

Ketamine Safety and Tolerability in Clinical Trials for Treatment-Resistant Depression

Le-Ben Wan, MD, PhD; Cara F. Levitch, BA; Andrew M. Perez, MD; Jess W. Brallier, MD; Dan V. Iosifescu, MD, MMSc; Lee C. Chang, MD; Alexandra Foulkes, MS; Sanjay J. Mathew, MD; Dennis S. Charney, MD; and James W. Murrough, MD

ABSTRACT

Objective: Ketamine has demonstrated rapid antidepressant effects in patients with treatment-resistant depression (TRD); however, the safety and tolerability of ketamine in this population have not been fully described. Herein we report the largest study to date of the safety, tolerability, and acceptability of ketamine in TRD.

Method: Data from 205 intravenous (IV) ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants with *DSM-IV*-defined major depressive disorder (MDD) were pooled from 3 clinical trials conducted between 2006 and 2012 at 2 academic medical centers. Safety and tolerability measures included attrition, adverse events (AEs), hemodynamic changes, and assessments of psychosis and dissociation.

Results: The overall antidepressant response rate, defined as a $\geq 50\%$ improvement in Montgomery-Asberg Depression Rating Scale score, was 67% (65 of 97 participants). Four of 205 infusions (1.95%) were discontinued due to AEs. The overall attrition rate was 3.1% (3 of 97). In the first 4 hours after the infusion, the most common general AEs were drowsiness, dizziness, poor coordination, blurred vision, and feeling strange or unreal. Approximately one third of individuals experienced protocol-defined hemodynamic changes. Ketamine resulted in small but significant increases in psychotomimetic and dissociative symptoms (all $P < .05$). There were no cases of persistent psychotomimetic effects, adverse medical effects, or increased substance use in a subgroup of patients with available long-term follow-up information.

Conclusions: In this relatively large group of patients with TRD, ketamine was safe and well tolerated. Further research investigating the safety of ketamine in severe and refractory depression is warranted.

Trial Registration: ClinicalTrials.gov identifiers: NCT00419003, NCT00548964, and NCT00768430.

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Corresponding author: James W. Murrough, MD, Department of Psychiatry, Mood and Anxiety Disorders Program, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Pl, Box 1230, New York, NY 10029 (james.murrough@mssm.edu).

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonist that has demonstrated rapid-onset antidepressant effects in patients with major depressive disorder (MDD)^{1–5} and bipolar depression.^{6,7} Notably, rapid antidepressant effects have been observed in patients with refractory forms of depression (eg, treatment-resistant depression ([TRD])).^{2–4} A single low-dose infusion of ketamine (0.5 mg/kg) results in a 50%–70% response rate in patients with TRD, with a variable duration of response.^{8,9}

Ketamine has been used extensively over the past 50 years as an anesthetic agent in children and adults at doses of 1–3 mg/kg and is considered to be very safe in patient populations.¹⁰ More recent investigations of the analgesic and antidepressant properties of ketamine have been conducted at lower doses, ranging from 0.1 to 1 mg/kg.^{11,12} Subanesthetic doses of ketamine have been associated with a range of acute neuropsychiatric effects, including neurocognitive disturbances, sensory-motor disturbances, and dissociation.^{13–16} Ketamine is also associated with cardiovascular and respiratory effects—specifically, stimulation of the cardiovascular system (heart rate, cardiac output, and blood pressure) and mild respiratory depression.^{10,17,18}

In the face of a growing evidence base for the short-term efficacy of ketamine in depression, concern has been raised about the possibility of persistent neuropsychiatric effects and medical sequelae as well as the abuse potential of ketamine.^{19–25} A retrospective analysis of healthy subjects who received subanesthetic intravenous (IV) ketamine in a research setting found no persistent adverse mental status events, no residual medical sequelae, and no long-term increased risk of ketamine abuse.²⁶ No study to date, however, has systematically investigated the neuropsychiatric or medical effects of ketamine in depressed patients.

The purpose of this study is to evaluate the short-term safety, tolerability, and acceptability of ketamine for TRD patients in a research setting. We also investigated potential predictors of response and the relationship between adverse effects and efficacy. We analyzed patient-level data from ketamine clinical trials in TRD and conducted longer-term follow-up surveys on a subset of participants. Herein we report findings related to the acute neuropsychiatric and general side effects of ketamine and longer-term consequences and overall acceptability in TRD patients.

METHOD

Three studies involving ketamine administration for TRD were conducted at the Icahn School of Medicine at Mount Sinai and Baylor College of Medicine between 2006 and 2012 (Table 1; clinicaltrials.gov identifiers NCT00419003, NCT00548964, and NCT00768430). All studies were approved by the institutional review board of the participating institutions. Participants in all studies had a primary diagnosis of chronic or recurrent MDD, as assessed by a trained rater with the Structured Clinical Interview for *DSM-IV*²⁷ and a diagnostic

- Ketamine is a promising treatment option for refractory depression that carries acceptable short-term risk in the context of a medical research setting.
- Important risks associated with ketamine include transient changes in hemodynamic parameters and dissociation.
- The use of adequate vital signs and behavioral monitoring and the availability of medical support during infusions are important to optimize safety.
- The longer-term safety and effectiveness of ketamine in psychiatric populations are largely unknown, dissuading widespread clinical use pending future studies.

interview with a study psychiatrist. Depending on the study, participants had to have failed to respond to at least 2 or 3 US Food and Drug Administration (FDA)-approved antidepressant medications according to the Antidepressant Treatment History Form.²⁸ Exclusion criteria included recent substance abuse or dependence, lifetime history of psychosis or any psychotic disorder, bipolar disorder, developmental disorder, or recreational use or abuse of ketamine or phencyclidine. Physical examination, vital signs, electrocardiogram, standard blood tests, urinalysis, and urine toxicology confirmed the absence of unstable medical illnesses and illicit substance use. Subjects in all studies were washed off psychotropic medications 2–4 weeks prior to randomization. Treatment response was defined as a $\geq 50\%$ improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score. See the primary references for further details.^{3–5}

For each infusion, an anesthesiologist administered racemic ketamine (0.5 mg/kg) over 40 minutes by IV infusion pump with standard telemetry monitoring (eg, pulse oximetry, heart rate, blood pressure, end-tidal CO₂). Dissociative and psychotomimetic effects of ketamine were assessed before the start of each infusion, immediately upon completion of each infusion (40 minutes), and after 240 minutes. Behavior and adverse events measures at 24 hours were available for a subset of infusions.^{4,5} See the study by Murrough et al⁴ for a detailed description of the ketamine administration protocol. Psychotomimetic effects were measured with the 4-item positive symptom subscale of the Brief Psychiatric Rating Scale (BPRS+; scale range, 4–28)²⁹; dissociative effects were measured with the Clinician-Administered Dissociative States Scale (CADSS; scale range, 0–92).³⁰ General side effects were measured with the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI)³¹ or the Patient-Rated Inventory of Side Effects (PRISE).³² General side effects according to the SAFTEE-SI or the PRISE were defined as moderate to severe increases in symptoms in the period from baseline to 120 minutes, and persistence of side effects was noted at the 240-minute and 24-hour time points. The same or similar SAFTEE-SI and PRISE items were combined as single composite items. Per protocol, a study anesthesiologist,

present throughout the infusion, had the option to treat increases in blood pressure to levels exceeding 180/100 mm Hg or heart rate greater than 110 bpm (for example, with the short-acting β -blocker labetalol). If these elevations resolved spontaneously within a short time period, they were generally not treated. The study infusion was discontinued in the event that 3 consecutive measurements remained above protocol-defined limits despite anesthesiology intervention.

Longer-term follow-up assessments were conducted including all available subjects to determine whether there were any long-term adverse effects of ketamine exposure and to assess the overall acceptability of ketamine as a treatment for depression. Subjects were contacted by telephone at varying intervals depending on the study (range, 8 months to 6 years). The study was approved by the institutional review boards at each institution, and all subjects gave verbal consent before participating. The interviews were conducted by a trained clinician or study coordinator. See eAppendix 1 at Psychiatrist.com for the questionnaire, which was adapted from Perry et al²⁶ and included an assessment of how acceptable treatment with ketamine would be in the future if ketamine were to gain FDA approval for this indication. We attempted to re-contact all study participants by telephone and e-mail when available. Telephone contact was attempted at least 3 times prior to determining that the subject was not available for follow-up assessment.

All statistical analyses were performed with IBM SPSS Statistics software (version 20; IBM Corporation, Armonk, New York). Repeated-measures analysis of variance (ANOVA) was used to assess within-subject differences in continuous measures across time. Two-tailed, paired *t* tests were conducted to localize significant differences. Mann-Whitney *U* tests or *t* tests were used to compare means across 2 independent groups. The relationship between hemodynamic change and comorbid medical conditions was assessed using χ^2 tests. Univariate tests were also used to assess relationships between ketamine response at 24 hours and demographic and clinical characteristics, comorbid medical conditions, hemodynamic change, ketamine dose, change in CADSS score, and change in BPRS score. Follow-up Pearson correlation analyses were used to assess the relationship between change in MADRS score and change in CADSS and BPRS scores.

RESULTS

The study included 205 intravenous ketamine infusions (0.5 mg/kg over 40 minutes) in 97 enrolled participants across 3 clinical trials at 2 centers (Table 1). Demographic and clinical features for 84 unique subjects are presented in Table 2 (13 individuals participated in more than 1 trial). The 24-hour response rate among all participants was 67%, with a mean MADRS decrease of 19 ± 11.7 points compared to baseline. The mean age of ketamine responders was significantly higher (50.4 ± 11.7 years) than nonresponders (43.2 ± 12.4 years; $P = .01$). Other demographic and clinical characteristics did not differ between ketamine responders and nonresponders ($P > .05$ for all univariate analyses).

Table 1. Ketamine Studies in Subjects With Treatment-Resistant Unipolar Depression

Reference	Subjects Receiving Ketamine, N ^a	No. of Infusions per Subject	Dose (mg/kg) and Duration of Infusion	Route	Design
Mathew et al, 2010 ³	26	1	0.5 over 40 min	IV	Open-label followed by riluzole RCT
Murrough et al, 2013 ⁴	24	6 ^b	0.5 over 40 min	IV	Open-label
Murrough et al, 2013 ⁵	47	1	0.5 over 40 min	IV	RCT with active placebo (midazolam)

^aNumber of unique subjects = 84 since 13 subjects participated in more than one protocol.

^bNot all subjects received all 6 infusions.

Abbreviations: IV = intravenous, RCT = randomized placebo-controlled trial.

Table 2. Characteristics of the 84 Unique Subjects^a

Variable	Value ^b
Demographic	
Age at enrollment, y	47.2 (12.1)
Male, n (%)	46 (54.8)
White, n (%)	69 (82.1)
African American, n (%)	12 (14.3)
Asian, n (%)	4 (4.8)
Hispanic, n (%)	10 (11.9)
Clinical	
Age at onset of MDD, y	21.1 (11.1)
Length of current episode, y	16.1 (15.2)
Length of illness, y	25.6 (13.7)
No. of failed antidepressant trials	5.4 (3.0)
Baseline MADRS score	35.8 (7.5)

^aFor subjects who participated in more than one study, values are based on the earliest screening visit.

^bValues are mean (SD) unless otherwise noted.

Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

The overall attrition rate due to any cause was 3.1% (3 of 97 subjects). Of the 205 infusions, 4 were discontinued due to AEs (1.95% of infusions; 4.1% of subjects). Of these 4 discontinuations, 2 subjects experienced elevated blood pressure during the infusion that did not respond satisfactorily to 3 separate administrations of antihypertensive medication (maximum blood pressure: 180/115 mm Hg and 187/91 mm Hg, respectively). In both cases, vital signs normalized shortly after ketamine discontinuation. A third subject experienced an increase in anxiety and requested that the infusion be stopped. A fourth subject, while undergoing venipuncture for a blood draw, experienced transient hypotension and bradycardia and was placed on cardiac monitoring for 24 hours. The event was considered a serious adverse event (SAE) due to prolongation of existing hospitalization. The single SAE represented 0.49% of infusions. Other nonserious adverse events are presented in Table 3. Side effects peaked within the 120-minute period after infusion and largely resolved by the 240-minute and 24-hour time points.

As expected, transient increases in mean blood pressure were observed during the ketamine infusion (Figure 1). The mean peak systolic blood pressure was 141.9 ± 21.2 mm Hg (mean increase of 19.6 ± 12.8 mm Hg, $P < .001$) and peak diastolic blood pressure was 86.4 ± 12.7 mm Hg (mean

increase of 13.4 ± 9.8 mmHg, $P < .001$). Transient increases in pulse were also observed during the ketamine infusion. There was no change in blood oxygen level ($P = .3$).

A protocol-defined increase in blood pressure or pulse was experienced by 29.8% of participants (25/84). A total of 14.3% of participants (12/84) received medication intervention for these changes, which lasted a mean of 14.4 ± 12.6 minutes. The occurrence of hemodynamic changes was associated with a body mass index (BMI) of 30 or greater ($P = .03$) and with a higher ketamine dose (45.8 ± 9.3 mg compared to 41.5 ± 11.1 mg, $P = .03$). Hemodynamic change, comorbid medical conditions, and mean

ketamine dose did not differ between ketamine responders and nonresponders ($P > .05$ for all analyses).

BPRS+ and CADSS scores are presented in Figure 2. Ketamine was associated with a small but significant increase in psychotic symptoms as measured by the BPRS+ (increase from a mean baseline of 4.2 ± 1.3 to 4.5 ± 1.3 at the 40-minute time point, $P = .001$). Ketamine resulted in a mild, significant increase in dissociative symptoms as measured by the CADSS (increase from a mean baseline of 0.7 ± 2.9 to 9.8 ± 13.9 at the 40-minute time point, $P < .001$). For a subset of infusions (no. = 72), delayed effects were measured after 24 hours and did not differ significantly from baseline.

Changes in CADSS score did not differ significantly between ketamine responders (12.4 ± 14.1) and nonresponders (8.6 ± 10.2 , $P = .2$). The mean increase in BPRS+ score was also not significantly different ($P = .2$). Pearson correlation analysis showed no association between change in MADRS score and change in CADSS score or change in BPRS score (See Supplementary eFigure 1).

Of 84 unique subjects who participated in the ketamine studies included in this analysis, 46 could be reached and consented to a phone interview to assess longer-term or persistent adverse effects of ketamine (Supplementary eTable 1). The mean length of time from the first ketamine administration was 2.9 ± 1.9 years, with a range of 8 months to 6 years. In general, subjects did not report persistent physical, emotional, or psychological symptoms. One subject did endorse increased levels of anxiety and dysphoria after ketamine administration, persisting for slightly over 1 month. There were no reports of increased cravings or use of ketamine or other illicit substances.

The mean score for acceptability was 3.7 ± 1.5 ("somewhat acceptable" to "very acceptable") out of 5, with a median of 4 (Supplementary eFigure 2). Of those subjects who rated ketamine "not at all acceptable," 5 cited lack of improvement in depressive symptoms, 1 cited increased anxiety, and 1 cited dissociative effects. There was no reason given for 1 subject.

DISCUSSION

The findings from this study show that low-dose ketamine is safe and well tolerated in depressed patients in the context of a well-controlled medical research setting. The overall

Table 3. Frequency of General Adverse Events in Ketamine Studies of Treatment-Resistant Unipolar Depression^a

Item ^b	≤ 120 min ^c	240 min	24 h
Feeling drowsy or sleepy	31 (15.1)	3 (1.5)	1 (0.5)
Dizziness or faintness ^d	29 (14.1)	5 (2.4)	2 (1.0)
Poor coordination or unsteadiness ^d	29 (14.1)	5 (2.4)	1 (0.5)
Dizziness when standing up ^d	26 (12.7)	3 (1.5)	2 (1.0)
Blurred vision ^d	25 (12.2)	1 (0.5)	1 (0.5)
Feeling strange or unreal	24 (11.7)	1 (0.5)	1 (0.5)
Abnormal sensations	19 (9.3)	0 (0.0)	0 (0.0)
Slurred speech	19 (9.3)	0 (0.0)	0 (0.0)
Headache ^d	19 (9.3)	8 (3.9)	8 (3.9)
Dry mouth ^d	18 (8.8)	1 (0.5)	3 (1.5)
Trouble concentrating ^d	18 (8.8)	2 (1.0)	1 (0.5)
Numbness or tingling	13 (6.3)	0 (0.0)	3 (1.5)
Diminished mental capacity	11 (5.4)	1 (0.5)	0 (0.0)

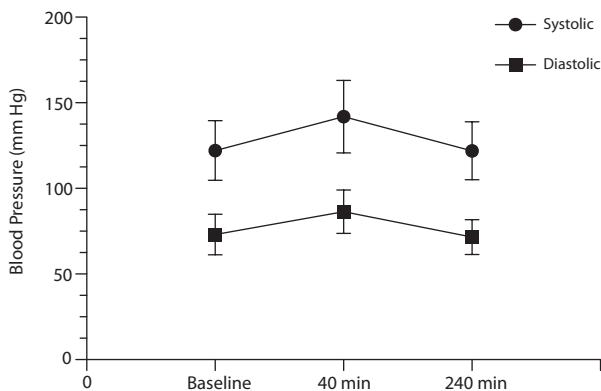
^aFrequency values are shown as No. (%) of events. A total of 205 infusions were done.

^bItems have a reported frequency of at least 5% (eg, > 10 infusions).

^cAssessments conducted immediately upon completion of each infusion (40 minutes) and again at 120 minutes. A positive response at either time point is represented in the count.

^dItems that were the same or similar on the Systematic Assessment For Treatment Emergent Effects Self-Report Inventory (SAFTEE-SI) and Patient Rated Inventory of Side Effects (PRIZE) are represented as single composite items.

Figure 1. Change in Blood Pressure During Ketamine Infusion in 97 Subjects With Treatment-Resistant Depression^a

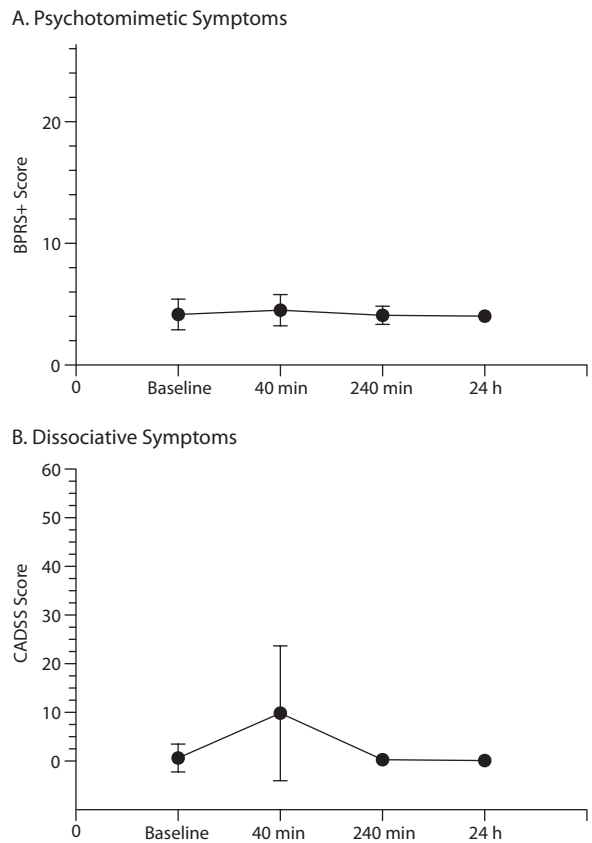


^aMean (SD) hemodynamic and blood oxygen level changes after ketamine infusions are shown. Values represent mean baseline, peak (40-minute), and 240-minute systolic and diastolic blood pressure.

antidepressant response rate across 3 studies and 97 enrolled participants was 67%. General side effects and acute behavioral changes associated with ketamine in depressed subjects resolved by 4 hours after ketamine administration. Across all study participants, a single SAE consisted of an overnight hospitalization for cardiac monitoring. In our longer-term follow-up data, we found no evidence of ketamine abuse, increased drug cravings, or substance abuse following study participation. We found that older age was associated with better response to ketamine. No other demographic or clinical variable was associated, and there was no association between antidepressant response and dissociation or other side effects.

Protocol-defined changes in vital signs—by and large, elevations in blood pressure—were experienced by 29.8% of subjects receiving ketamine and 14.3% of subjects received a medication intervention for these changes (typically a short-

Figure 2. Change in (A) Psychotomimetic and (B) Dissociative Symptoms Following Ketamine Infusion in Subjects With Treatment-Resistant Depression^a



^aMean (SD) scores on the Brief Psychiatric Rating Scale (BPRS+) and Clinician-Administered Dissociative States Scale (CADSS) at baseline and 40 minutes, 240 minutes, and 24 hours after ketamine infusion are shown. Results are based on 205 total infusions for all time points except for the 24-hour time point (72 infusions).

acting antihypertensive agent). In all but 2 cases, the elevated blood pressure responded rapidly to the intervention. In the other 2 cases, the infusion was discontinued, at which time the blood pressure returned to normal. These findings underscore the need for adequate hemodynamic monitoring during ketamine infusions. These changes were associated with both obesity and total ketamine dose, suggesting that ketamine doses below 0.5 mg/kg may be appropriate in some patients. More research investigating the safety and efficacy of doses other than 0.5 mg/kg is required in order to determine the optimal dosing strategy for individual patients.

We found small but statistically significant increases in psychotomimetic and dissociative effects during ketamine administration. The 4-item positive symptom subscale of the BPRS—measuring conceptual disorganization, hallucinations, suspiciousness, and unusual thought content—was used as an index of psychosis based on previous reports.^{13,33} The average observed peak score of 4.5 in this sample is consistent with symptom severity described as “very mild” (scale range, 4–28).²⁹ In our studies, we excluded patients with a history of psychosis due to concerns regarding the potential for ketamine to exacerbate or

trigger psychotic symptoms. Therefore, while we found that ketamine was associated with minimal psychotic symptoms in our samples, caution is warranted in extrapolating our findings to larger patient groups with more diverse symptom histories. Dissociative symptoms associated with ketamine were pronounced in a minority of patients in our sample. The average observed peak score of 9.8 (scale range, 0–92)³⁰ falls within a range defining mild symptomatology in the context of what has been reported in disorders characterized by dissociation. In a validation study, roughly half the average baseline score of a cohort of subjects with PTSD fell in this range.³⁰ Our findings suggest that psychotomimetic effects associated with ketamine are uncommon in this patient group, while dissociative effects are relatively more common. In some reports, healthy subjects seem to have more severe psychotic reactions than those we observed in our sample of depressed patients¹³; however, a quantitative comparison is difficult in this context.

Our longer-term follow up data were noteworthy for the absence of persistent dissociative or psychotomimetic effects. There were no cases of persistent physical symptoms or increased substance use. Case reports of depressed patients receiving repeated ketamine infusions have generally reported favorable long-term outcomes. For example, Correll and Futter³⁴ described 2 subjects with TRD; the first received continuous low-dose IV ketamine (up to 0.27 mg/kg/h) for 5 days, and the second received 3 ketamine infusions (up to 0.3 mg/kg/h for 5 days) over 6 months. Both subjects demonstrated marked functional improvement after 12 months without reported adverse consequences. Another case report described a subject who received 6 ketamine infusions (0.5 mg/kg) over 2 weeks and did not report long-term adverse consequences after 12 months.³⁵ On the other hand, 2 cases of delayed-onset suicidal ideation and dysphoria following ketamine administration in patients with obsessive-compulsive disorder were recently reported.³⁶ An isolated case of mania following ketamine treatment has also been reported.³⁷ Clearly, substantially more data on longer-term safety and efficacy of ketamine in these populations are required.

This study has several limitations. The efficacy and side-effect profile of ketamine reported herein result from combining patient-level data from studies utilizing different clinical trial designs, including controlled and uncontrolled designs, thereby limiting the confidence in the pooled summary statistics. Rates of adverse events were derived from 2 different assessment instruments, potentially biasing results toward shared items. The study is limited to short-term administration of ketamine. If ketamine were to be used as a treatment for refractory depression, patients may be exposed to ketamine over longer periods of time. There are currently very few data regarding the safety and efficacy of longer-term use of ketamine to treat TRD, and much more research is required to more fully understand the risks and benefits of this approach. In particular, future studies should assess the persistence of hemodynamic changes in repeated-infusion studies. The generalizability

of this study is limited by the exclusion of subjects with concurrent psychotropic treatment, current substance use, lifetime psychotic or manic symptoms, and unstable medical illnesses. Particularly important given our observations of increased blood pressure with ketamine, we excluded uncontrolled hypertension and history of arrhythmia or other cardiac disease. Since participants were not taking concomitant medication treatment for depression, we are unable to assess potential interactions. Future studies will be needed to more fully document the longer-term safety profile of ketamine in depression.

In conclusion, this study is the first systematic analysis of the acute and longer-term neuropsychiatric and physical adverse effects of ketamine in subjects with TRD. The data suggest that subanesthetic doses of ketamine administered to unipolar depressed patients in a controlled research setting present a low and acceptable level of risk. Notably, almost 30% of patients experienced transient but significantly elevated blood pressure or other hemodynamic changes, compelling the use of adequate monitoring and medical support during infusions.

Drug names: ketamine (Ketalar and others), labetalol (Trandate and others), riluzole (Rilutek and others).

Author affiliations: Department of Psychiatry, Mood and Anxiety Disorders Program (Drs Wan, Perez, Iosifescu, Charney, and Murrrough and Ms Levitch); Department of Anesthesiology (Drs Perez and Brallier); Department of Neuroscience (Drs Iosifescu, Charney, and Murrrough); Department of Pharmacology and Systems Therapeutics (Dr Charney); and Friedman Brain Institute (Drs Iosifescu and Murrrough), Icahn School of Medicine at Mount Sinai, New York, New York; Department of Anesthesiology (Dr Chang) and Menninger Department of Psychiatry and Behavioral Sciences (Dr Mathew and Ms Foukes), Baylor College of Medicine; and Mental Health Care Line, Michael E. DeBakey VA Medical Center (Dr Mathew), Houston, Texas.

Author contributions: Drs Murrrough and Charney contributed equally to the preparation of this manuscript.

Potential conflicts of interest: In the past 2 years, **Dr Murrrough** has received research support from NIMH, the American Foundation for Suicide Prevention, the Doris Duke Charitable Foundation, Janssen Pharmaceuticals, and Avanir Pharmaceuticals and has served on advisor boards for Genentech and Janssen Pharmaceuticals and has received consulting fees from ProPhase. **Dr Iosifescu** has received research support from AstraZeneca, Brainsway, Euthymics, Neosync, and Roche and has received consulting fees for CNS Response, Otsuka, Servier, Sunovion, and Avanir Pharmaceuticals. **Dr Charney** has received consulting fees or research support from the US Dept of Defense, NIH, NIMH, NARSAD, USAMRAA, and *CNS Spectrums* and is a member of the Advisory and Editorial Boards of the Institute of Medicine Committee on DHS Workforce Resilience. Dr Charney and the Icahn School of Medicine at Mt Sinai have been named as inventors on a pending use patent of ketamine as a rapid treatment for posttraumatic stress disorder (PTSD). If ketamine were shown to be effective as a rapid treatment of PTSD and received approval from the US Food and Drug Administration for this indication, Dr Charney and Mount Sinai School of Medicine could benefit financially. Dr Charney and the Icahn School of Medicine at Mt Sinai have also been named as inventors on a pending use patent of intranasal neuropeptide Y (NPY) for the treatment of mood and anxiety disorders. If NPY were shown to be effective for the treatment of mood and anxiety disorders and received approval from the US Food and Drug Administration for this indication, Dr Charney and Mount Sinai School of Medicine could benefit financially. **Dr Mathew** has received consulting fees or research support from Allergan, AstraZeneca, Bristol-Myers Squibb, Cephalon Inc, Corcept, Johnson & Johnson, Naurex, Noven, Roche, and Takeda. Drs Charney (Dean of Icahn School of Medicine at Mount Sinai) and Mathew and Icahn School of Medicine at Mount Sinai have been named on a use patent on ketamine for the treatment of depression. The Icahn School of Medicine has entered into a licensing agreement for the use of ketamine as therapy for treatment-resistant depression. Dr. Charney and Icahn School of Medicine at Mount Sinai could potentially benefit if ketamine were to gain approval 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 Wan, Perez, Brallier, and Chang and Mss Levitch and Foulkes declare no conflict of interest.

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Supplementary Material

Article Title: Ketamine Safety and Tolerability in Clinical Trials for Treatment-Resistant Depression

Author(s): Le-Ben Wan, MD, PhD; Cara F. Levitch, BA; Andrew M. Perez, MD; Jess W. Brallier, MD; Dan V. Iosifescu, MD, MMSc; Lee C. Chang, MD; Alexandra Foulkes, MS; Sanjay J. Mathew, MD; Dennis S. Charney, MD; and James W. Murrough, MD

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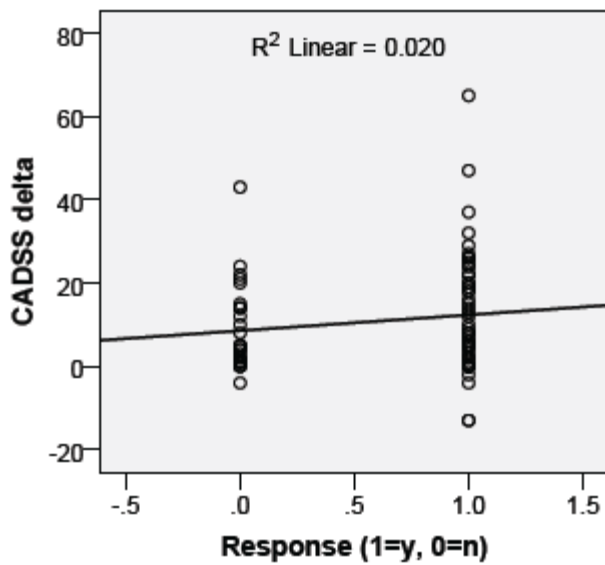
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Supplementary eTable 1. Long-Term Follow-Up Data Summary

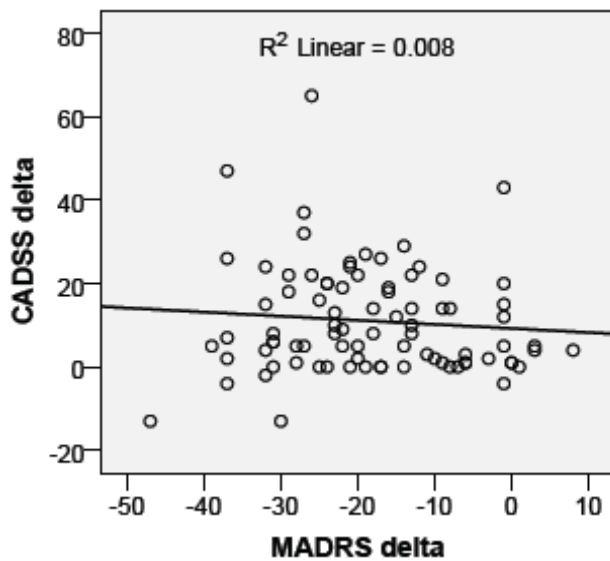
Item	Yes, Count	Notes
Physical Problems	0	-
Emotional/Psychological Problems	1	Resolved 1 month post-study
Cravings for Ketamine	0	-
Use of Ketamine	0	-
Cravings for Other Substances	0	-
Increased Use of Other Substances	0	-

n=46, average follow-up time 2.9±0.2 years

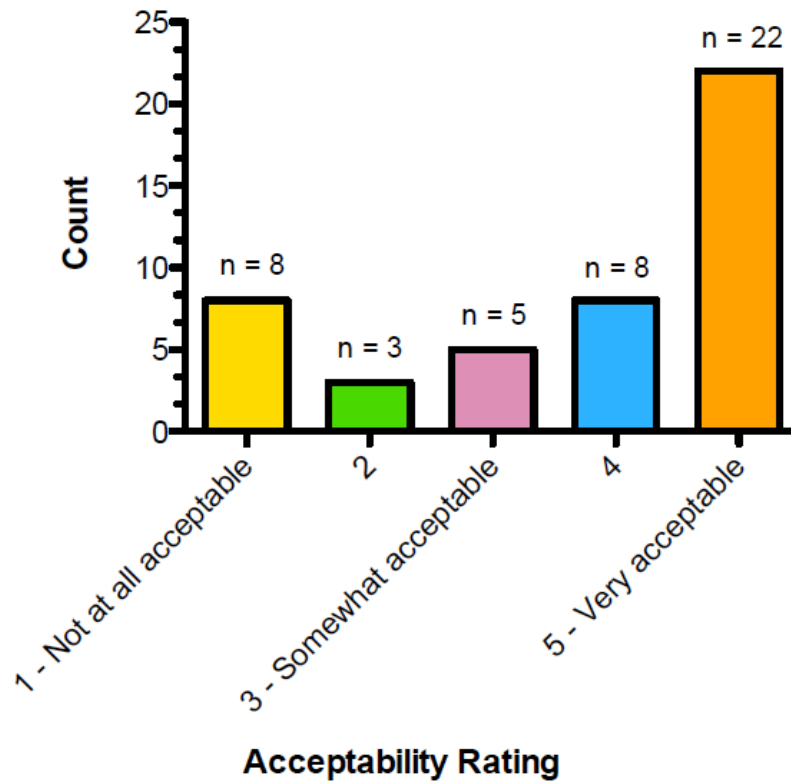
A.



B.



Supplementary eFigure 1. Lack of Correlation between Acute Dissociation and Subsequent Antidepressant Response. Scatter plots showing change in CADSS score at 40 min post-infusion versus ketamine responder status (A; $r=0.14$; $p=0.20$) and change in MADRS score (B; $r=0.09$; $p=0.34$) at 24 hrs post-infusion. Results are based on 84 unique subjects.



Supplementary eFigure 2. Distribution of Responses to Ketamine Acceptability

Questionnaire. Graph depicts frequency histogram of responses to a questionnaire

assessing patient report of the potential acceptability of ketamine as a treatment for

depression. 1 = not at all acceptable, 3 = somewhat acceptable, and 5 = very

acceptable. n=46 subjects re-contacted for long-term follow-up.

eAppendix 1. Adapted from Perry EB Jr, Cramer JA, Cho HS, et al. Psychiatric safety of ketamine in psychopharmacology research. *Psychopharmacology (Berl)*. 2007;192(2):253-260.

- Since your participation in the study, have you experienced any physical problems that you believe are related to ketamine?
- Since your participation in the study, have you experienced any emotional or psychological problems that you believe are related to ketamine?
- Since your participation in the study, have you had any cravings for ketamine?
- Since your participation in the study, have you used ketamine outside of a research setting?
- Since your participation in the study, have you had cravings for any other illicit drug?
- Since your participation in the study, have you used any other illicit drug?
- Using a 5-point scale, where “1” is not at all acceptable, “3” is somewhat acceptable, and “5” is very acceptable, how acceptable would ketamine be to you for the treatment of your depression if ketamine were to become an approved treatment option in the future? In deciding on the acceptability of the treatment, please consider factors including perceived benefit compared to risk, convenience, and potential stigma of the treatment.