Single, Repeated, and Maintenance Ketamine Infusions for Treatment-Resistant Depression: A Randomized Controlled Trial

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Objective: Subanesthetic ketamine doses have been shown to have rapid yet transient antidepressant effects in patients with treatment-resistant depression, which may be prolonged by repeated administration. The purpose of this study was to evaluate the antidepressant effects of a single ketamine infusion, a series of repeated ketamine infusions, and prolongation of response with maintenance infusions.

Methods: Forty-one participants with treatment-resistant depression completed a single-site randomized double-blind crossover comparison of single infusions of ketamine and midazolam (an active placebo control). After relapse of depressive symptoms, participants received a course of six open-label ketamine infusions administered thrice weekly over 2 weeks. Responders, classified as those participants who had a ≥50% decrease in their scores on the Montgomery-Åsberg Depression Rating Scale (MADRS), received four additional infusions administered once weekly (maintenance phase).

Results: Compared with midazolam, a single ketamine infusion elicited a significantly greater reduction in depressive symptoms at the primary efficacy endpoint (24 hours postinfusion). Linear mixed models revealed cumulative antidepressant effects with repeated infusions and doubling of the antidepressant response rate. Fifty-nine percent of participants met response criteria after repeated infusions, with a median of three infusions required before achieving response. Participants had no further change in MADRS scores during weekly maintenance infusions.

Conclusions: Repeated ketamine infusions have cumulative and sustained antidepressant effects. Reductions in depressive symptoms were maintained among responders through once-weekly infusions. These findings provide novel data on efficacious administration strategies for ketamine in patients with treatment-resistant depression. Future studies should further expand on optimizing administration to better translate the use of ketamine into clinical settings.

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Worldwide, major depressive disorder imposes the largest burden of disease, measured in disability-adjusted life years, among mental, neurological, and substance use disorders (1). Although major depressive disorder is amenable to pharmacotherapy, there remain major unmet needs for the treatment of depression, including the need for drugs with rapid therapeutic action and improved treatment response and remission rates for patients.

In recent years, considerable attention has been dedicated to the potential role of the glutamate system in antidepressant response. The most striking breakthrough in this field has been the discovery of the rapid antidepressant effects of ketamine, a primarily glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist. Subanesthetic doses of intravenous ketamine have been shown to elicit rapid, albeit transient, reductions in depressive symptoms in patients with unipolar and bipolar depression (2). Although the antidepressant effects of ketamine become evident within a few hours or 1 day of a single infusion, the benefits generally disappear within 1 week (3). To date, multiple randomized double-blind studies have shown that single ketamine infusions acutely reduce depressive symptoms when administered as monotherapy (4–7) and as an adjunctive medication (8–10).

More recent studies have examined whether repeated ketamine infusions can sustain the effects. Both twice-weekly (11–13) and thrice-weekly (14–17) administration schedules have resulted in sustained antidepressant effects as infusions are repeated. However, although repeated ketamine infusions may prolong antidepressant effects, relapse still occurs after cessation of infusions (on average, 18–19 days

See related feature: **CME course** *(p. 415)*

postinfusion) (14, 15). Given the rapid relapse rates that follow ketamine infusion, the field requires the development of strategies that will permit a reduction in the frequency of infusions after response to acute treatment, with maintenance of the beneficial effects.

In the present study, the antidepressant effects of single, repeated, and maintenance ketamine infusions were characterized in a sample of patients with treatment-resistant depression. We hypothesized that the antidepressant effects of a single infusion of ketamine would be superior to an active control in a randomized double-blind crossover design; that increased response rates would be obtained with a course of repeated open-label ketamine infusions compared with those obtained with the single infusion; and that once-weekly maintenance infusions would prolong the antidepressant response obtained with acute ketamine treatment.

METHODS

Participants

Male and female outpatients with treatment-resistant depression (age range, 18–65) completed a single-center randomized controlled trial of ketamine at the Royal's Institute of Mental Health Research in Ottawa between January 2013 and December 2017. Participants were recruited from physician referrals and advertisements. Participants met DSM-IV-TR criteria for major depressive disorder (18), single or recurrent episode without psychotic features, confirmed with the Mini-International Neuropsychiatric Interview (19). Treatment resistance was defined as failure to respond to at least two antidepressant medications of different pharmacological classes and two augmentation strategies at adequate dosages for at least 6 weeks each during the present episode, as recorded in the Antidepressant Treatment History Form (20). Inclusion criteria were a score ≥25 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (21) at screening and at randomization, with no more than 20% improvement between these visits. Participants remained on stable dosages of concomitant psychotropic medication with treatment durations of at least 6 weeks with no changes to their treatment regimens during the trial. Exclusion criteria included a history of drug abuse or dependence as defined by DSM-IV-TR criteria (18) or confirmed by positive urine toxicology screen, a body mass index ≥35, a history of mania or hypomania, and unstable medical conditions identified by physical examination and measurement of vital signs, ECG, standard blood tests, and urinalysis. Female participants of childbearing potential required a negative pregnancy test at enrollment and use of adequate birth control throughout the study. The study protocol was approved by the Royal Ottawa Mental Health Centre Research Ethics Board. All participants provided written informed consent.

Study Design

The data derive from a three-phase clinical trial (Figure 1). The purpose of phase 1 was to test the efficacy of ketamine compared with an active control. In phase 1, participants received a single ketamine infusion during a randomized double-blind crossover with midazolam (a short-acting benzodiazepine that serves as an active placebo control for ketamine) (5). Phase 1 infusions occurred at least 7 days apart, and participants were required to have a return of 80% of their baseline MADRS score to proceed to the second phase 1 infusion and to begin phase 2. The goal of phase 2 was to test reinstatement of antidepressant response after relapse and to evaluate the efficacy of repeated infusions. In phase 2, participants received a course of six open-label ketamine infusions, administered thrice weekly over a 2-week period. The aim of phase 3 was to test maintenance of antidepressant effects when the frequency of infusions was reduced. In phase 3, participants who obtained an antidepressant response after repeated administration received once-weekly infusions for an additional 4 weeks. Antidepressant response was defined as a ≥50% decrease in MADRS total score from baseline (before the first infusion in phase 1) to the end of phase 2. Nonresponders exited the study after phase 2.

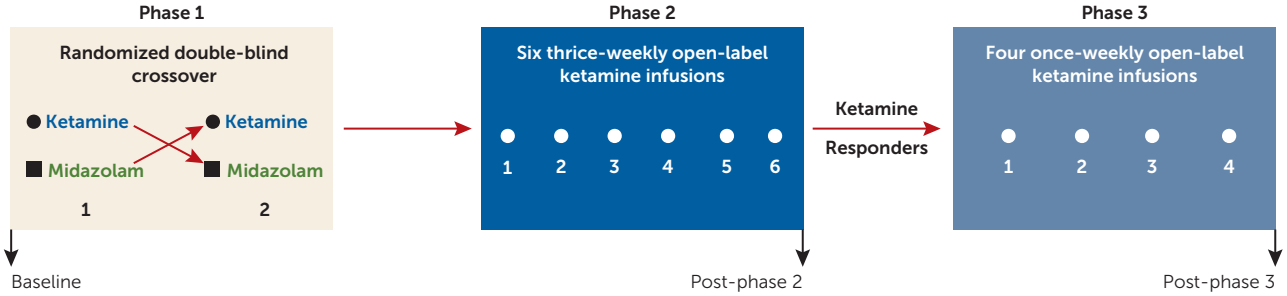
Randomization and Blinding

In phase 1, participants were randomly assigned, in a 1:1 ratio, to receive midazolam or ketamine first. Ketamine and midazolam doses were prepared by a nurse in correctly labeled separate bags. To maintain the study blind, medication bags were then relabeled as drug A and drug B by an independent randomizer in accordance with a randomization log. Blinded study staff were subsequently provided with the correctly coded randomly assigned bag for infusion, and the unused bag (labeled A or B) was sent to the pharmacy to be destroyed. All study personnel and participants remained blind to phase 1 data until study completion.

Drug Administration

Ketamine hydrochloride was administered at a dose of 0.5 mg/kg, diluted in 0.9% saline, over a 40-minute period by intravenous pump. The dose of 0.5 mg/kg was selected because this dose has been used in almost all previous clinical trials of ketamine for depression. Midazolam was administered at a dose of 30 μg/kg, to obtain an approximate dose of 2 mg, diluted in saline. The midazolam dose was selected on the advice of a consultant anesthesiologist. Infusions were administered in an outpatient clinic by a study physician and a research nurse under cardiorespiratory monitoring. Blood pressure and pulse were monitored at 5-minute intervals throughout each infusion and afterward until return of preinfusion levels. Participants were discharged approximately 2 hours postinfusion. On infusion days, participants were required to abstain from consuming grapefruit juice (a potent 3A4 cytochrome inhibitor that may slow the elimination of midazolam and possibly ketamine) (22) and to avoid taking any benzodiazepines the preceding day, as they attenuate ketamine response (23).

FIGURE 1. Study design for a randomized double-blind crossover clinical trial of subanesthetic ketamine for treatment-resistant depression[a]



[a] Antidepressant response to ketamine was defined as a ≥50% improvement in Montgomery-Åsberg Depression Rating Scale total score from baseline to post-phase 2 assessment.

Outcome and Measures

Measures included the 10-item clinician-administered MADRS and the 16-item patient-administered Quick Inventory of Depressive Symptomatology–Self Report (QIDS-SR) (24). For phase 1, the primary outcome measure was change in MADRS total score from preinfusion to 24 hours postinfusion. Secondary outcome measures included MADRS scores at additional postinfusion time points (2 hours and 7 days) and QIDS-SR scores (assessed preinfusion and 24 hours, 4 days, and 7 days postinfusion). For phase 2, the primary outcome measure was change in MADRS score throughout the course of repeated infusions. Additional study measures included the proportion of individuals who met antidepressant response and remission criteria (MADRS total score ≤10) after single and repeated infusions. Change in MADRS score over phase 3 was also examined. Follow-up measures for phases 2 and 3 were obtained 3 days after the final infusion in each phase. Ratings were conducted by study physicians who trained together to establish interrater reliability.

The safety and tolerability of ketamine were assessed at regular intervals. General adverse events were recorded with the Systematic Assessment for Treatment Emergent Events (25). Dissociative effects were assessed in a subgroup of participants with the Clinician-Administered Dissociative States Scale (CADSS) (26). The CADSS was administered during both phase 1 infusions and during the final ketamine infusion in phase 2 at three time points: preinfusion, immediate postinfusion, and 2 hours postinfusion.

Statistical Analysis

The baseline characteristics of responders and nonresponders were compared with independent-samples t tests for continuous variables and chi-square tests for categorical variables. For phase 1, a random-effects linear mixed model was used to evaluate changes in MADRS score between ketamine and midazolam infusions across four time points from preinfusion to 7 days postinfusion. The model included participants as a random effect, drug and time as fixed within-subject factors, interaction between drug and time, and a fixed intercept. Baseline MADRS score and order of drug administration were included as covariates with fixed within-subject and between-subject effects, respectively. An unstructured variance-covariance matrix best fit the data using Akaike's information criterion. Restricted maximum likelihood estimation was used. Significant effects were examined with simple-effects tests. For phases 2 and 3, random-effects models were used to quantify changes in MADRS score over time, adjusting for phase-specific baseline MADRS score. Analyses of QIDS-SR data were performed as described above for MADRS data. CADSS scores were analyzed with paired t tests and Pearson's correlation coefficient. Statistical analyses were performed with IBM SPSS Statistics, version 24.0 (IBM, Armonk, N.Y.). Results were considered significant at a two-tailed p value of 0.05.

RESULTS

Participants

Sixty-three individuals were prescreened for eligibility through consultation with a study physician. Of these, 46 signed consent forms and underwent formal screening (see the CONSORT diagram in Figure SF1 in the online supplement). There were three screen failures. Forty-three participants met criteria for the intent-to-treat sample and received at least one infusion. Four participants withdrew during the course of the study. Participants' baseline characteristics are summarized in Table 1.

Single Ketamine Infusion

Forty-one participants completed the randomized double-blind crossover comparison of single infusions of ketamine and midazolam. Participants received the two infusions an average of 10 days apart (SD=6, range=7–36 days). There was no difference in the elapsed time between phase 1 infusions for participants who received ketamine first compared with those who received midazolam first ($t=0.25$, $df=39$, $p=0.80$). Using random-effects modeling, after adjustment for baseline MADRS score and order of drug administration, there were significant main effects for drug ($F=8.84$, $df=1, 40$, $p<0.001$) and time ($F=30.77$, $df=3, 40$, $p<0.001$) and a significant drug-by-time interaction ($F=13.15$, $df=3, 40$, $p<0.001$). Simple-effects analyses revealed that participants had significantly lower MADRS total scores at each postinfusion time point

TABLE 1. Baseline demographic and clinical characteristics of patients with treatment-resistant depression treated with single and repeated subanesthetic infusions of ketamine

Characteristic	Total Sample (N=43)[a]		Responders (N=23)[b]		Nonresponders (N=16)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	41.7	12.3	42.0	12.0	39.9	13.4
Body mass index	26.6	4.6	26.1	4.4	27.0	4.5
Duration of current episode (years)[c]	5.7	5.9	4.0	3.2	8.1	7.9
Failed antidepressant trials[d]	3.3	1.6	3.0	1.5	3.6	1.8
Failed augmentations[d]	2.9	1.3	2.6	0.8	3.3	1.5
MADRS total score	34.7	4.2	34.9	3.2	34.9	5.0
	N	%	N	%	N	%
Female	24	56	15	65	7	44
Major depressive episodes						
Single	21	49	11	48	9	56
Recurrent	22	51	12	52	7	44
Lifetime history of suicide attempt	10	23	6	26	3	18
ECT nonresponse in current episode	7	22	3	17	4	29
Current comorbid diagnosis[e]						
Panic disorder	4	9	1	4	2	13
Agoraphobia	10	23	4	17	5	31
Social phobia	10	23	3	13	6	38
Obsessive-compulsive disorder	2	5	1	4	1	6
Alcohol dependence	1	2	0	0	1	6
Bulimia nervosa	1	2	1	4	0	0
Generalized anxiety disorder	10	23	7	30	3	18

[a] Data are based on the intent-to-treat sample.
[b] Responders met antidepressant response criteria (≥50% improvement in Montgomery-Åsberg Depression Rating Scale [MADRS] total score) after the course of repeated ketamine infusions; there were no significant differences between the responder and nonresponder groups except as otherwise indicated.
[c] The duration of the current episode was significantly longer in nonresponders (t=2.26, df=37, p=0.03).
[d] Data represent the number of failed antidepressant trials and augmentations during the current episode according to the Antidepressant Treatment History Form.
[e] Assessed with the Mini-International Neuropsychiatric Interview.

after ketamine infusion compared with midazolam infusion (Figure 2A). At the a priori primary efficacy endpoint 24 hours after ketamine infusion, participants had a mean decrease of 10.9 points (SD=8.9) in MADRS total score relative to preinfusion scores compared with a mean decrease of 2.8 points (SD=3.6) with midazolam.

Examination of the model covariates revealed significant main effects for baseline MADRS total score (F=359.95, df=1, 37, $p<0.001$) and order of drug administration (F=4.24, df=1, 37 p=0.047), indicating carryover effects between phase 1 infusions. Although participants who received midazolam first had similar preinfusion MADRS total scores for both phase 1 infusions (mean, 35.4 [SD=5.6] compared with 34.9 [SD=4.5]; t=0.36, df=20, p=0.72), those who received ketamine first had slightly lower preinfusion scores at their second phase 1 infusion (mean, 34.6 [SD=4.1] compared with 32.6 [SD=5.6]; t=3.44, df=20, p=0.006).

Twenty-four hours after the single ketamine infusion, 11 participants (27%) met antidepressant response criteria, and two participants (5%) achieved remission. Single-infusion responders had a mean decrease of 22.3 points (SD=5.3) in MADRS total score (Figure 2B) 24 hours postinfusion, and nonresponders had a mean decrease of 6.7 points (SD=5.6) (Figure 2C). No participants met antidepressant response criteria with midazolam at any postinfusion time point.

Repeated Ketamine Infusions

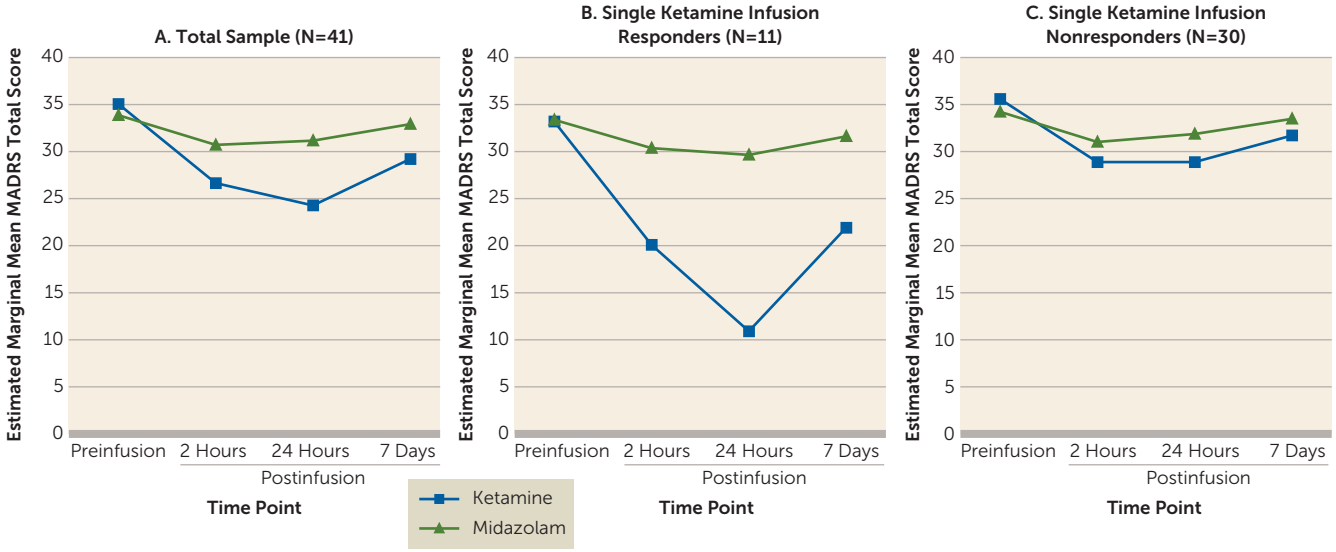
The primary outcome for phase 2 was change in MADRS scores over the course of six repeated infusions. A random-effects model that was adjusted for participant and depression severity at the start of phase 2 revealed a significant main effect for time (F=11.16, df=6, 39, $p<0.001$) (Figure 3A). On average, participants' MADRS total score decreased by 2 points with each infusion.

Of the 41 participants treated in phase 2, 39 completed the full course of infusions. At the post–phase 2 follow-up visit, 23 participants (59%) met antidepressant response criteria, and nine (23%) achieved remission. Responders had a mean decrease of 21.6 points (SD=5.8) in MADRS total score overall, and nonresponders had a mean decrease of 3.1 points (SD=5.7) (Figure 3B). Responders included nine (82%) of the 11 participants who met response criteria after the single phase 1 ketamine infusion, and 14 additional phase 1 nonresponders. The median number of infusions participants needed to first meet response criteria was three. Seventy-seven percent of phase 2 responders received three or more infusions before meeting response criteria (Figure 3C).

Maintenance Infusions

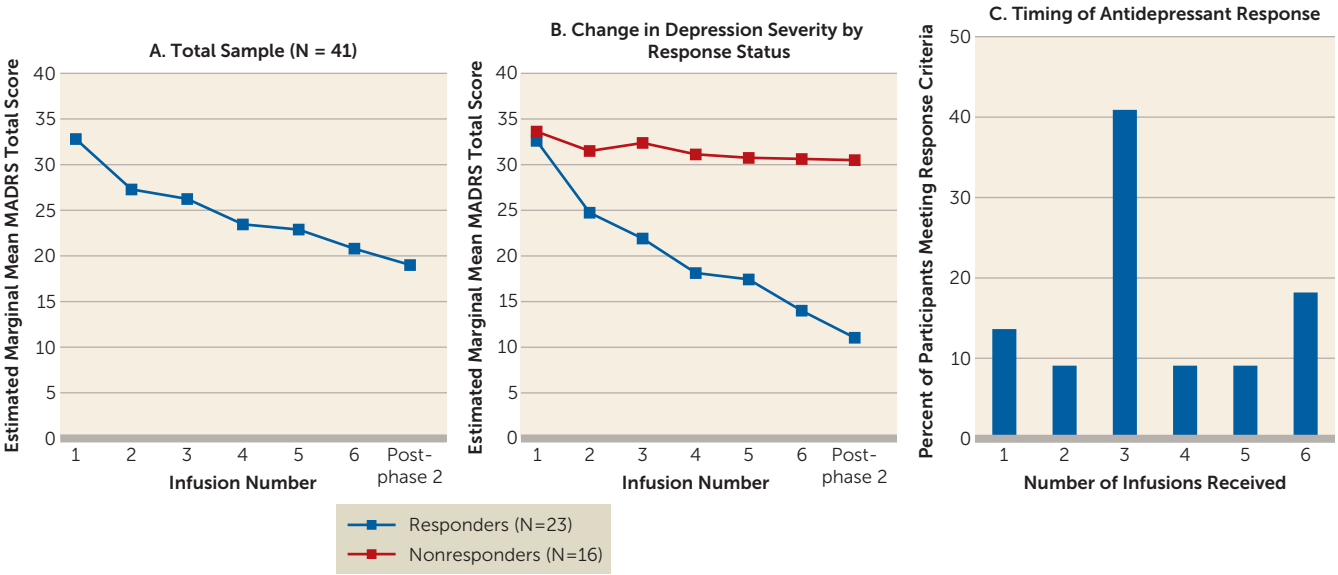
Participants who had at least a 50% improvement in MADRS scores after repeated infusions (N=23) continued to phase 3, the maintenance phase. A linear mixed model that was

FIGURE 2. Change in depression severity over time in patients with treatment-resistant depression treated with single infusions of ketamine and midazolam in a randomized double-blind crossover design[a]



[a] The primary outcome measure was change in Montgomery-Åsberg Depression Rating Scale (MADRS) total scores from preinfusion to 24 hours postinfusion. As shown in panel A, participants had a significantly greater decrease in MADRS total score with ketamine compared with midazolam ($p<0.001$). Single-ketamine-infusion responders (panel B) met antidepressant response criteria (≥50% decrease in MADRS total score from preinfusion) at 24 hours postinfusion. Nonresponders (panel C) did not meet antidepressant response criteria.

FIGURE 3. Change in depression severity over time in patients with treatment-resistant depression treated with a 2-week course of thrice-weekly subanesthetic infusions of open-label ketamine[a]



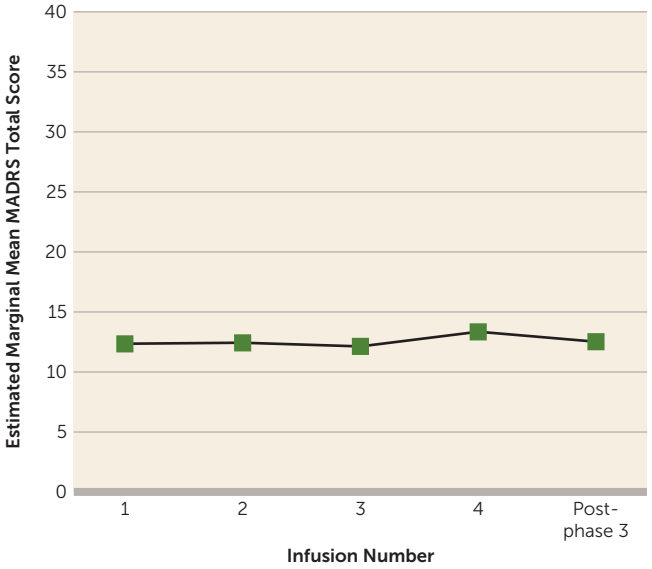
[a] As shown in panel A, with repeated ketamine infusions, participants had a significant cumulative decrease in depression severity assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS), administered before each infusion ($p<0.001$). Responders to repeated ketamine infusions (panel B) met antidepressant response criteria (≥50% decrease in MADRS total scores from baseline) at the post-phase 2 assessment. As shown in panel C, the median number of infusions required to meet response criteria during repeated administration was three.

adjusted for the random effect of participant and phase-specific baseline depression severity revealed no main effect of time on change in MADRS total score during maintenance infusions ($F=0.88$, $df=4, 22$, $p=0.49$). This indicates no further change in MADRS score once ketamine infusions were reduced to once-weekly administration (Figure 4). Examination of individual-level data revealed that 21 responders (91%) met antidepressant response criteria throughout maintenance infusions.

Self-Reported Depression Severity

Linear mixed models were used to evaluate participants' self-reported change in depression severity by using QIDS-SR total scores. For phase 1, there were significant main effects

FIGURE 4. Change in depression severity over time in ketamine responders treated with weekly subanesthetic maintenance infusions of open-label ketamine[a]



[a] With once-weekly maintenance ketamine infusions, participants had no significant change in depression severity assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) (p=0.49).

for drug (F=6.60, df=1, 40, p=0.01) and time (F=6.76, df=3, 36, p=0.001) and a significant drug-by-time interaction (F=3.46, df=3, 37, p=0.03). Simple-effects analyses revealed that participants had significantly lower QIDS-SR total scores with ketamine compared with midazolam at 24 hours and 4 days postinfusion (see Figure SF2 in the online supplement). Consistent with the analyses of clinician-administered MADRS scores, there was a significant fixed effect of time on QIDS-SR total score in phase 2 (F=7.67, df=6, 39, p<0.001) (see Figure SF3 in the online supplement) and no effect for time in phase 3 (F=1.29, df=4, 22, p=0.30) (see Figure SF4 in the online supplement).

Safety Outcomes

No serious adverse events were reported during the trial. The most common side effects associated with ketamine were cardiorespiratory effects, numbness or tingling, dissociation, dizziness, and visual disturbances. Vital signs were continuously evaluated at each infusion throughout the study. Mean ketamine doses and overall changes to cardiorespiratory values were calculated for participants' first ketamine infusion. The mean absolute dose of ketamine administered was 40 mg (range, 26–60 mg). During ketamine infusions, participants experienced transient elevation of blood pressure (maximum mean change, systolic, 25.3 mmHg; diastolic, 15.7 mmHg) and heart rate (maximum mean change, 10.2 bpm). On average, values returned to preinfusion levels at 24 minutes postinfusion (range, 5–40 minutes). No infusions were discontinued as a result of cardiorespiratory effects, and no rescue medications were administered during the study.

The dissociative effects of ketamine were formally assessed in a subgroup of study participants (N=22). A paired t test comparing participants' preinfusion change with their immediate postinfusion change in CADSS total score during their phase 1 infusions revealed significantly higher CADSS scores with ketamine compared with midazolam (t=5.70, df=21, p<0.001). The dissociative effects associated with ketamine returned to baseline levels by 2 hours postinfusion (t=1.70, df=21, p=0.10). In phase 1, participants' dissociative side effects (change in CADSS score) during the ketamine infusion were significantly correlated with antidepressant response at 24 hours postinfusion (change in MADRS total score, Pearson's r=–0.46, p=0.03) (see Figure SF5 in the online supplement). Comparison of change in CADSS scores before and after participants' first ketamine infusion (mean=18.0, SD=14.3) and their final ketamine infusion in phase 2 (7th infusion overall; mean=4.6, SD=7.3) revealed a decrease in dissociative side effects with repeated infusions (t=4.06, df=19, p=0.001).

Although drug craving was not formally assessed during the study, there were no spontaneous reports of craving or drug-seeking behavior among the participants during the trial nor in any participants seen since in follow-up.

DISCUSSION

The results of this clinical trial confirm that subanesthetic ketamine infusions can provide safe and efficacious reduction in depressive symptoms in patients with treatment-resistant depression. Major novelties of this study include that it is the first trial, to our knowledge, to use a randomized double-blind crossover design to elicit superior antidepressant effects with a single infusion of ketamine compared with a psychoactive control. The study also showed restoration of antidepressant response with ketamine after relapse of depressive symptoms, allowing for the first direct comparison of response rates for single and repeated infusions, and evidence of a lack of tachyphylaxis to the benefits of ketamine. Additionally, this is the largest study to date to report maintenance of antidepressant effects in responders when the frequency of infusions was reduced to once weekly. Together, these findings help further inform the use of ketamine in clinical practice.

Consistent with previous studies, the single ketamine infusion had maximal antidepressant effects at 24 hours postinfusion, which abated within 7 days. Randomized clinical trials have consistently and repeatedly demonstrated the rapid antidepressant effects of single infusions of ketamine compared with saline (4, 6, 8–10) and midazolam (5, 7). What is unique to the present study is the use of an active placebo control with a crossover design. All participants received both study medications, and none exhibited a clinically meaningful response to midazolam. This lack of placebo response and the relatively low overall antidepressant response to the single ketamine infusion (27%) highlight the illness severity and treatment resistance among the study participants. It may also suggest enhanced reliability of the findings, because the rapid reduction in depressive symptoms observed in single-infusion responders is more likely

attributable to the ketamine infusion than to other factors associated with study initiation in a highly supportive clinical setting. Other studies that have employed a parallel design and reported higher response rates to single ketamine infusions have also reported notable response rates with midazolam, ranging from 11% (7) to 28% (5). The response rate with midazolam in the present study was 0%. These findings suggest that the response rates with ketamine reported in previous studies may need to be adjusted for placebo response.

Because all participants had a relapse of depressive symptoms before entering the repeated administration phase, it was possible to compare antidepressant response to single and repeated infusions in the same individuals. Results revealed a doubling of the antidepressant response rate with repeated infusions and no evidence of tachyphylaxis. Nine of 11 participants who responded to the single infusion also responded to repeated infusions despite relapsing in between. This suggests that ketamine may differ from other medications used to treat mood disorders, with which patients may fail to achieve a response after relapse if a medication is discontinued prematurely (27).

Overall, more than half of the study participants met response criteria, and almost a quarter achieved remission by the end of the course of six repeated ketamine infusions administered over 2 weeks. The antidepressant effects of repeated infusions were cumulative, with depression severity further decreasing with each infusion and an increasing number of participants meeting response criteria as infusions continued. The prevalent late response to serial ketamine administration is consistent with the findings of Shiroma et al. (16), with more than three-quarters of study participants requiring three or more infusions before meeting response criteria. This indicates that individuals who initially fail to respond to a single ketamine infusion may respond to repeated administration.

The goal of the final phase of the trial was to test, in all 23 ketamine responders (the largest group, to our knowledge, examined with maintenance infusions to date), whether antidepressant response could be prolonged when the frequency of ketamine infusions was reduced. Results clearly demonstrated that weekly maintenance infusions were sufficient to maintain the antidepressant effects obtained with repeated infusions.

Although there was no formal follow-up of study participants after the completion of phase 3, 10 study participants were subsequently enrolled in a psychotherapy study led by one of the authors (J.T.). Participants who enrolled in the secondary study within 2 weeks of completing the ketamine trial maintained their antidepressant response (N=6). However, participants who enrolled 3 or more weeks after their final ketamine infusion relapsed, and each presented with severe depressive symptoms at the initiation of the psychotherapy study (N=4). These findings, although descriptive in nature, suggest that continuation of ketamine infusions is necessary to sustain the antidepressant benefits even after a course of successful maintenance infusions. Wilkinson et al. (13) recently provided preliminary evidence of the safety and tolerability of long-term ketamine administration, which mirrors our own clinical experience. Nevertheless, the prolonged use of ketamine warrants further study.

Overall, ketamine infusions were safe and well tolerated by study participants, with only transient side effects. Dissociation was among the most commonly reported side effects experienced. There have been reports of an association between dissociative side effects and antidepressant response to ketamine (28, 29). In the present study, although participants' initial antidepressant response to ketamine was associated with dissociative experience, dissociation decreased with repeated infusions despite increasing therapeutic benefits. This suggests that dissociative side effects do not entirely account for the antidepressant efficacy of ketamine, and additional research is required to further elucidate the relationship between these variables and to clarify the mechanisms underlying the antidepressant effects of ketamine.

Despite the strengths of this study, it has several limitations. These include the absence of dissociative side effects with midazolam, which has implications for the integrity of the blind in the crossover comparison in phase 1. Although the use of an alternate active control that has dissociative effects comparable to ketamine without antidepressant properties would have been ideal, no such drug has been identified to date. Another consideration is that the repeated and maintenance phases of the trial were open-label with no active control. Ketamine was shown to be superior to midazolam in this sample through the single-infusion comparison. The goal of phase 2 was to test reinstatement of the antidepressant response to ketamine after relapse. The use of a control during phases 2 and 3 would not have been successful, because after patients' exposure to both midazolam and ketamine in phase 1, nearly all would be able readily to discriminate ketamine because of its mild but clear dissociative effects, thus compromising any future blinding of study medications. Furthermore, the fact that the 16 individuals who did not meet response criteria with repeated infusions showed virtually no decrease in MADRS score over time suggests that there was no interference from the clinical setting. Moreover, although these results are based on a modest sample size, the study was sufficiently powered to detect outcomes with the crossover design. Finally, given that participants maintained their concomitant medication regimen throughout the trial, it can only be concluded that ketamine is an effective adjunctive treatment, and it remains to be determined whether the same effects would be observed when ketamine is used as a monotherapy.

A recently published consensus statement recommended the use of ketamine in treatment-resistant depression provided that safety measures are in place and adequate psychiatric follow-up is available (2). Within the field, however, an effective strategy to maintain antidepressant

response in patients after cessation of infusions remains elusive. Although this study provides evidence of sustained antidepressant effects with once-weekly maintenance infusions, a future research goal will be to determine the degree to which the frequency of infusions can be decreased while maintaining response. Additionally, there is a need to directly compare the efficacy of ketamine to treatments with demonstrated antidepressant properties, such as ECT; such research is currently being conducted by our team. Ketamine shows great promise in providing rapid therapeutic action and improving response and remission rates in treatment-resistant depression. Although research into the mechanisms underlying the antidepressant effects of ketamine continues, this and future clinical studies can provide essential information on effective administration strategies that will permit sustained therapeutic benefits for patients.

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