Safety and Efficacy of Repeated-Dose Intravenous Ketamine for Treatment-Resistant Depression

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Background: A single subanesthetic (intravenous) IV dose of ketamine might have rapid but transient antidepressant effects in patients with treatment-resistant depression (TRD). Here we tested the tolerability, safety, and efficacy of repeated-dose open-label IV ketamine (six infusions over 12 days) in 10 medication-free symptomatic patients with TRD who had previously shown a meaningful antidepressant response to a single dose.

Methods: On day 1, patients received a 40-min IV infusion of ketamine (.5 mg/kg) in an inpatient setting with continuous vital-sign monitoring. Psychotomimetic effects and adverse events were recorded repeatedly. The primary efficacy measure was change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) score. If patients showed a ≥50% reduction in MADRS scores on day 2, they received five additional infusions on an outpatient basis (days 3, 5, 8, 10, and 12). Follow-up visits were conducted twice-weekly for ≥4 weeks or until relapse.

Results: Ketamine elicited minimal positive psychotic symptoms. Three patients experienced significant but transient dissociative symptoms. Side effects during and after each ketamine infusion were generally mild. The response criterion was met by nine patients after the first infusion as well as after the sixth infusion. The mean (SD) reduction in MADRS scores after the sixth infusion was 85% (12%). Postketamine, eight of nine patients relapsed, on average, 19 days after the sixth infusion (range 6 days– 45 days). One patient remained antidepressant-free with minimal depressive symptoms for >3 months.

Conclusions: These pilot findings suggest feasibility of repeated-dose IV ketamine for the acute treatment of TRD.

Ketamine has been safely used for induction and maintenance of anesthesia for many years and also plays a well-established role in analgesia (1). Ketamine is a noncompetitive, high-affinity antagonist of the *N*-methyl-D-aspartate type glutamate receptor, with additional effects on dopamine and μ-opioid receptors (2–4). Two placebo-controlled studies have reported rapid and robust antidepressant effects of a single subanesthetic (.5 mg/kg) intravenous (IV) dose of ketamine in symptomatic patients with major depressive disorder (MDD) (5,6). Across studies, a clinically significant antidepressant response was maintained for >72 hours in 12 of 25 patients. Nonetheless, all but two patients relapsed <2 weeks postketamine.

To translate these findings into clinical practice, a critical question is how to prevent relapse after the initial antidepressant response to a single IV ketamine dose. Here we investigated repeated IV ketamine dosing as a relapse-prevention strategy. The objectives were: 1) to test the tolerability and safety of repeated-dose IV ketamine in patients with treatment-resistant depression (TRD); and 2) to assess whether patients would derive a meaningful clinical benefit from ketamine throughout the period of infusions. We also explored the durability of the antidepressant response during a naturalistic follow-up period.

Methods and Materials

Participants

Participants were patients with chronic or recurrent MDD, as per the Structured Clinical Interview for DSM-IV-TR (7), who had had an insufficient therapeutic response to ≥2 adequate antidepressant medication trials in the current episode, as per the Antidepressant Treatment History Form (ATHF) (8). All had previously participated in an open-label, single-dose IV ketamine study; had evinced a ≥50% reduction in the severity of their depressive symptoms for at least 24 hours without any significant adverse side effects; and had subsequently experienced relapse (9). Participants were required to have a score of ≥32 on the Clinician-Administered Inventory for Depressive Symptoms (IDS-C_{30}) (10) at screening and again approximately 24 hours before the first infusion (see following text).

Psychiatric exclusion criteria included a lifetime history of psychotic symptoms or (hypo)mania; a substance use disorder <3 months before screening; and current active suicidal ideation judged to cause imminent danger. Medical exclusions were an abnormal electrocardiogram, any unstable illness as determined by history or laboratory tests, uncorrected hyperthyroidism or hypothyroidism, and, for women, pregnancy or the initiation of female hormonal treatments <3 months of screening. Women of childbearing age were required to use a medically accepted contraceptive method for the duration of the study. Psychotherapy and other nonpharmacological antidepressant treatments were not permitted during the study. All participants were free of psychotropic medication for ≥2 weeks (4 weeks for fluoxetine) before the first infusion, except for stable doses of zolpidem 10 mg qhs for insomnia.

The study was conducted at the Mount Sinai School of Medicine (MSSM), approved by its institutional review board, and registered at http://ClinicalTrials.gov. All participants were assessed for capacity to consent by a psychiatrist not otherwise affiliated with the research. Thirteen individuals consented to

Table 1. Patient Demographic and Clinical Characteristics

Variable	Mean ± SD	Variable	n (%)
Age (yrs)	51.4 ± 14.6	Female gender	5 (50%)
Body Mass Index (kg/m²)	30.1 ± 6.4	Ethnic minority	3 (30%)
Education (yrs)	15.6 ± 3.1	Received psychiatric disability	6 (60%)
IQ (WASI-2 score)	115.7 ± 11.8	Single MDE in lifetime[a]	5 (50%)
Adequate Antidepressant Trials (n)	8.2 ± 3.4	Comorbid anxiety disorder	7 (70%)
Age at First MDE (yrs)	20.9 ± 15.4	Past alcohol use disorder	0 (0%)
Duration of Current MDE (yrs)	21.7 ± 18.6	Family history of alcohol use disorder	4 (40%)
Baseline Depression (IDS-C_{30} score)	44.3 ± 10.6	Past substance use disorder	2 (20%)
Patient Expectancy Rating (1 = lowest, 5 = highest)	3.9 ± .7	Family history of MDD	5 (50%)

$N = 10$.

WASI-2, Wechsler Abbreviated Scale of Intelligence, two subtests; IQ, intelligence quotient; MDE, major depressive episode; IDS-C_{30}, Clinician-Administered Inventory for Depressive Symptoms; MDD, major depressive disorder.

[a]Excludes temporary symptom relief in response to single intravenous ketamine infusion during previous study.

participate in the current study. One patient was excluded after a positive toxicology for cocaine. Two patients withdrew consent. The demographic and clinical characteristics of the 10 patients who received at least one infusion are provided in Table 1. On average, patients had had an insufficient response to 8 (SD = 3) adequate antidepressant medication trials. Details on their previous antidepressant trials are described online in Table S1 in Supplement 1. Nine of 10 patients required a taper off medication before study entry. The mean number of days between participation in the present repeated-dose study and in the previous single-dose study was 311 (SD = 116). The effects of IV ketamine on explicit and implicit measures of suicidality in this sample were reported previously (11).

Measures

Safety and tolerability measures included the four-item positive symptom subscale (consisting of: suspiciousness, hallucinations, unusual thought content, and conceptual disorganization) of the Brief Psychiatric Rating Scale (BPRS+) (12), the Clinician-Administered Dissociative States Scale (CADSS) (13), and the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI) (14). The primary efficacy measure was the Montgomery-Åsberg Depression Rating Scale (MADRS) (15); the Quick Inventory of Depressive Symptoms, self-report version (QIDS-SR_{16}) (10) was also used. Three clinical raters, all with graduate degrees and extensive training, provided outcome ratings. A two-way mixed model with measures of consistency was employed to determine the interclass correlation coefficients, which were as follows: .97 for the BPRS+ and .96 for the MADRS. The same continuous rater generally followed a participant until study exit.

Procedure

Screening included an interval assessment for Axis I disorders, administration of the IDS-C_{30}, and a physical examination and

laboratory tests to confirm absence of any unacceptable medical condition.

All infusions took place at the MSSM General Clinical Research Center (GCRC) in a private room over the course of 2 weeks (days 1, 3, 5, 8, 10, and 12). The IDS-C_{30} was re-administered approximately 24 hours before the first infusion to document sufficient severity of depressive symptoms. Patients arrived at the GCRC at 7 AM after an overnight fast. Repeat urine toxicology and, if applicable, pregnancy tests were performed, and weight was assessed. An indwelling catheter was placed in the nondominant arm for ketamine administration. A heplock was placed in the opposite arm for blood sampling. Oxygen was administered via nasal cannula. Digital pulse oximetry, respiratory rate, heart rate, blood pressure, and heart monitoring were recorded every 5 min on a standard anesthesia record for 1 hour beginning 5 min before each infusion.

Pre-infusion (t_0) ratings included the BPRS+, CADSS, SAFTEE-SI, MADRS, and QIDS-SR_{16}. Patients and raters also provided a score from 1 to 5 indicating their expectations about the treatment. Higher scores signified more confidence that ketamine would be efficacious. During each infusion, the BPRS+ was administered every 5 min. At the end of each infusion (t_{+40min}), safety and tolerability were assessed with the BPRS+, CADSS, and SAFTEE-SI. At t_{+2h} and t_{+4h}, safety and tolerability were assessed again, and mood was assessed with a modified MADRS that carried forward from t_0 the sleep and appetite items and a modified QIDS-SR_{16} that carried forward the sleep, appetite, and weight items (16).

During the first infusion, racemic ketamine hydrochloride (Bedford Laboratories, Bedford, Ohio) diluted in saline to .5 mg/kg was administered over 40 min by IV pump (Baxter International, Deerfield, Illinois). A study psychiatrist and an anesthesiologist were present throughout the infusion. The infusion was followed by a 4-hour monitoring period. Lunch was provided after the t_{+4h} ratings. Patients then remained overnight at the GCRC with regular assessment of clinical status and vital signs. At t_{+24h}, all pre-infusion measures were repeated. Patients meeting response criteria (≥50% reduction in MADRS score from the preketamine baseline) received five subsequent infusions, whereas non-responders were exited from the study.

Procedures for the subsequent infusions were identical to those of the first infusion, except patients did not remain at the GCRC overnight and complete t_{+2h} and t_{+24h} ratings but, provided vital signs were stable, were discharged after the t_{+4h} ratings and lunch. The protocol stipulated that if patients experienced distressing positive psychotic symptoms during the first infusion, as evidenced by an increase in the BPRS+ score and verbal report, then the dose for subsequent infusions would be reduced to $.0125 \times .80 \times T_i$, where T_i represents the time at which these symptoms first occurred (for $T_i > 40$ min, the reduced dose would be .4 mg/kg). No patients reported distressing positive psychotic symptoms at any time point during the first infusion; thus, all responders received .5 mg/kg ketamine for the subsequent infusions.

After the final infusion, patients who met response criteria, as previously defined, remained medication-free. They were assessed twice-weekly with the MADRS, QIDS-SR_{16}, and SAFTEE-SI for ≥4 weeks or until relapse, defined as a MADRS score >50% of the preketamine baseline and >20 for two consecutive visits or a Clinical Global impression-Improvement scale (CGI-I) score of 6 ("much worse") at any visit. A MADRS score ≤9 signified remission. Patients who relapsed were exited from the protocol and resumed treatment as usual.

Data Analysis

SAS 9.1.3 for Windows (SAS, Cary, North Carolina) was used for statistical testing. Treatment effects on BPRS+ and CADSS scores during the first infusion were analyzed with Wilcoxon signed rank tests comparing scores at two time points (t_0, t_{+40min}). Data from the intent-to-treat sample of 10 patients were used. Kruskal-Wallis tests, including a variable Time with four levels (t_0, t_{+2h}, t_{+4h}, t_{+24h}), were used to assess the treatment effects on MADRS and QIDS-SR$_{16}$. For these analyses, scores during the first infusion visit were analyzed in responders only.

Treatment effects on peak BPRS+ and CADSS scores at t_{+40min} across the six infusions that responders received were analyzed with Friedman tests.

The GCRC charts were reviewed for clinically relevant vital-signs changes, specifically for low (<90/60 mm Hg) or high (>140/90 mm Hg) blood pressure (BP); abnormal heart rate (HR; <60 bpm or >100 bpm) or respiratory rate (RR; <10 cycles/min or >20 cycles/min) or low oxygen saturation (<95%); and hypothermia (<35°C) or hyperthermia (>40°C).

The incidence of side effects at t_{+4h} postketamine was compared in the first week (days 1, 3, 5) versus the second week (days 8, 10, 12) by comparing the number of patients who endorsed moderate-to-severe increases in symptoms listed on the SAFTEE-SI from t_0 to t_{+4h}. The data provided in the following text are not raw scores reflecting how many patients rated a symptom as distressing but depict how many patients rated a symptom as more bothersome during the 4-hour period after infusions compared with the morning baseline rating. Thus, for example, a moderate increase was defined as an increase of 2 degrees of severity (e.g., from "not present" to "moderate" or from "mild" to "severe").

Results

Ten participants received the first IV ketamine infusion. Nine of these participants met response criteria at t_{+24h} (see following text for details) and were eligible for subsequent infusions. One patient missed the fourth infusion.

## Safety and Tolerability: Acute Psychotomimetic and Dissociative Effects

During the first infusion ($t_{0\rightarrow40min}$), BPRS+ scores nonsignificantly increased from 4.0 (SD 0) at t_0 to a mean peak of 5.3 (SD 2.2; $S = 5$, $p = .1$). By t_{+2h}, scores had returned to baseline (mean 4.0, SD 0). No patient reported any distressing psychotic symptoms. The CADSS scores increased from 1.0 (SD 2.1) at t_0 to 14.9 (SD 23.1) at t_{+40min} ($S = 21.5$, $p = .03$). At this time point, three patients had high or very high CADSS scores (≥11). However, at t_{+2h}, scores had normalized (mean .4, SD .8).

Figure 1 depicts changes in BPRS+ and CADSS scores during each of the six infusions. All patients had minimum BPRS+ and low CADSS scores (≤3) at each t_{+4h} rating. There was no significant change in peak BPRS+ scores [$\chi^2(5) = 3.41$, $p = .6$] and in t_{+40min} CADSS scores [$\chi^2(5) = 2.35$, $p = .7$] across the six infusions.

Safety and Tolerability: Vital Signs During Infusions

During the first infusion, two patients had brief hypertensive episodes and developed transient tachycardia. In both cases these symptoms resolved <5 min postinfusion. Both patients re-experienced these hypertensive episodes during subsequent infusions, as did another patient. One patient who developed transient tachycardia during the first infusion also developed tachycardia during all subsequent infusions (HR$_{max}$ 124 bpm). Despite a negative cardiac history and normal electrocardiogram at screening, this patient experienced premature ventricular contractions during infusions four and five; these were not accompanied by any symptoms and resolved by t_{+2h}.

One patient had bradycardia during the first infusion (HR 50–55 bpm) that resolved by t_{+1h}. This patient redeveloped bradycardia during most of the subsequent infusions; in no case did it persist for more than 2 hours. Another patient had low BP (80/55 mm Hg) approximately 13 hours after the first infusion; BP remained low until discharge at t_{+24h} (85/59 mm Hg). The patient had presented with low diastolic BP at baseline (107/48 mm Hg) and was asymptomatic throughout the observation period, and other vital signs remained stable. This patient also
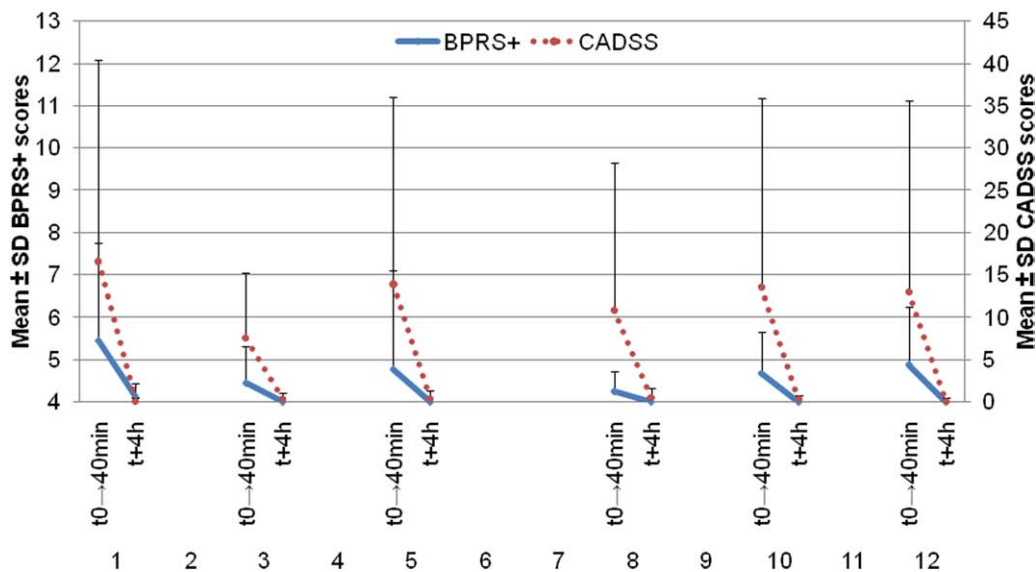
Figure 1. Mean peak Brief Psychiatric Rating Scale (BPRS+) scores and mean Clinician-Administered Dissociative States Scale (CADSS) scores across six intravenous ketamine infusions ($t_{0\rightarrow40min}$) and 4 hours after each infusion (t_{+4h}) in nine patients who responded to a single infusion and subsequently received five additional infusions.

developed mild hypotension during two subsequent infusions, but both times BP normalized immediately postinfusion.

Finally, during the first infusion oxygen saturation in one patient decreased from 99% at baseline to 94% at one reading during the night. It was 95% at discharge. The patient re-experienced low oxygen saturation after infusion 4 (minimum 94%). This patient also developed bradypnea during several infusions (RR_{min} = 7), but there was no evidence of an effect of ketamine on RR beyond the drug administration period.

All hemodynamic parameters were considered manageable by the administering anesthesiologist and did not necessitate termination of the infusions.

Safety and Tolerability: Self-Reported Side Effects on Infusion Days and During the Post-Treatment Period

Table 2 lists the number of patients who endorsed moderate to severe increases in specific symptoms from t_0 to t_{+4h}. Only "abnormal sensations" and "weakness or fatigue" were more prevalent in the second week compared with the first week of infusions. Overall, no patient reported the total number of symptoms as greater than mildly bothersome at any time.

After the first infusion, three patients verbally reported headache of mild-to-moderate severity. During subsequent infusions, headache was reported four times by four different patients.

The SAFTEE-SI data from the naturalistic follow-up visits were available for seven of the nine repeated-dose patients. One patient reported a moderate increase in "sleep disturbance" from the preketamine baseline at the first follow-up visit but no longer did so at the second visit. Another patient reported a moderate increase in "blurred vision" at the third follow-up visit after missing the first two; this patient had no further visits. No other symptoms increased more than mildly (1 degree of severity) from baseline. There were no increases in "poor memory," "trouble concentrating," or "word-finding difficulties," suggesting that ketamine did not have any persistent cognitive impact as per self-report.

Mood: First Infusion

At t_0, the mean (SD) MADRS score of the 10 participants was 32.7 (6.4). At t_{+24h}, nine patients met response criteria. Their

Table 2. Numbers of Patients Who Endorsed Moderate-to-Severe Increases in Specific Symptoms on the SAFTEE-SI

	Moderate		Severe	
Symptom	Week 1	Week 2	Week 1	Week 2
Abnormal Sensations	0	2	1	1
Blurred Vision	0	0	1	1
Diminished Mental Capacity	1	1	1	1
Dizziness or Faintness	1	0	0	0
Feeling Drowsy or Sleepy	2	0	0	0
Feeling Strange or Unreal	1	1	0	0
Headache	1	0	2	1
Hearing or Seeing Things	2	0	0	0
Numbness or Tingling	0	1	1	1
Poor Coordination or Unsteadiness	1	1	0	0
Poor Memory	1	0	0	0
Rapid or Pounding Heartbeat	1	0	0	0
Weakness or Fatigue	0	1	0	0

Numbers of patients who endorsed moderate-to-severe increases in specific symptoms on the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI) from pre-infusion (t_0) to 4 hours postinfusion (t_{+4h}) collapsed across infusions 1–3 (week 1) and infusions 4–6 (week 2).

mean (SD) MADRS scores at t_0, t_{+2h}, t_{+4h}, and t_{+24h} were 33.8 (5.8), 16.9 (10.3), 11.4 (5.3), and 6.9 (2.8), respectively. In this group there was a significant main effect of time [$\chi^2(3) = 22, p < .0001$].

At t_0, the mean (SD) QIDS-SR_{16} score of the 10 participants was 18.7 (4.5). For the nine responders, mean (SD) QIDS-SR_{16} scores at t_0, t_{+2h}, t_{+4h}, and t_{+24h} were 19.6 (3.8), 9.3 (4.0), 7.4 (2.0), and 4.1 (2.8), respectively. In this group there was a significant main effect of time [$\chi^2(3) = 25, p < .0001$]. At t_{+24h} eight of nine responders also had a 50% reduction in QIDS-SR_{16} scores.

There was no significant Spearman correlation between MADRS scores at t_{+24h} and either peak BPRS+ scores during the infusion ($r = -.11, p = .75$) or CADSS scores at t_{+40min} ($r = -.24, p = .5$).

Mood: Repeated Infusions in Responders

Mean MADRS and QIDS-SR_{16} scores during all six visits of the nine acute responders are depicted in Figure 2. At t_{+4h} after the sixth infusion, all nine patients met the response criterion, whereas eight patients met the remission criterion. Mean (SD) MADRS and QIDS-SR_{16} scores at this time were 5.0 (3.7) and 3.4 (1.8), respectively. Percentage MADRS reductions from baseline did not correlate significantly with patient expectancies averaged across their infusion visits ($r = .37, p = .4$, controlling for baseline MADRS scores). There was no significant difference between patient expectancies before the first infusion and before the last infusion [$t(8) = .61, p = .6$].

Mood: Naturalistic Follow-Up

Of the nine patients who received repeated infusions, eight relapsed within an estimated mean 30 (SD = 13) days after the first infusion or 19 (SD = 13) days after the sixth infusion. Thus, on average these eight patients remained well for almost 3 weeks after treatment ended. Specifically, one patient relapsed <1 week posttreatment, three patients relapsed after <2 weeks, and two patients relapsed after <3 weeks, whereas one patient remained depression-free for >4 weeks, one patient for almost 7 weeks, and one patient remained depression-free for more than 3 months postketamine. The mean (SD) MADRS score at study exit was 29.7 (6.4) for seven patients; no score was available for one patient, due to travel abroad. Individual MADRS and QIDS-SR_{16} scores obtained during follow-up visits are available online as Table S2 in Supplement 1.

Discussion

We have presented preliminary data supporting feasibility of repeated-dose IV ketamine in a group of TRD patients who had previously shown a favorable response to a single IV ketamine infusion. Safety, tolerability, and duration of symptom relief during the course of treatment were the criteria established to assess feasibility. Six IV infusions of ketamine administered thrice-weekly over 40 min at a .5 mg/kg dose were well-tolerated. No patient reported greater than mildly bothersome side effects at any time. The BPRS+ and CADSS scores showed moderate increases during each infusion but returned to baseline within 2–4 hours. This effect is consistent with that observed in previous single-dose ketamine studies (17). No patient reported distressing psychotic symptoms at any time.

The observed vital-signs changes were transient and did not warrant treatment cessation. Patients with medication-controlled hypertension ($n = 2$) did not predictably experience hypertensive episodes during the infusions. However, the emergence of
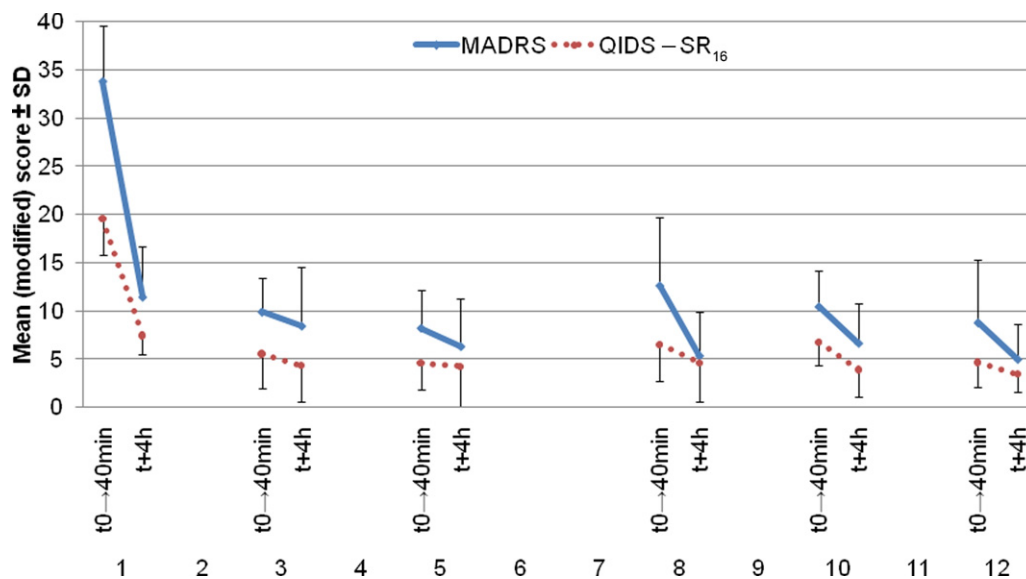
Figure 2. Mean (modified) Montgomery-Åsberg Depression Rating Scale (MADRS) and Quick Inventory of Depressive Symptoms, Self-Report Version (QIDS-SR$_{16}$) scores before (t$_0$) and 4 hours after (t$_{+4h}$) six intravenous ketamine infusions in nine patients who responded to a single infusion and subsequently received five additional infusions.

transient hypertension and tachycardia in two other patients and premature ventricular contractions in one patient suggest that appropriate precautions are necessary, including preketamine electrocardiography and close monitoring by an anesthesiologist.

Notably, previous open-label repeated-dose IV ketamine studies in other populations have also found the treatment to be safe. For example, patients with schizophrenia tolerated up to four infusions (.1–.5 mg/kg) administered over 2 weeks (18). In a group of patients with refractory pain receiving 10 4-hour infusions (10–20 mg/hour), treatment-related side effects were minimal with only approximately 10% of patients experiencing restlessness, headaches, or significant tachycardia (19). In 15 patients with treatment-resistant eating disorders who received on average four 10-hour infusions (20 mg/hour), side effects reported by some (headaches, nausea, sedation, and revival of distant memories) were no longer apparent or unpleasant after the first or second infusion (20).

Concern regarding long-term cognitive impairment caused by repeated ketamine administration has been raised (21). In our study, during the follow-up period no patient reported any cognitive deficits in excess of what was reported at the preketamine baseline; however, a limitation was the lack of formal cognitive testing. To adequately test ketamine's impact on cognitive function, future studies should administer neuropsychological tests at several time points including preketamine, immediately postketamine when ketamine responders are depression-free, and then again when patients have relapsed.

Previous data on the antidepressant potential of multiple IV ketamine infusions in patients with depressive symptoms are limited. In two patients with TRD 5 days of continuous administration (.27–.3 mg/kg/hour) had an antidepressant effect that lasted more than 1 year in one patient and 2.5 months in the other; after a second treatment this latter patient remained depression-free for another 6 months (22). Furthermore, in a group of patients with treatment-resistant eating disorders, after on average four 10-hour infusions (20 mg/hour), a majority reported fewer compulsive eating behaviors and also less de-

pression. Treatment responders remained well on average for >1 year (20).

Our data suggest that patients who respond to an initial IV ketamine dose generally maintain their response for as long as they receive additional doses and for at least 6 days after that. Because of our small sample size, the open-label design, and the inclusion of participants who previously responded to a single IV ketamine dose, it is necessary to consider the possibility that a type I error occurred or that future blinded studies with naïve patients will not replicate the response and remission rates observed. Still, Zarate *et al.* (6) found that after a single IV ketamine dose only 35% of responders maintained their response for at least 1 week. Furthermore, although four of nine patients in the present study relapsed <2 weeks postketamine, five patients remained depression-free beyond this time. Across the two published single-dose, placebo-controlled studies (5,6), 23 of 25 patients relapsed within 2 weeks postketamine (92%). Thus, the response durability of repeated-dose IV ketamine infusions might be greater than that of a single infusion. However, because of the individual variability in the duration that patients remained well after completing all six infusions, the most practical use of repeated IV ketamine infusions might be to elicit and maintain rapid relief until a less-invasive relapse prevention strategy could be implemented.

To enhance comparability with electroconvulsive therapy (ECT), another hospital-based treatment requiring hemodynamic monitoring and an anesthesiologist, we administered IV ketamine at a similar frequency (three times/week), with the minimal number of treatments generally required for remission with ECT (six treatments). On the basis of the present results and in support of previous single-dose placebo-controlled IV ketamine studies (5,6), the most consistent and therefore promising aspect of this approach might be IV ketamine's rapid onset of antidepressant activity. In contrast, the durability of the therapeutic effect after cessation of IV ketamine treatment (mean duration approximately 3 weeks) was highly variable. High relapse rates are also observed after discontinuation of ECT,

particularly in the initial month post-ECT (23,24). It is noteworthy that only 2 of the 10 medication-resistant patients in this study had received a previous course of ECT; 4 of the remaining 8 patients had refused ECT due to concerns about cognitive side effects. Future prospective randomized trials should compare repeated administration of IV ketamine with ECT with respect to onset of antidepressant action, remission rates, response durability, safety/tolerability, and impact on cognition.

We acknowledge limitations in comparing the antidepressant efficacy of a single IV ketamine dose administered in a placebo-controlled crossover study (5,6) with that of multiple open-label doses administered to a preselected sample who had previously shown favorable tolerability and responsivity to a single IV dose of ketamine. The two published reports of IV ketamine as a potential rapid intervention for MDD included IV saline as an inactive placebo control (5,6). Thus, it is possible that the treatment blind was not maintained throughout the study. Patients' awareness of the treatment might indeed explain the low number of placebo responders across the two studies ($n = 1$).

Another important characteristic of the two published single-dose IV ketamine studies (5,6) is that participants were inpatients for the entire duration of the protocol. In contrast, participants in the present study were treated as outpatients for infusions 2–6, thus offering a more practical indication of ketamine's clinical potential.

Future directions for research on IV ketamine will include multiple-dose studies involving an active control (e.g., a different anesthetic) rather than an inactive placebo as well as studies examining different maintenance therapies for patients who have successfully responded. It is also unknown which patient characteristics—such as comorbid Axis I or Axis II diagnoses, family histories of psychiatric illness, or individual genotypes and ketamine metabolism rates—might predict durability of response. Finally, repeated-dose IV ketamine was administered here to a preselected group of patients with previous exposure to ketamine; controlled investigations in ketamine-naïve patients are necessary to further support the present findings.

Supplementary material cited in this article is available online.

1. Green SM, Li J (2000): Ketamine in adults: What emergency physicians need to know about patient selection and emergence reactions. *Acad Emerg Med* 7:278–281.
2. Krystal JH, D'Souza DC, Karper LP, Bennett A, Abi-Dargham A, Abi-Saab D, *et al.* (1999): Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. *Psychopharmacology* 145:193–204.
3. Krystal JH, Madonick S, Perry E, Gueorguieva R, Brush L, Wray Y, *et al.* (2006): Potentiation of low dose ketamine effects by naltrexone: Potential implications for the pharmacotherapy of alcoholism. *Neuropsychopharmacology* 31:1793–1800.
4. Javitt DC (2007): Glutamate and schizophrenia: Phencyclidine, N-methyl-d-aspartate receptors, and dopamine–glutamate interactions. *Int Rev Neurobiol* 78:69–108.
5. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000): Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47:351–354.
6. 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.
7. First MB, Spitzer RL, Gibbon M, Williams JBW (2001): *Structured Clinical Interview for DSM-IV TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P).* New York: New York State Psychiatric Institute, Biometrics Research.
8. Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62(suppl 16):10–17.
9. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS (2009): Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial [published online ahead of print March 17]. *Int J Neuropsychopharmacol.* doi:10.1017/S1461145709000169.
10. Rush AJ, Carmody TJ, Ibrahim HM, Trivedi MH, Biggs MM, Shores-Wilson K, *et al.* (2006): Comparison of self-report and clinician ratings on two inventories of depressive symptomatology. *Psychiatr Serv* 57:829–837.
11. Price RB, Nock MK, Charney DS, Mathew SJ (2009): Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 66:522–526.
12. Overall JE, Gorham DR (1962): The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799–812.
13. Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, *et al.* (1998): Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS). *J Trauma Stress* 11:125–136.
14. Levine J, Schooler NR (1986): SAFTEE: A technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull* 22:343–381.
15. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.

16. Lenderking WR, Hu M, Tennen H, Cappelleri JC, Petrie CD, Rush AJ (2008): Daily process methodology for measuring earlier antidepressant response. *Contemp Clin Trials* 29:867–877.

17. Duncan EJ, Madonick SH, Parwani A, Angrist B, Rajan R, Chakravorty S, *et al.* (2001): Clinical and sensorimotor gating effects of ketamine in normals. *Neuropsychopharmacology* 25:72–83.

18. Lahti AC, Warfel D, Michaelidis T, Weiler MA, Frey K, Tamminga CA (2001): Long-term outcome of patients who receive ketamine during research. *Biol Psychiatry* 49:869–875.

19. Goldberg ME, Domsky R, Scaringe D, Hirsh R, Dotson J, Sharaf I, *et al.* (2005): Multi-day low dose ketamine infusion for the treatment of complex regional pain syndrome. *Pain Physician* 8:175–179.

20. Mills IH, Park GR, Manara AR, Merriman RJ (1998): Treatment of compulsive behaviour in eating disorders with intermittent ketamine infusions. *Q J Med* 91:493–503.

21. Tsai GE (2007): Searching for rational anti N-methyl-D-aspartate treatment for depression. *Arch Gen Psychiatry* 64:1099–1100.

22. Correll GE, Futter GE (2006): Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med* 7:92–95.

23. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, *et al.* (2001): Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: A randomized controlled trial. *JAMA* 285:1299–1307.

24. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, *et al.* (2006): Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: A multisite study from the Consortium for Research in electroconvulsive therapy (CORE). *Arch Gen Psychiatry* 63:1337–1344.