ARCHIVAL REPORT

Rapid and Longer-Term Antidepressant Effects of Repeated Ketamine Infusions in Treatment-Resistant Major Depression

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Background: Ketamine is reported to have rapid antidepressant effects; however, there is limited understanding of the time-course of ketamine effects beyond a single infusion. A previous report including 10 participants with treatment-resistant major depression (TRD) found that six ketamine infusions resulted in a sustained antidepressant effect. In the current report, we examined the pattern and durability of antidepressant effects of repeated ketamine infusions in a larger sample, inclusive of the original.

Methods: Participants with TRD ($n = 24$) underwent a washout of antidepressant medication followed by a series of up to six IV infusions of ketamine (.5 mg/kg) administered open-label three times weekly over a 12-day period. Participants meeting response criteria were monitored for relapse for up to 83 days from the last infusion.

Results: The overall response rate at study end was 70.8%. There was a large mean decrease in Montgomery–Åsberg Depression Rating Scale score at 2 hours after the first ketamine infusion (18.9 $\pm$ 6.6, $p < .001$), and this decrease was largely sustained for the duration of the infusion period. Response at study end was strongly predicted by response at 4 hours (94% sensitive, 71% specific). Among responders, median time to relapse after the last ketamine infusion was 18 days.

Conclusions: Ketamine was associated with a rapid antidepressant effect in TRD that was predictive of a sustained effect. Future controlled studies will be required to identify strategies to maintain an antidepressant response among patients who benefit from a course of ketamine.

Key Words: Antidepressant, experimental therapeutics, glutamate, ketamine, major depressive disorder, treatment-resistant depression

Major depressive disorder (MDD) is associated with a very high degree of morbidity and public health cost, in part due to the limited effectiveness of current antidepressant treatments (1–3). Against this background, reports of a rapid-onset antidepressant effect associated with the *N*-methyl-D-aspartate glutamate receptor antagonist ketamine have generated considerable interest among both clinicians and researchers (4–7). Notably, rapid antidepressant effects are observed even in individuals who have failed to respond to previous treatment attempts. This group of patients can be described as suffering from treatment-resistant depression (TRD), and as a group, they suffer more severe depressive symptoms, exhibit more illness-related disability, and experience a more chronic or relapsing course of illness compared with their non-TRD counterparts (8,9).

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The large majority of clinical research involving ketamine in depression has focused on the safety and efficacy of a single low-dose (.5 mg/kg) IV infusion (4–6). An initial placebo-controlled, double blind crossover study in inpatients with major depression reported a large mean reduction in depression severity (14 $\pm$ 12 points on the 25-item Hamilton Depression Rating Scale) 72 hours after a single ketamine infusion (4). A second study using a similar design reported a rapid antidepressant effect within 2 hours and a 71% response rate at 24 hours (5). In total, four placebo-controlled studies of a single ketamine infusion in unipolar or bipolar depression support the rapid antidepressant effects of ketamine in mood disorders (4,5,10,11).

Most individuals who respond to ketamine experience a relapse within several days or up to 1 week, although there is considerable variability in time to relapse after a single infusion (5,12,13). A paramount clinical issue, therefore, is to identify a strategy to maintain the antidepressant effects of ketamine (7,14). To begin to address this question, our group previously reported on the safety and efficacy of up to six infusions of ketamine over a 12-day period in 10 patients with TRD (15). In that study, ketamine was found to be safe and well-tolerated.

In the current study, we sought to extend the findings of our previous study (15) to further characterize the pattern of change in depressive symptoms and durability of response in the context of repeated ketamine infusions in a larger sample of subjects with TRD (inclusive of participants from the original report). Specifically, we: 1) measured the overall proportion of response after up to six ketamine infusions; 2) determined the time-point associated with the largest change in symptom severity; 3) compared the trajectory of symptom change between study responders and nonresponders; 4) estimated time to relapse among responders after cessation of ketamine, and 5) investigated the effects of ketamine on individual symptoms of depression.

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Methods and Materials

Participants

Study participants were recruited from physician referrals, media advertisement, or an academic outpatient psychiatric clinic. Participants had chronic or recurrent MDD that was the primary presenting problem as assessed by a trained rater with the Structured Clinical Interview for DSM-IV (16) and a diagnostic interview with a study psychiatrist. To be eligible, participants had to have failed to respond to at least two U.S. Food and Drug Administration-approved antidepressant medications in the current episode according to the Antidepressant Treatment History Form (17). If a participant was taking antidepressant medication at the time of screening, a washout of ≥2 weeks (or 4 weeks for fluoxetine) was required before enrollment, and participants remained free of antidepressant medication throughout the infusion period. Additional inclusion criteria included a score of ≥ 32 on the Inventory of Depressive Symptomatology—Clinician Rated (IDS-C) (18) at screen and baseline and a negative urine toxicology screen. Exclusion criteria included uncontrolled hypertension, any unstable medical condition, any Axis I disorder other than MDD that was judged to be the primary presenting problem, substance abuse or dependence in the 3 months before screen, lifetime history of psychosis, any psychotic disorder, bipolar disorder, developmental disorder, or recreational use or abuse of ketamine or phencyclidine. Physical examination, vital signs, weight, electrocardiogram, standard blood tests, and urinalysis confirmed absence of unstable medical illnesses. Women of childbearing potential were required to have a negative pregnancy test before enrollment.

The Mount Sinai School of Medicine Institutional Review Board approved the study, and written informed consent was obtained from all subjects before participation. The study is registered at http://ClinicalTrials.gov (NCT00548964).

Study Procedures and Rating Instruments

The study consisted of two phases. In phase I, participants received up to six IV infusions of ketamine (.5 mg/kg) on a Monday-Wednesday-Friday schedule over a 12-day period. In phase II, participants who met response criteria after the last dose of ketamine in phase I were followed until relapse or for the maximum follow-up time of 83 days, whichever came first. Response in phase I was defined as a ≥ 50% improvement in depressive symptoms as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) (19). Relapse in phase II was defined as <50% improvement in MADRS score at that visit compared with baseline for two consecutive visits.

Results from the first 10 participants enrolled in the current study were previously reported in part, and the methods for the current report are very similar to what was described therein (15). Briefly, participants were admitted to the Mount Sinai Clinical Research Unit on the morning of the first infusion for a 24-hour stay to optimize safety and monitoring. All subsequent infusions occurred as an outpatient procedure at the Clinical Research Unit. An anesthesiologist (A.M.P.) administered racemic ketamine hydrochloride (Bedford Laboratories, Bedford, Ohio) diluted in normal saline over 40 min by IV infusion pump with standard telemetry monitoring. In the first cohort, participants were exited from the study if they failed to achieve response after the first infusion (this occurred in one case among the $n = 10$) (15). The protocol was subsequently changed to allow participants to remain in the study regardless of response status after the first infusion ($n = 14$) to measure the effect of repeated ketamine infusions among initial nonresponders.

The primary outcome for phase I was change in depressive symptoms measured by the MADRS over the 12-day infusion period. Depression severity was measured in the morning before the first ketamine infusion (−60 min) and then at +120 min, +240 min, and 24 hours. Depression severity was measured at −60 min and +240 min for each subsequent infusion day. Responder status after the sixth infusion or the last observation for noncompleters was used to determine overall phase I responder status. During phase II, responders were followed twice weekly for 4 weeks, then every other week for 8 weeks or until relapse, which ever came sooner. All but two participants remained free of antidepressant medication for the duration of the follow-up period. Three of the 17 responders were enrolled in a separate relapse prevention study of venlafaxine extended-release (ER) up to 300 mg daily during the follow-up period (two were randomized to medication, one was randomized to placebo).

Acute dissociative and psychotomimetic effects of ketamine were measured before the start of each infusion, during or immediately upon completion of each infusion (+40 min), and then +240 min after infusion. Psychotomimetic effects were measured with the four-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS) (scale range 4–28) (20); dissociative effects were measured with the Clinician-Administered Dissociative States Scale (scale range 0–92) (21); manic-like mood elevation was measured with the mood item of the Young Mania Rating Scale (scale range 0–4) (22); a feeling of being "high" was measured with a Visual Analog Scale (range 0–10). General side effects were measured with the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (23) administered in the morning before each infusion and then immediately upon completion of the infusion (+40 min) and at +240 min.

Guidelines established for clinically significant changes in vital signs during the ketamine infusions were as follows: systolic or diastolic blood pressure (BP) >180/100 or >20% increase above pre-infusion reading or tachycardia >110 beats/min. The infusion was discontinued in the event that significant changes in vital signs occurred that did not respond to medication intervention (see Supplement 1 for details).

Statistical Analysis

Baseline characteristics were compared between responders and nonresponders with the Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Changes between two time-points for continuous variables were tested with paired *t* tests, and associations between continuous variables were quantified with the Spearman correlation coefficient. Random effects models were used to summarize and quantify changes in the MADRS score and its component items over time and to compare temporal differences between eventual responders and nonresponders. Splines were used to determine differences in the pattern of response over time among all patients and to identify the time at which there was no additional improvement in depressive symptoms. Additionally, the relationship between response status at 2, 4, and 24 hours after baseline and end of study was summarized with sensitivity, specificity, and positive and negative predictive values. Time to relapse for patients who met response criteria at the end of phase I was estimated with the Kaplan-Meier method. Analyses were performed with IBM SPSS Statistics (version 19; SPSS, Chicago, Illinois) and SAS (version 9.2; SAS, Cary, North Carolina).

Results

Twenty-four participants received at least one ketamine infusion. Twenty-two participants received at least two infusions, and

Table 1. Demographic and Clinical Characteristics of Total Study Sample and Responder/Nonresponder Subgroups

	Total Sample	Responder Subgroup	Nonresponder Subgroup	*p*
Participants, *n* (%)	24 (100%)	17 (71%)	7 (29%)	—
Gender (M/F)	15/9	10/7	5/2	.56
Age at Enrollment (yrs)	48.1 ± 13.0	48.9 ± 11.8	46.1 ± 16.5	.73
Education (yrs)	16.0 ± 2.5	15.2 ± 2.7	17.1 ± 1.0	.016
Age at Onset of MDD (yrs)	22.8 ± 13.6	26.4 ± 14.2	14.0 ± 6.8	.039
Length of Current Episode (yrs)	18.1 ± 16.8	17.0 ± 16	20.6 ± 19.4	.74
Lifetime Episodes, *n*	1.8 ± 1.1	1.7 ± .9	2.0 ± 1.5	.89
First-Degree Relative with Mood Disorder, *n* (%)	14 (58.3%)	10 (58.8%)	4 (57.1%)	.94
Failed Antidepressants (Current Episode)[a], *n*	6.1 ± 3.3	6.1 ± 3.6	6.0 ± 2.7	.70
Failed Antidepressant Augmentations (Current Episode)[a], *n*	2.3 ± 2.3	2.4 ± 2.2	2.0 ± 2.5	.65
Lifetime History of ECT, *n* (%)	4 (16.7%)	2 (11.8%)	2 (28.6%)	.32
Lifetime History of Suicide Attempt, *n* (%)	3 (12.5%)	1 (5.9%)	2 (28.6%)	.13
Past Substance Use Disorder, *n* (%)	8 (33.3%)	5 (29.4%)	3 (42.9%)	.53
Current Anxiety Disorder, *n* (%)	6 (25%)	4 (23.5%)	2 (28.6%)	.80
Current Pain Disorder, *n* (%)	3 (12.5%)	2 (11.8%)	1 (14.3%)	.87
Baseline MADRS Score	31.8 ± 6.1	31.6 ± 6.3	32.1 ± 6.2	.63
Baseline IDS-C Score	44.0 ± 9.8	45.1 ± 10.5	41.6 ± 8.1	.46

The *p* values result from Mann-Whitney *U* or χ^2 tests comparing study phase I responder and nonresponder subgroups. Statistical significance was defined at the .05 level, two-tailed.

ECT, electroconvulsive therapy; F, female; IDS-C, Inventory of Depressive Symptomatology—Clinician Rated; MADRS, Montgomery–Åsberg Depression Rating Scale; M, male; MDD, major depressive disorder.

[a]Only includes failed trials with a score ≥3 according to the Antidepressant Treatment History Form.

21 participants received all six scheduled ketamine infusions. Among the three participants who did not receive the full schedule of ketamine infusions: one was exited after one infusion due to nonresponse as per protocol for the first cohort (see Methods); one experienced hemodynamic elevation during the first infusion resulting in study exit as per protocol (see Methods and Hemodynamic Changes sections); and one withdrew consent after three infusions due to perceived lack of response and desire for standard treatment.

Baseline Characteristics

Demographic and clinical characteristics of the study sample are presented in Table 1. Participants were 48.1 ± 13.0 years of age with an age of onset of MDD of 22.8 ± 13.6 years and had failed to respond to 6.1 ± 3.3 antidepressant treatment trials and 2.3 ± 2.3 augmentation trials in the current major depressive episode.

Phase I: Time-Course of Antidepressant Effects of Ketamine

The overall response rate at study end was 70.8% (17 of 24 participants). Within 2 hours of the first dose of ketamine, there was a large and statistically significant mean improvement in MADRS score from baseline to 2 hours across the full study sample: 18.9 ± 6.6 (decrease from 31.8 to 12.9, $p < .001$) (Figure 1).

The large magnitude of the 2-hour response was generally maintained over the infusion period as estimated by a random

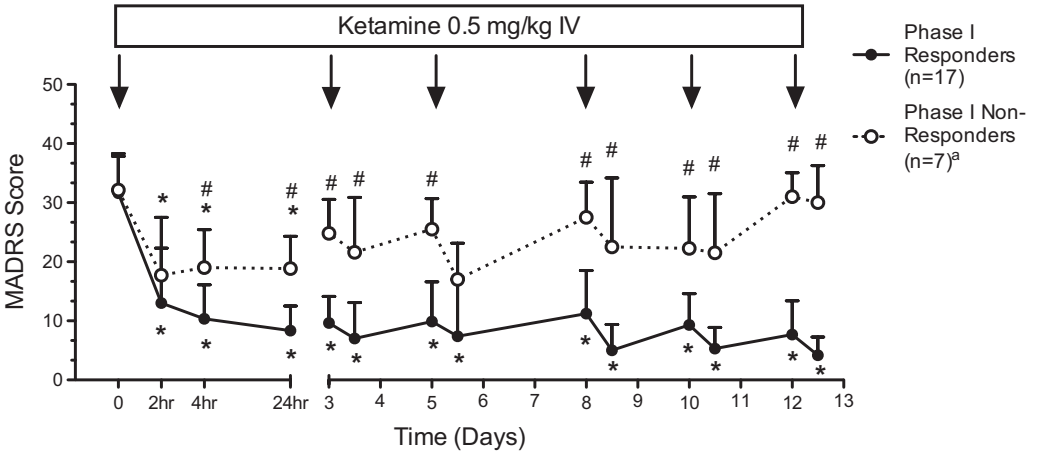

Figure 1. Change in depression severity after repeated ketamine infusions in treatment-resistant major depression. Figure depicts change in depression severity as measured by the Montgomery–Åsberg Depression Rating Scale (MADRS) (mean ± SD) over a 12-day period during which ketamine (.5 mg/kg) was administered IV on a Monday-Wednesday-Friday schedule, corresponding to study days 0, 3, 5, 8, 10, and 12. Trajectories of depression severity are plotted for phase I responder and nonresponder subgroups, defined with the final observed MADRS score. Depression severity was initially measured at baseline before the first ketamine infusion and then at 2, 4, and 24 hours while participants were inpatients. Subsequent infusions occurred on an outpatient basis, and depression severity was measured in the morning before each infusion and then at 4 hours. *MADRS score significantly decreased at given time point compared with baseline, $p < .05$. #MADRS score significantly different at given time point between responder and nonresponder subgroups. [a]Three participants in the nonresponder group did not receive all six ketamine infusions.

effects model: average daily decrease in MADRS score of .128 ± .17 ($p = .45$). Phase I responders continued to improve slightly but significantly after the initial 2-hour improvement (average daily decrease in MADRS score of .35 ± .10, $p = .004$), whereas phase I nonresponders tended to worsen over time (average daily increase in MADRS score of .78 ± .40, $p = .096$).

The separation of responders from nonresponders was clearly evident by 4 hours (MADRS score 10.35 ± 5.74 vs. 19.0 ± 6.46, $p = .013$) and was large at 24 hours (8.35 ± 4.2 vs. 18.8 ± 5.5, $p = .002$) (Figure 1). Ninety-four percent of study responders had responded by 4 hours (i.e., sensitivity was 94%), as did 29% of nonresponders (i.e., specificity was 71%), with positive and negative predictive values of .89 and .83, respectively (Table 2). The relative risk of overall study nonresponse for 2-hour nonresponders was 4.0 (95% confidence interval: 1.23–12.99).

Phase I: Effect of Ketamine on Individual Symptoms of Depression

Within 2 hours of the first dose of ketamine, there was a significant reduction in each individual MADRS item score compared with baseline across the full study sample ($p < .01$; with the exception of the appetite and sleep items that were not examined at the 2-hour time-point) (Figure 2). The nonresponder subgroup manifested significant reductions in reported sadness, inner tension, pessimistic thoughts, and suicidal thoughts but not the other items ($p < .05$) (Figure 2). The largest difference in magnitude between the phase I responders and nonresponders at 2 hours was change in lassitude (Cohen's $d = 1.34$). The observed difference between decrease in apparent sadness and concentration difficulty between the responder and nonresponder subgroups was also large (Cohen's $d =$ .88 and .96, respectively).

Phase II: Risk of Relapse After Response to Ketamine

The 17 phase I responders were followed for up to 83 days to estimate time to relapse (Figure 3). The median time to relapse was 18 days, and the 24th and 75th percentiles were 11 and 27 days, respectively. Four participants did not relapse, and the estimated risk of remaining relapse-free for up to 83 days is .25 ± .11. Fourteen individuals received no psychotropic medication during the follow-up period, whereas 3 individuals participated in a placebo-controlled study of venlafaxine ER for relapse prevention after ketamine (Methods). The relapse experience of the three participants receiving psychotropic medication was similar to the other responders: of the two participants randomized to venlafaxine ER, one relapsed at day 20, and one was a responder at day 83. The participant randomized to placebo after ketamine was also relapse-free at day 83.

Table 2. Diagnostic Test Statistics Considering the Validity of Early Antidepressant Response Predicting End of Study Response During Repeated Ketamine Infusions in Treatment-Resistant Major Depression

Hours	Sensitivity	Specificity	PPV	NPV
2	.65	.57	.79	.40
4	.94	.71	.89	.83
24	.88	.71	.88	.71

Table reports statistics of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) considering response status at the 2-, 4-, and 24-hour time points after the first dose of ketamine as a diagnostic test for predicting subsequent phase I response. See text for details.

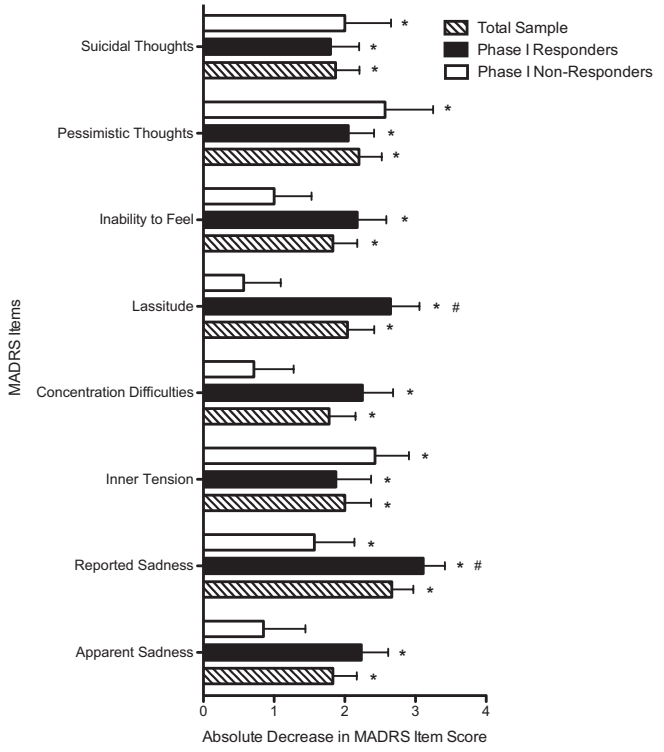

Figure 2. Change in individual depressive symptoms 2 hours after the first infusion of ketamine. Figure depicts absolute decrease in individual items of the Montgomery–Åsberg Depression Rating Scale (MADRS) from baseline to 2 hours after the first infusion of ketamine for the total sample, phase I responders and nonresponders. The score of each item of the MADRS ranges from 0 (no symptom) to 6 (maximally severe symptom). Bars represent means ± SEM. *Item score significantly decreased at 2-hour time point compared with baseline, $p < .05$. #Change in item score from baseline to 2 hours significantly different between responder and nonresponder subgroups.

Acute Dissociative and Psychotomimetic Effects Associated with Ketamine

Ketamine was associated with a small but significant increase in psychotomimetic symptoms as measured by the BPRS (increase from a mean of 4.0 ± .1 before infusion to 4.5 ± .9 at the peak of the

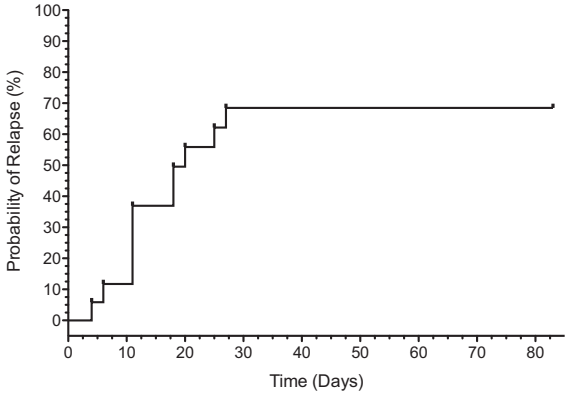

Figure 3. Risk of relapse among responders to repeated ketamine infusions in treatment-resistant major depression. Figure depicts survival analysis conducted in 17 phase I responders after six infusions of ketamine (maximum follow-up time = 83 days). Relapse in phase II was defined as <50% improvement in Montgomery–Åsberg Depression Rating Scale score at that visit compared with baseline for two consecutive visits.

infusion, $p = .013$). The BPRS score returned to a mean of 4.0 by +240 min after infusion. Ketamine resulted in a mild, significant increase in dissociative symptoms as measured by the Clinician-Administered Dissociative States Scale (increase from a mean of .3 ± .5 before infusion to 7.8 ± 12.0 at the peak of the infusion, $p = .001$), which returned to baseline by +240 min after infusion. A similar pattern was observed for elevated mood as measured by the Young Mania Rating Scale-1 ($p = .002$) or the Visual Analog Scale High ($p < .001$). There was no trend toward increasing dissociative or psychotomimetic effects over the course of the trial. See Table S1 in Supplement 1 for details.

There was no difference in dissociative, psychotomimetic, or high feeling between responders and nonresponders or any correlation between change in MADRS score and change in any of the acute measures across the infusion period.

General Side Effects

General side effects were measured in the morning before each infusion and then immediately upon completion of the infusion (+40 min), at +120 min and at +240 min (Table S2 in Supplement 1). The most commonly reported side effects during the 4-hour period after each infusion included feeling strange or unreal (58.3%), abnormal sensations (54.2%), blurred vision (50.0%), and feeling drowsy or sleepy (45.8%). These side effects were largely not reported at the morning pre-infusion assessments for infusions 2–6, suggesting the transient nature of the side effects. Notably, only four participants (16.7%) reported that any side effect impaired functioning at any time during the study.

Hemodynamic Changes

Sixteen participants (67%) did not experience any clinically significant change in vital signs during any of the ketamine infusions. Eight participants (33%) experienced elevated BP and/or heart rate according to pre-defined study criteria at least once during the series of infusions (see Methods section and Supplement 1). One participant experienced elevated BP during the first infusion that did not respond satisfactorily to administration of antihypertensive medication, resulting in discontinuation of the infusion and study exit (maximum BP: 180/115). The BP of that participant stabilized shortly after discontinuation of the ketamine infusion. No serious adverse events occurred during the study.

Discussion

Herein we report the results of the largest study conducted to date on the antidepressant effects of repeated ketamine infusions in TRD. The major findings of this study are that: 1) the antidepressant effect of ketamine is evident very early in the course of treatment, 2) ketamine exerts a broad-spectrum effect on individual symptoms of depression, and 3) rapid response to the first infusion is highly predictive of a sustained response to subsequent infusions.

An initial infusion of ketamine was associated with a large antidepressant effect (MADRS score decreased 18.9 ± 6.6 from baseline to 2 hours), and this effect was generally maintained throughout the course of up to five additional infusions. The effect of ketamine was observed across nearly the full spectrum of depressive symptoms in the total study sample. Of particular note, suicidal ideation (SI) rapidly decreased across the total study sample, even among study nonresponders. Although preliminary, this result suggests that ketamine might exert a unique anti-SI effect even in the absence of a full response and is consistent with previous reports highlighting the potential anti-SI effects of ketamine in depressed populations (10,24,25).

We found that antidepressant response very early in the course of treatment with ketamine strongly predicted subsequent antidepressant response. Specifically, response status at 4 hours was 94% sensitive and 71% specific for predicting response status at the end of phase I. Although preliminary, these findings suggest that patients who will benefit from a course of repeated ketamine infusions will manifest a rapid improvement in depression that is then maintained over the course of treatment. Conversely, lack of a rapid response is a poor prognostic indicator for improvement after additional ketamine infusions. These data are in contrast to the time-course of response to standard antidepressants. For example, in the first step of the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study, 56% of participants who responded at some point during a 12-week trial of the serotonin selective reuptake inhibitor citalopram did so only at or after 8 weeks of treatment (26). Other groups, however, have reported that improvements within a few weeks of initiating standard antidepressant treatment are predictive of a later stable response (27,28). A more definitive conclusion with regard to the validity of early response to ketamine predicting a more durable response must await the results of future controlled studies.

After the final ketamine infusion, the observed median time to relapse among responders was 18 days, and there was considerable inter-subject variability (range 4 to >83 days). Characterizing the durability of antidepressant response after ketamine is a critical issue in determining the potential clinical utility of ketamine as a treatment for TRD. Initial reports suggested a duration of response of several days or up to 1 week after a single ketamine infusion (5). A recent study of a single ketamine infusion in bipolar depression found a time to relapse of just 2 days with the Kaplan-Meier method (11). The findings of the current study might therefore suggest that repeated infusions yield a more durable antidepressant response compared with a single infusion, even after the infusions are discontinued. Interestingly, in a previous placebo-controlled study of riluzole for relapse prevention after a single administration of ketamine we observed a mean time-to-relapse of 22 and 24.4 days for placebo or riluzole, respectively (6). This difference was not significant in part due to the unexpectedly long time-to-relapse of the placebo group (6). A second study of riluzole for relapse prevention after ketamine reported a time-to-relapse of 9.8 and 17.2 days for placebo and riluzole, respectively (12). Taken together, the data from the current study provide preliminary evidence for an enhanced durability of response after repeated ketamine infusions but also highlights the need to identify effective relapse prevention strategies for patients who respond to ketamine.

Future studies testing relapse prevention strategies after response to ketamine might be guided by hypothesized mechanistic synergy. Although the riluzole for relapse prevention strategy was based on potential synergy between ketamine and riluzole involving modulation of glutamate signaling, the recent identification of additional signaling pathways implicated in the antidepressant action of ketamine suggests new targets for synergy (7,29–31). In particular, the finding that inhibition of glycogen synthase kinase-3 is obligatory for the antidepressant effect of ketamine in mice (31) suggests lithium—a well-known inhibitor of glycogen synthase kinase-3—as a potential pharmacotherapeutic strategy after ketamine.

With regard to side effects observed in this study, dissociative and psychotomimetic changes associated with ketamine were only present acutely (during and immediately after infusions) and were generally mild and well-tolerated. We observed an expected increase in dissociative symptoms during administration of ketamine that returned to baseline within 4 hours of the start of the infusion.

At no time did any participant evidence clinically significant psychotomimetic effects resulting from ketamine (e.g., paranoid, delusions, hallucinations). Other adverse effects were generally mild, and no individual discontinued study participation due to side effects. Importantly, there was no evidence of increasing severity of these effects over the 12-day infusion period. There was no correlation between acute dissociative or psychotomimetic effects of ketamine and antidepressant treatment response.

Overall, our results suggest that repeated ketamine infusions might be a viable treatment strategy in the future for patients suffering from TRD. A strategy involving repeated ketamine infusions is currently being investigated as treatment for chronic pain disorders in ambulatory patients that might provide a model for ketamine treatment in TRD in the future (32). Concerns persist, however, with regard to the safety and feasibility of prolonged treatment with ketamine and the optimal number of repeated treatments for safety and efficacy purposes. More preclinical and clinical research will be required before this treatment strategy can be recommended (33,34). Chief among our concerns are a series of early preclinical studies showing that repeated administrations of very high doses of ketamine or other *N*-methyl-D-aspartate receptor antagonists might be neurotoxic in rodents (35,36). Neuroimaging studies in human populations suggest that prolonged abuse of ketamine as an illicit drug might result in deleterious brain changes (37,38), although these studies have been cross-sectional in nature and are confounded by significant comorbid substance abuse beyond ketamine. Research investigating the role of ketamine in TRD must balance concerns regarding potential toxicity against the unmet need for rapidly acting, more effective treatments for patients suffering from enormous morbidity and disability.

Our study has several limitations. Most notably, the open-label design limits the interpretation of efficacy. Specifically, it is not known to what extent the observed decrease in depression severity would have occurred even under placebo conditions. However, there are currently at least four placebo-controlled studies of ketamine in TRD or bipolar depression showing that ketamine results in a rapid antidepressant effect superior to placebo (4,5,10,11). Therefore, the current study was not designed to test the antidepressant effect of ketamine per se but rather to investigate the pattern for response to repeated administrations of ketamine over time. The second significant limitation is the modest sample size of 24 that limits the interpretations that can be drawn and the generalizability of the sample to the broader population of patients with TRD. Despite the limited sample size, however, the current report represents the largest prospective study of repeated ketamine administrations in TRD conducted to date. Notwithstanding the important limitations, we believe that the current report contributes significantly to the small but growing literature on the clinical impact of ketamine in patients with TRD.

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Dr. Charney, Dean of Mount Sinai School of Medicine, has been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and received approval from the Food and Drug Administration for this indication, Dr. Charney and Mount Sinai School of Medicine could benefit financially. Within the past 2 years, Dr. Murrough completed a research fellowship at Mount Sinai School of Medicine that was supported in part by an educational grant from AstraZeneca to Mount Sinai. Dr. Iosifescu in the last 2 years has been a consultant for Central Nervous System Response. Lifetime, Dr. Iosifescu has received research support from Aspect Medical Systems, Forest Laboratories, and Janssen Pharmaceutica; he has been a consultant for Forest Laboratories, Gerson Lehrman Group, and Pfizer; and he has been a speaker for Eli Lilly and Company, Forest Laboratories, Pfizer, and Reed-Elsevier. Dr. Mathew has received research funding or salary support over the last 2 years from the Banner Family Fund, Brain and Behavior Fund, The Brown Foundation, Bristol-Myers Squibb, Department of Veterans Affairs, Evotec, Johnson and Johnson, and the National Institute of Mental Health (5R01MH81870). He has received consulting fees or honoraria from Allergan, AstraZeneca, Cephalon, Corcept, Roche, and Takeda and has received medication from Sanofi-Aventis for an NIH-sponsored study. Dr. Mathew has been named as an inventor on a use patent of ketamine for the treatment of depression. Dr. Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine were approved for this use. Drs. Perez, Parides and aan het Rot and Ms. Pillemer, Stern, and Collins reported no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: Continuation Intravenous Ketamine in Major Depressive Disorder; http://clinicaltrial.gov/ct2/show/NCT00548964?term=NCT00548964&rank=1; NCT00548964.

Supplementary material cited in this article is available online.

1. 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.
2. 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.
3. Rush AJ, Trivedi MH, Stewart JW, Nierenberg AA, Fava M, Kurian BT, *et al.* (2011): Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and long-term outcomes of a single-blind randomized study. *Am J Psychiatry* 168:689–701.
4. 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.
5. 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.
6. 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.
7. Murrough JW (2011): Ketamine as a novel antidepressant: From synapse to behavior. *Clin Pharmacol Ther* 91:303–309.
8. Mathew SJ (2008): Treatment-resistant depression: Recent developments and future directions. *Depress Anxiety* 25:989–992.
9. Shelton RC, Osuntokun O, Heinloth AN, Corya SA (2010): Therapeutic options for treatment-resistant depression. *CNS Drugs* 24:131–161.
10. 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.

11. Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, *et al.* (2012): Replication of ketamine's antidepressant efficacy in bipolar depression: A randomized controlled add-on trial. *Biol Psychiatry* 71:939–946.
12. 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.
13. Phillips ML, Drevets WC, Rauch SL, Lane R (2003): Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54:515–528.
14. Murrough JW, Charney DS (2010): Cracking the moody brain: Lifting the mood with ketamine. *Nat Med* 16:1384–1385.
15. 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.
16. First MB, Spitzer RL, Gibbon M, Williams JBW (1995): *Structured Clinical Interview for DSM-IV Axis Disorders (SCID)*. New York: New York State Psychiatric Institute, Biometrics Research.
17. Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62(Suppl 16):10–17.
18. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996): The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 26:477–486.
19. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
20. Overall JE, Gorham DR, Shawver JR (1961): Basic dimensions of change in the symptomatology of chronic schizophrenics. *J Abnorm Soc Psychol* 63:597–602.
21. 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.
22. Young RC, Biggs JT, Ziegler VE, Meyer DA (1978): A rating scale for mania: Reliability, validity and sensitivity. *Br J Psychiatry* 133:429–435.
23. Levine J, Schooler NR (1986): SAFTEE: A technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull* 22:343–381.
24. 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.
25. Larkin GL, Beautrais AL (2011): A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. *Int J Neuropsychopharmacol* 14:1127–1131.
26. 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.
27. Szegedi A, Müller MJ, Anghelescu I, Klawe C, Kohnen R, Benkert O (2003): Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. *J Clin Psychiatry* 64:413–420.
28. Henkel V, Seemuller F, Obermeier M, Adli M, Bauer M, Mundt C, *et al.* (2009): Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. *J Affect Disord* 115:439–449.
29. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, *et al.* (2010): mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329:959–964.
30. Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng PF, *et al.* (2011): NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475:91–95.
31. Beurel E, Song L, Jope RS (2011): Inhibition of glycogen synthase kinase-3 is necessary for the rapid antidepressant effect of ketamine in mice. *Mol Psychiatry* 16:1068–1070.
32. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M (2009): Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: A double-blind placebo controlled study. *Pain* 147:107–115.
33. Wolff K, Winstock AR (2006): Ketamine: from medicine to misuse. *CNS Drugs* 20:199–218.
34. Perry EB Jr, Cramer JA, Cho HS, Petrakis IL, Karper LP, Genovese A, *et al.* (2007): Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)* 192:253–260.
35. Olney JW, Labruyere J, Price MT (1989): Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science* 244:1360–1362.
36. Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA (1991): NMDA antagonist neurotoxicity: mechanism and prevention. *Science* 254:1515–1518.
37. Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, *et al.* (2010): Frontal white matter abnormalities following chronic ketamine use: A diffusion tensor imaging study. *Brain* 133:2115–2122.
38. Liao Y, Tang J, Corlett PR, Wang X, Yang M, Chen H, *et al.* (2011): Reduced dorsal prefrontal gray matter after chronic ketamine use. *Biol Psychiatry* 69:42–48.