Figure 2).

When the analysis adjusted for site and baseline scores, the scores on the MADRS and Quick Inventory of Depressive Symptomatology—Self-Report at 7 days postinfusion no longer demonstrated a statistically significant difference between treatment groups. Responder status at day 7 did not differ as a function of site (exact p=0.11). Similarly, there was no significant difference between groups in the response rate or the proportion of patients with CGI improvement scores of 2 or less. Relative to midazolam, ketamine demonstrated greater odds of a CGI severity score of 2 or less after 7 days (odds ratio, 2.26; 95% CI, 1.07 to 5.76) (see Table ST1 in the online data supplement).

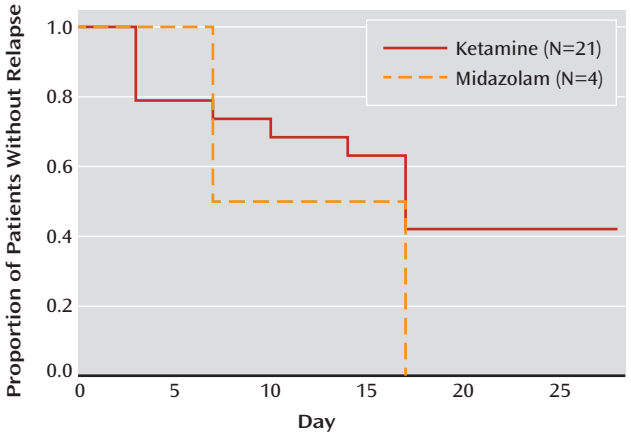
At day 7, four patients in the midazolam group and 21 in the ketamine group still met the criteria for response and elected to continue in the study. For these 7-day responders, Figure 3 displays the time to relapse over the subsequent 4 weeks.

FIGURE 2. Response Rates Over Time in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]



[a] Modified intention-to-treat group. Response at each time point was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale.

FIGURE 3. Time to Relapse for Responders at Day 7 Among Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine or Midazolam[a]



[a] Response was defined as a decrease from baseline of at least 50% in score on the Montgomery-Åsberg Depression Rating Scale (MADRS). Relapse was defined as a MADRS score of 20 or higher maintained for two consecutive visits and meeting criteria for a major depressive episode for 1 week.

Adverse Events

The most common adverse events in the ketamine group for up to 4 hours after infusion were dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration, and restlessness. Within this same time period, the most common adverse events in the midazolam group were general malaise, dizziness, headache, restlessness, nausea or vomiting, dry mouth, decreased energy, and poor coordination (Table 3).

Eight of the 47 patients receiving ketamine (17%) had significant dissociative symptoms (i.e., feeling outside of one's body or perceiving that time is moving more slowly or more quickly than normal) immediately after the ketamine infusion; these symptoms resolved by 2 hours postinfusion. No severe psychotic symptoms (paranoia, hallucinations, delusions, or thought disorder) occurred in any patient (see Table ST2 and Figure SF2 in the online data supplement).

On average, mild transient changes in blood pressure were observed on the infusion day (Table 4). The infusion was discontinued for two patients in the ketamine group because of hemodynamic changes. In one case, a blood pressure elevation (peak, 187/91 mm Hg) unresponsive to beta-blocker therapy resulted in infusion termination after 30 minutes. The blood pressure normalized within 10 minutes of infusion cessation. In the other case, there was transient but pronounced hypotension and bradycardia that resolved without sequelae and was followed by overnight observation in the hospital (see Table ST3 in the online data supplement for a description of the serious adverse events).

Discussion

In this two-site trial in treatment-resistant patients with moderate-to-severe and persistent depressive symptoms, we found that a single low dose of ketamine, as compared with a psychoactive placebo control medication, was associated with a rapid-onset antidepressant effect. We found marked improvements in clinician-administered and patient self-report ratings of depression severity 24 hours after the ketamine infusion. The ketamine responders generally maintained the gains for several days beyond the 24-hour time point; we no longer observed statistically significant differences between treatment groups 7 days following the infusion. These data provide new support for the hypothesis that NMDA receptor modulation can accelerate clinical improvement in patients with severe and chronic forms of depression.

We consistently demonstrated the magnitude and duration of ketamine's benefit across two sites in an ethnically and racially diverse patient group, enhancing confidence in the reliability of these findings. The large and rapid antidepressant effect of ketamine we observed in these patients with a history of three or more failed antidepressant trials is especially significant given the poor prognosis for improvement with currently available antidepressant treatments in treatment-resistant major depression (3–5, 29). To maximize internal and external validity, we standardized infusion-monitoring procedures and shielded the primary outcome rater from knowledge of side effects on the day of infusion. Improvements in secondary outcomes of global illness severity also supported the efficacy of ketamine in this trial.

Patients in the ketamine group experienced transient psychoactive and hemodynamic effects consistent with those in previous reports and clinical experience (11–15). Ketamine treatment did not increase the risk of emergent

TABLE 3. Adverse Events in Patients With Treatment-Resistant Major Depression Given a Single Infusion of Ketamine (N=47) or Midazolam (N=25)

	Infusion Day[b]								Days 1–7 After Infusion[c]							
	New Onset or Worsening				Distressing				New Onset or Worsening				Distressing			
	Ketamine		Midazolam		Ketamine		Midazolam		Ketamine		Midazolam		Ketamine		Midazolam	
Adverse Event[a]	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gastrointestinal																
Nausea/vomiting	16	34	3	12	3	6	1	4	7	15	2	8	1	2	0	0
Dry mouth	12	26	4	16	2	4	2	8	4	9	3	12	1	2	0	0
Constipation	2	4	0	0	0	0	0	0	4	9	1	4	1	2	0	0
Diarrhea	2	4	1	4	1	2	0	0	9	19	4	16	1	2	0	0
Heart																
Dizziness on standing	10	21	2	8	3	6	0	0	6	13	5	20	2	4	1	4
Palpitation	5	11	0	0	2	4	0	0	6	13	2	8	2	4	0	0
Chest pain	2	4	0	0	1	2	0	0	2	4	2	8	0	0	0	0
Skin																
Increased perspiration	5	11	1	4	1	2	1	4	5	11	1	4	0	0	0)	0)
Itching	2	4	1	4	2	4	0	0	6	13	1	4	1	2	0	0
Dry skin	1	2	1	4	1	2	1	4	12	26	5	20	1	2	0	0
Rash	1	2	0	0	1	2	0	0	5	11	1	4	1	2	0	0
Nervous system																
Dizziness	21	45	5	20	6	13	1	4	6	13	1	4	2	4	0	0
Headache	15	32	5	20	4	9	1	4	15	32	7	28	3	6	1	4
Poor coordination	12	26	3	12	2	4	3	12	2	4	1	4	0	0	1	4
Tremors	6	13	0	0	0	0	0	0	3	6	2	8	1	2	1	4
Eyes or ears																
Blurred vision	20	43	2	8	5	11	1	4	5	11	2	8	1	1	0	0
Ringing in ears	2	4	1	4	0	0	0	0	1	2	1	4	2	2	0	0
Genital/urinary																
Frequent urination	0	0	0	0	0	0	0	0	4	9	0	0	0	0	0	0
Painful urination	0	0	0	0	0	0	0	0	3	6	0	0	0	0	0	0
Difficulty urinating	0	0	0	0	0	0	0	0	1	2	0	0	0	0	0	0
Other																
Poor concentration	12	26	2	8	9	19	0	0	12	26	3	12	7	15	2	8
Restlessness	10	21	5	20	2	4	1	4	19	41	7	28	6	13	3	12
Anxiety	7	15	0	0	4	9	0	0	14	30	7	28	9	19	5	20
Decreased energy	7	15	3	12	3	6	1	4	7	15	4	16	5	11	1	4
Fatigue	7	15	2	8	4	9	1	4	10	21	4	16	8	17	1	4
General malaise	3	6	7	28	0	0	2	8	10	21	7	28	3	6	4	16

[a] From the modified version of the Patient Rated Inventory of Side Effects (26), excluding sleep and sexual functioning domains.
[b] Measured at 40 minutes, 120 minutes, and 240 minutes after the infusion.
[c] Measured at 24 hours, 48 hours, 72 hours, and 7 days after the infusion.

TABLE 4. Blood Pressure of Patients With Treatment-Resistant Major Depression Following a Single Infusion of Ketamine or Midazolam

	Blood Pressure (mm Hg)							
	Ketamine (N=47)				Midazolam (N=25)			
	Systolic		Diastolic		Systolic		Diastolic	
Time	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	121.7	13.8	71.7	11.3	120.8	17.5	72.4	9.6
40 minutes after infusion	140.7	17.8	80.8	12.7	111.8	14.8	67.9	9.9
240 minutes after infusion	125.4	17.6	70.6	8.9	113.9	13.0	71.6	7.7

psychotic or manic symptoms over the follow-up period (see Figure SF2 in the data supplement accompanying the online version of this article). These findings suggest that ketamine is safe in the short term for nonpsychotic depressed patients when administered at a subanesthetic dose of 0.5 mg/kg over 40 minutes. It is important to note

that the safety and efficacy of ketamine in depression beyond a single infusion are largely unknown and that abuse liability and other safety concerns associated with ketamine dictate a cautious approach to its application outside of research (30, 31). The observed hemodynamic changes in a subgroup of patients in our study encourage cardiorespiratory monitoring as an essential component of risk management.

The use of the anesthetic benzodiazepine midazolam as a control condition is a strength of the current study, although there is likely no perfect control condition for ketamine. Our objective was to select an agent that would function as a placebo (devoid of specific antidepressant effects) yet induce transient psychoactive effects designed to enhance study blinding and mitigate the nonspecific salutary impact of receiving an anesthetic agent. While the rates of general adverse events were similar across the two conditions, transient dissociative side effects immediately following study drug infusion were higher in the ketamine condition. Other agents that we considered for use as an active placebo included a sympathomimetic agent such as amphetamine. Amphetamine would have mimicked more closely the known sympathomimetic effects of ketamine (30); however, in contrast to midazolam, amphetamine is devoid of anesthetic properties. Finally, while we considered using a true active comparator with intrinsic antidepressant properties, we found that no pharmaceutical agents were readily available that had established antidepressant properties across a time scale similar to that for ketamine. Following the establishment of the antidepressant properties of ketamine in an optimized placebo-controlled design, future studies may compare schedules of ketamine to active comparators such as electroconvulsive therapy or antidepressant-antipsychotic medication combinations.

The biological mechanisms underlying ketamine's antidepressant activity remain largely unknown. The rapid onset of antidepressant activity we observed is consistent with preclinical work indicating that ketamine rapidly (within hours) increases the number and functioning of synaptic connections involving cortical or hippocampal neurons (32–34). Ketamine appears to rapidly reverse both behavioral and neuronal changes associated with chronic stress, in part through activation of the mammalian target of the rapamycin signaling pathway and stimulation of brain-derived neurotrophic factor signaling (35). It is interesting that a recent study of patients with major depressive disorder found that carriers of the Val66Met (rs6265) single nucleotide polymorphism—representing an attenuation of BDNF functioning—had a smaller antidepressant response to ketamine (36), in line with findings in animal models (34, 37, 38).

Limitations of our trial include stringent enrollment criteria due to concerns about ketamine's psychoactive effects and abuse liability. We believe that the exclusion of patients with histories of psychotic symptoms or substance or alcohol use disorders does not diminish the generalizability of our findings but, rather, offers a clinically relevant risk-mitigation strategy. A proportion of screened patients (17.2%) refused or were unable to tolerate psychotropic medication washout prior to randomization, thereby restricting participants to medication-free individuals or those able to tolerate medication washout. The efficacy of ketamine as an adjunct to ongoing therapies is a clinically relevant question not addressed in our study. Finally, we tested the efficacy of a single infusion over a brief follow-up period. The transient antidepressant response to ketamine highlights the need to identify strategies to maintain and prolong the initial response. Two studies of the glutamate-modulating drug riluzole failed to find benefit in prevention of relapse following ketamine administration (13, 39). Additional infusions of ketamine have recently been explored to prolong the antidepressant response (22, 40), although controlled data testing this strategy are not currently available.

In conclusion, treatment-resistant patients in a major depressive episode showed a rapid antidepressant response to a single infusion of ketamine. To our knowledge, the current study represents the largest investigation to date of ketamine in treatment-resistant major depression. Utilizing an optimized active placebo design, the trial provides new evidence for the specific antidepressant effects of ketamine, apart from its nonspecific anesthetic properties. Future research is required to test the antidepressant effects of ketamine beyond a single administration and to characterize its longer-term safety profile.

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Medicine at Mount Sinai could benefit financially; Dr. Charney receives research support from NIH, NIH/NIMH, NARSAD, and USAMRAA; he also served on the 2012 Institute of Medicine Committee on DHS Workforce Resilience and was on the 2012 Editorial Board of *CNS Spectrums*. Dr. Mathew has been named as an inventor on a pending use patent of ketamine for depression; he has relinquished his claim to any royalties and will not benefit financially if ketamine is approved for this use; Dr. Mathew has received consulting fees or research grants/support from Allergan, AstraZeneca, Bristol-Myers Squibb, Cephalon, Corcept, Johnson & Johnson, Naurex, Noven, Roche, and Takeda. The other authors report no financial relationships with commercial interests.

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Clinical Guidance: Intravenous Ketamine's Brief Antidepressant Effect

Intravenous ketamine administered to depressed patients who had not responded to at least three previous antidepressants improved depression in 64% of patients 24 hours after a single dose, compared to 28% of patients who received the anesthetic midazolam. The 73 patients studied by Murrough et al. were carefully screened to exclude those with substance abuse, psychotic illness, suicide risk, and unstable medical conditions. Dissociative symptoms, such as feeling outside one's body, occurred in 17% of the ketamine group, and blood pressure changes in two patients required termination of the infusion. Depression scores did not differ between treatment groups 7 days after the infusion. Ketamine is not ready for clinical use, states Rush in an editorial (p. 1079), but it is a promising lead for new therapeutic development.