A Randomized Controlled Trial of Intranasal Ketamine in Major Depressive Disorder

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Background: The *N*-methyl-D-aspartate glutamate receptor antagonist ketamine, delivered via an intravenous route, has shown rapid antidepressant effects in patients with treatment-resistant depression. The current study was designed to test the safety, tolerability, and efficacy of intranasal ketamine in patients with depression who had failed at least one prior antidepressant trial.

Methods: In a randomized, double-blind, crossover study, 20 patients with major depression were randomly assigned, and 18 completed 2 treatment days with intranasal ketamine hydrochloride (50 mg) or saline solution. The primary efficacy outcome measure was change in depression severity 24 hours after ketamine or placebo, measured using the Montgomery-Åsberg Depression Rating Scale. Secondary outcomes included persistence of benefit, changes in self-reports of depression, changes in anxiety, and proportion of responders. Potential psychotomimetic, dissociative, hemodynamic, and general adverse effects associated with ketamine were also measured.

Results: Patients showed significant improvement in depressive symptoms at 24 hours after ketamine compared to placebo ($t = 4.39$, $p < .001$; estimated mean Montgomery-Åsberg Depression Rating Scale score difference of 7.6 ± 3.7; 95% confidence interval, 3.9–11.3). Response criteria were met by 8 of 18 patients (44%) 24 hours after ketamine administration compared with 1 of 18 (6%) after placebo ($p = .033$). Intranasal ketamine was well tolerated with minimal psychotomimetic or dissociative effects and was not associated with clinically significant changes in hemodynamic parameters.

Conclusions: This study provides the first controlled evidence for the rapid antidepressant effects of intranasal ketamine. Treatment was associated with minimal adverse effects. If replicated, these findings may lead to novel approaches to the pharmacologic treatment of patients with major depression.

Key Words: Antidepressant, depression, glutamate, intranasal, ketamine, treatment resistant

Major depressive disorder (MDD) is common and a leading cause of disability worldwide (1). Treatment-resistant depression (TRD), characterized by nonresponse to at least one antidepressant, is associated with a high degree of morbidity and functional disability and is estimated to occur in one third of patients with MDD (2). For patients who do respond to standard antidepressant treatments, there is a significant delay in the onset of therapeutic benefit, which further increases illness burden and risks of associated morbidity and suicidality (3). Although research in neuroscience has elucidated some of the basic mechanisms of depression and antidepressant action (4), current antidepressant drugs primarily target the monoaminergic system identified decades ago. More recently, the glutamate system has emerged as a critical focus of novel therapeutic development for MDD and particularly TRD (5,6).

Evidence from postmortem and in vivo brain imaging studies implicates amino acid neurotransmitter systems, particularly glutamate, and *N*-methyl-D-aspartate receptor in the pathophysiology of MDD (7–10). Several studies have demonstrated rapid antidepressant effects of intravenous (IV) administration of ketamine, a high-affinity *N*-methyl-D-aspartate receptor antagonist, in patients with TRD (11–15). However, there may be limitations to a therapy requiring IV administration, including lack of availability in common mental health practices, requirement for support services and monitoring, and patient discomfort. In contrast, ketamine administered via an intranasal route may provide a feasible and safer alternative.

Intranasal ketamine has shown safety and efficacy as an anesthetic and analgesic agent (16–20). In particular, ketamine administered via an intranasal route has been successfully used in the treatment of headache and pain in ambulatory patients (21–23). In one study, 50 mg of ketamine administered intranasally was well tolerated and led to symptomatic improvement in chronic pain (23). The objective of the current proof-of-concept clinical trial was to test the rapid antidepressant effect of a single 50-mg administration of ketamine via an intranasal route in patients with MDD who had failed to respond to at least one prior antidepressant trial. Based on accumulating evidence supporting the efficacy and tolerability of IV administration of ketamine in patients with depression and prior research examining intranasal administration of ketamine in patients with pain, we hypothesized that a dose of 50 mg administered via an intranasal route would be safe and well tolerated and lead to a rapid reduction in depressive symptoms.

Methods and Materials

Participants

Study participants were recruited from physician referrals, media advertisements, and an academic outpatient psychiatric clinic. Men and women, 21–65 years old, with a primary diagnosis of MDD, chronic or recurrent, without psychotic features, as

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assessed by a trained rater with the Structured Clinical Interview for DSM-IV (24) and a diagnostic interview with a study psychiatrist were eligible to participate. All study treatments were performed at Mount Sinai Medical Center between April 2012 and June 2013. Participants were required to have failed to respond to at least one trial of adequate dose and duration of an antidepressant medication approved by the U.S. Food and Drug Administration in the current episode according to the Antidepressant Treatment History Form (25). Participants were allowed to remain on stable doses of psychotropic medication, including antidepressant treatment. Negative urine toxicology for illicit drugs was required. Participants were required to have a baseline score of ≥30 on the Inventory of Depressive Symptoms–Clinician Rated (26) to proceed in the trial. Exclusion criteria included any unstable medical or neurologic condition, any Axis I disorder other than MDD that was judged to be the primary presenting problem, high risk of suicide, substance abuse or dependence in the 6 months before screen, any psychotic disorder, bipolar disorder, developmental disorder, or lifetime abuse or dependence on 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 and to maintain adequate birth control for the duration of the study. Individuals with nasal obstructions or history of nasal surgery were not enrolled.

The Icahn School of Medicine at Mount Sinai 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 (NCT01304147).

Study Design

Eligible participants received 50 mg of racemic ketamine hydrochloride (Mylan Pharmaceuticals, Morgantown, West Virginia, and JHP Pharmaceuticals, Parsippany, New Jersey) and placebo (.9% saline solution) at least 7 days apart in a randomized, double-bind crossover design. Each treatment period (ketamine or placebo) consisted of 7 days. In each treatment period, assessments occurred at +40 min, +120 min, +240 min, +24 hours, +48 h, +72 hours, and +7 days after the start of treatment intervention. For subjects to proceed from the first to the second treatment period, they needed to exhibit a sufficient level of depressive symptoms, defined as Inventory of Depressive Symptoms–Clinician Rated ≥24. The order of treatment periods was randomly assigned by the research pharmacy using permuted blocks of size four. All study investigators, anesthesiologists, and raters were blind to treatment assignment.

Study drug or placebo was provided in identical syringes, containing clear solutions of either 100 mg/mL ketamine in .9% saline or saline alone. An LMA MADgic Mucosal Atomization Device (LMA North America, Inc., San Diego, California) was used to provide five intranasal applications of solution (volume 100 μL), separated by 5 min. Each of five ketamine applications provided 10 mg of study drug. Administrations were provided over 20 min by an anesthesiologist in a clinical research unit. Patients were monitored for at least 4 hours in the research unit after administration, including continuous monitoring of vital signs (i.e., heart rate, blood pressure [BP], respiration, and pulse oximetry). In the original protocol, patients stayed overnight in the research unit. However, after safety was demonstrated, the protocol was modified, allowing patients to be discharged 4 hours after administration and subsequently followed as outpatients. On completion of the second treatment period, patients were seen for final safety and efficacy evaluation and were exited from the protocol. All procedures aside from administration and monitoring after administration occurred in an outpatient context at Mount Sinai Medical Center.

Outcome Measures

The primary study outcome was change in depression severity, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) at 24 hours after intervention. Subjects were rated before each administration (−60 min) and +40, +120, and +240 min and 1, 2, 3, and 7 days after each administration. Secondary measures included the Quick Inventory of Depressive Symptomatology–Self Report (QIDS–SR), the Hamilton Anxiety Rating Scale (HAM-A), and the proportion of individuals meeting response or remission criteria. Response was defined as a ≥50% decrease in MADRS score from baseline. Safety and tolerability were assessed using the Brief Psychiatric Rating Scale–Positive Subscale, the Clinician-Administered Dissociative States Scale (CADSS), the mood item of the Young Mania Rating Scale, and the Systematic Assessment for Treatment Emergent Effects instrument. Clinically significant changes were defined in the protocol as systolic or diastolic BP >180/100 mmHg or heart rate >110 beats/min. Management and medication intervention was to be provided per protocol or as deemed necessary by the treating anesthesiologist.

Bioanalytical Methods

Plasma samples were collected at 20 min (end of administration) and 40 min after start of administration. Samples were frozen at −80°C until analysis. Plasma concentrations of ketamine and norketamine (ketamine's primary active metabolite) were determined using gas chromatography/mass spectrometry at NMS Labs (Willow Grove, Pennsylvania) as previously described (27). The lower limit of quantification was 40 ng/mL.

Statistical Analyses

The primary analysis adhered to a modified intent-to-treat principle, including all 18 patients with outcome assessment from both periods. A mixed model approach was employed to test effects of treatment (ketamine vs. placebo), period, and carryover both for differences in MADRS score and for rates of clinical response. Changes over time up to 7 days were also assessed using mixed models. The mixed models approach accounts for the fact that each patient is assessed under both treatments per the crossover design. Secondary analyses of additional endpoints, notably the QIDS–SR and HAM-A, followed the same analytical approach as for the primary endpoint. Treatment effects are quantified as mean difference between groups and associated 95% confidence interval (CI) for continuous outcomes and by odds ratio and associated 95% CI for categorical outcomes.

All statistical tests were two-sided .05 level tests. No adjustment for multiple tests was employed; all *p* values are reported at their nominal level. Patient characteristics and safety and tolerability are summarized using descriptive statistics. All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary North Carolina).

Results

Patient Characteristics

There were 36 individuals who provided signed consent and underwent screening. All eligibility requirements were met by 20 individuals, who were randomly assigned to one of two treatment orders: ketamine-placebo or placebo-ketamine. Two subjects withdrew consent after randomization and did not

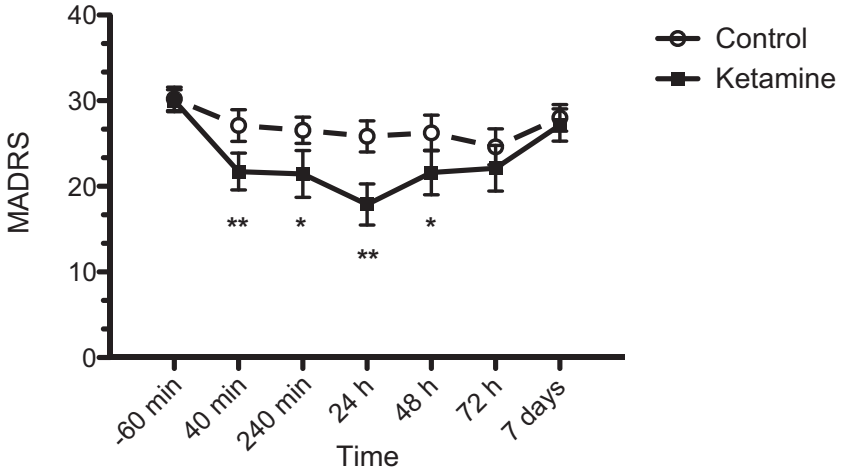

Figure 1. Change in depression severity in patients with treatment-resistant depression after intranasal administration of ketamine or placebo. Change in Montgomery-Åsberg Depression Rating Scale (MADRS) depression severity 24 hours after administration was the primary outcome measure and was significantly greater after intranasal ketamine than placebo in the modified intention-to-treat group ($n = 18$; $p < .001$). Range is 0–60 with higher scores indicating greater severity of depressive symptoms. *$p < .05$, **$p < .01$.

complete both treatment periods (one after ketamine administration and one after placebo). There were 18 patients who completed both treatment periods and constituted the modified intention to treat sample (Figure S1 in Supplement 1).

Demographic and clinical characteristics of study participants are summarized in Table 1. Participants had failed on average 4.1 ± 3.9 adequate antidepressant treatment trials and had been experiencing symptoms of depression for an average of 27 years. A history of treatment with electroconvulsive therapy was present in 20% of the sample. Patients who met inclusion criteria and were on a stable dose of antidepressant medication were allowed to continue their concomitant treatment (Table S1 in Supplement 1). No patients had previously been exposed to ketamine as per protocol.

Table 1. Characteristics of Study Sample

Characteristic	Value
Participants Treated, *n* (%)	20 (100)
Gender (Male/Female)	10/10
Age at Enrollment (Years)	48.0 ± 12.8
Race (%)	
Caucasian	18/20 (90)
Asian	1/20 (5)
Black	0/20 (0)
Other	1/20 (5)
Hispanic (%)	3/20 (15)
Married (%)	6/20 (30)
Employed (%)	10/20 (50)
Age of Onset (Years)	21.4 ± 12.0
Illness Duration (Years)	27.4 ± 13.7
Chronic (%)	9/20 (45)
Recurrent (%)	17/20 (85)
Length of Current Episode (Years)	15.2 ± 17.4
Failed Antidepressant Medications[a]	4.1 ± 3.9
History of ECT (%)	4/20 (20)
History of Psychotherapy[a] (%)	17/19 (89)
History of Suicide Attempts (%)	2/20 (10)
Past Substance Use Disorder (%)	3/20 (15)
Current Anxiety Disorder (%)	4/20 (20)
Melancholic (%)	9/20 (45)
Atypical (%)	2/20 (10)
Baseline IDS-C (Screen)	42.7 ± 8.5

ECT, electroconvulsive therapy; IDS-C, Inventory of Depressive Symptoms–Clinician Rated.
[a]$n = 19$.

Efficacy

Depressive symptoms 24 hours after treatment were significantly improved in the patients receiving ketamine compared with patients receiving placebo ($t = 4.39$, $p < .001$). The estimated mean difference in MADRS score between ketamine and placebo groups was 7.6 ± 3.7 (95% CI, 3.9–11.3) (Figure 1). There was no evident residual effect of treatment. Treatment with ketamine was associated with a greater likelihood of response at 24 hours compared with placebo ($p = .033$). Response criteria were met by 8 of 18 subjects (44%) at 24 hours after ketamine administration compared with 1 of 18 (6%) after placebo (number needed to treat = 2.6) (Figure 2). Based on a repeated measures mixed linear models analysis, subjects receiving ketamine exhibited greater improvement compared with subjects receiving placebo over the full 7-day follow-up period [$F_{1,18} = 28.10$, $p < .001$]. A significant time effect was also noted [$F_{5,95} = 10.65$, $p < .001$]. In

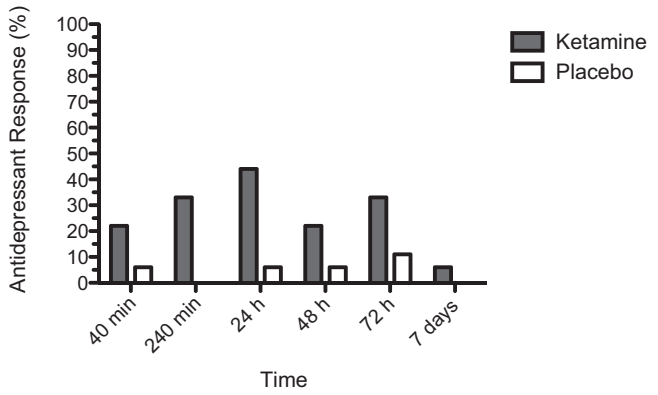

Figure 2. Response rates in the study sample after intranasal ketamine or placebo. Response was defined as a decrease from baseline of at least 50% on Montgomery-Åsberg Depression Rating Scale. Modified intention-to-treat group ($n = 18$).

Table 2. Acute Dissociative, Psychotomimetic, and Hemodynamic Effects of Intranasal Ketamine and Placebo in Treatment-Resistant Depression

	Ketamine			Placebo		
	Baseline	+40 Min	+240 Min	Baseline	+40 Min	+240 Min
Behavioral Changes						
BPRS+	4.0 ± 0	4.3 ± .7	4.1 ± .5	4.0 ± 0	4.0 ± 0	4.0 ± 0
CADSS	.8 ± 1.6	2.2 ± 3.7	.6 ± 1.9	.8 ± 2.3	1.2 ± 3.3	.3 ± 1.2
Hemodynamic Changes						
Systolic BP (mm Hg)	122.8 ± 11.1	130.4 ± 12.8	117 ± 14.1	117.2 ± 12.2	117.2 ± 12.7	116.5 ± 14.6
Diastolic BP (mm Hg)	68.5 ± 9.4	76.8 ± 10.1	67.5 ± 10.4	72.1 ± 10.6	71.2 ± 12.2	68.7 ± 9.1
Heart Rate (bpm)	72.4 ± 10.4	73.9 ± 8.9	72.7 ± 11.2	69.8 ± 6.7	69.6 ± 6.3	72.4 ± 7.6

Changes in acute behavioral and hemodynamic measures at +40 min and +240 min after a single intranasal administration of ketamine or placebo (saline) in the context of a randomized controlled trial.

BP, blood pressure; BPRS+, Brief Psychiatric Rating Scale–Positive Subscale (scale range 4–28; higher values indicate increased psychotic-like symptoms); CADSS, Clinician-Administered Dissociative States Scale (scale range 0–92; higher values indicate increased dissociative symptoms).

addition to the primary 24-hour outcome, response to ketamine was significantly different from response to placebo at 40 min ($p < .001$), 240 min ($p = .026$), and 48 hours ($p = .048$). There was no significant separation at 72 hours or 7 days.

Ketamine was associated with significant improvement on self-reports of depression as measured by the QIDS-SR at 24 hours ($t_{17} = 3.30$, $p = .004$; mean difference of 3.0 ± 2.4; 95% CI, 1.1–4.9). Ketamine was superior to placebo in improving anxiety symptoms at 24 hours as measured by HAM-A scores ($t_{17} = 3.06$, $p = .007$; mean benefit of 4.5 ± 3.2; 95% CI, 1.4–7.6).

Acute Psychotomimetic and Dissociative Effects

Intranasal ketamine was associated with small increases on measures of psychosis and dissociation (Table 2). No relationship between ketamine-associated changes in dissociative or psychotomimetic symptoms and antidepressant response was found ($p < .05$ for CADSS and Brief Psychiatric Rating Scale). Among subjects who responded to ketamine, the increase in CADSS score at +40 min was 1.75 ± 4.17 compared with 1.09 ± 1.76 in subjects who did not respond to ketamine.

Hemodynamic Effects

Intranasal ketamine was associated with small increases in systolic BP (mean increase of 7.6 mm Hg at +40 min compared with baseline) (Table 2). Four participants experienced treatment-emergent increases in systolic BP >130 mm Hg after ketamine, and three participants experienced systolic BP >130 mm Hg after placebo. No patients had diastolic BP >100 mm Hg. There were no clinically significant elevations in BP or heart rate that required intervention, and all hemodynamic changes resolved by 4 hours after infusion. No association was found between hemodynamic changes and antidepressant response to ketamine (all $p < .05$).

General Adverse Events

The most common treatment emergent adverse effects in the ketamine group for 4 hours after infusion were feeling strange or unreal, poor memory, and weakness or fatigue (Table 3). Most of these symptoms resolved within 4 hours of administration. No serious adverse events occurred during the study.

Blood Levels

After ketamine administration, plasma levels of ketamine were detectable (≥40 ng/mL) in 14 individuals at 20 min and in 17 individuals at 40 min. Norketamine was not detected at 20 min and was detected in 8 individuals at 40 min. Mean ketamine plasma level was 72 ng/mL at 20 min and 84 ng/mL at 40 min. Mean norketamine plasma level was 46 ng/mL at 40 min (Figure S2 in Supplement 1).

Discussion

In the present study, a single dose of 50 mg of ketamine administered via an intranasal route was associated with a rapid antidepressant response in patients with MDD who had failed at least one prior antidepressant trial. A significant antidepressant effect of ketamine was detected 40 min after administration, and there was a large difference in depression severity between the treatment conditions at the 24-hour primary outcome (mean difference in MADRS score of 7.6 ± 3.7). In total, there was significant antidepressant benefit after ketamine compared with placebo over the full 7-day assessment period, although when comparing individual time points, the treatment conditions no longer separated at 72 hours or 7 days. Ketamine was associated with significant improvement in anxiety symptoms and self-reports of depressive symptoms at 24 hours. Intranasal ketamine was well tolerated with only very minimal increases in dissociation, psychosis-like symptoms, or hemodynamic parameters. This study provides the first randomized, controlled evidence that intranasal ketamine is safe, well tolerated, and effective for rapid reduction of depressive symptoms in patients with MDD and at least mild treatment resistance.

Compared with prior studies of IV ketamine (.5 mg/kg) in patients with depression, our observed magnitude of antidepressant effect with intranasal administration may be reduced. Murrough *et al.* (15) reported a mean ketamine-placebo difference of 7.95 points (95% CI, 3.20–12.71) on MADRS 24 hours after a single IV infusion and a response rate of 64%. Response rates of 70% after IV administration have been reported in some studies (11,15), although other studies reported response rates from 50% to 30% after IV ketamine (28,29). Our mean drug-placebo difference is in line with what was reported previously (7.6 ± 3.7 points on MADRS), although the proportion of responders in our study may be lower at 44%. This lower proportion of treatment responders may be consistent with the lower blood ketamine levels achieved in our study compared with levels previously reported after IV administration. In our sample, the mean ketamine blood level was 72 ng/mL at 20 min and 84 ng/mL at 40 min. In contrast, mean ketamine levels reported after IV infusion (.5 mg/kg) are approximately 150 ng/mL at 30 min and 200 ng/mL at 40 min (27,30,31). It is unknown if efficacy equivalent to IV administration could be obtained by intranasal administration in the case that comparable blood levels could be achieved.

Table 3. General Adverse Treatment Effects

	Ketamine		Placebo	
	≤240 Min	240 Min–24 Hours	≤240 Min	240 Min–24 Hours
Feeling Strange or Unreal	8 (42)	0 (0)	0 (0)	0 (0)
Poor Memory	7 (37)	0 (0)	1 (5)	1 (5)
Weakness or Fatigue	5 (26)	1 (5)	1 (5)	0 (0)
Delayed or Absent Orgasm	4 (21)	1 (5)	0 (0)	0 (0)
Loss of Sexual Interest	4 (21)	0 (0)	1 (5)	0 (0)
Trouble Concentrating	4 (21)	0 (0)	1 (5)	1 (5)
Problems with Sexual Arousal	3 (16)	1 (5)	2 (11)	1 (5)
Dizziness or Fainting	3 (16)	0 (0)	0 (0)	0 (0)
Dizziness When Standing	3 (16)	0 (0)	1 (5)	1 (5)
Diminished Mental	3 (16)	0 (0)	2 (11)	1 (5)
Feeling Drowsy or Sleepy	3 (16)	0 (0)	3 (16)	1 (5)
Poor Coordination or Unsteadiness	2 (11)	1 (5)	0 (0)	0 (0)
Difficulties Finding Words	2 (11)	1 (5)	2 (11)	0 (0)
Abnormal Sensations	2 (11)	0 (0)	0 (0)	0 (0)
Numbness or Tingling	2 (11)	0 (0)	0 (0)	0 (0)
Strange Taste in Mouth	2 (11)	0 (0)	1 (5)	0 (0)
Nightmares or Other Sleep Disturbance	2 (11)	0 (0)	2 (11)	3 (16)
Blurred Vision	1 (5)	0 (0)	0 (0)	0 (0)
Appetite Decreased	1 (5)	0 (0)	0 (0)	0 (0)
Dry Mouth	1 (5)	0 (0)	0 (0)	1 (0)
Heartbeat Rapid or Pounding	1 (5)	0 (0)	0 (0)	1 (5)
Clenching of Teeth at Night	1 (5)	0 (0)	1 (5)	0 (0)
Stuffy Nose	1 (5)	0 (0)	1 (5)	1 (5)
Overall	1 (5)	0 (0)	1 (5)	3 (16)
Irritable	0 (0)	1 (5)	0 (0)	0 (0)
Headache	0 (0)	1 (5)	0 (0)	1 (5)
Tremor or Shakiness	0 (0)	1 (5)	0 (0)	1 (5)
Constipation	0 (0)	1 (5)	0 (0)	1 (5)
Trouble Sitting Still	0 (0)	1 (5)	1 (5)	0 (0)
Feeling Nervous or Hyper	0 (0)	1 (5)	1 (5)	1 (5)
Frequent Need to Urinate	0 (0)	1 (5)	1 (5)	1 (5)
Apathy/Emotional Indifference	0 (0)	1 (5)	1 (5)	1 (5)
Trouble Sleeping	0 (0)	1 (5)	2 (11)	7 (37)
Muscle Twitching or Movements	0 (0)	0 (0)	1 (5)	0 (0)
Stomach or Abdominal Discomfort	0 (0)	0 (0)	1 (5)	0 (0)
Appetite Increased	0 (0)	0 (0)	1 (5)	0 (0)
Ringing in Ears or Trouble Hearing	0 (0)	0 (0)	1 (5)	1 (5)
Unable to Sit Still	0 (0)	0 (0)	1 (5)	1 (5)

Adverse events reported on Systematic Assessment for Treatment Emergent Effects with intensity of moderate or severe and increased from baseline immediately after treatment and at 24 hours. All values listed are number (%).

We report a significant improvement in anxiety symptoms at 24 hours, as assessed with HAM-A. Two studies of IV ketamine for bipolar depression reported a significant improvement in anxiety symptoms measured with HAM-A and a visual analog scale (27,32). However, previous studies of patients with unipolar TRD did not describe effects of IV ketamine on anxiety, with the exception of an early randomized controlled trial (11) and an open-label study (33) reporting significant improvement in psychic anxiety measured as an individual symptom on the Hamilton Depression Rating Scale and another open-label study reporting significant decrease in anxiety symptoms on HAM-A at +230 min (34).

Previous studies of IV ketamine in patients with depression reported elevations in measures of psychotomimetic, dissociative, and hemodynamic parameters (11,13,15). In our study, the ketamine group experienced a very limited increase in dissociation at +40 min as measured by CADSS (mean, 1.4 points; scale range, 0–92). In comparison, Murrough *et al.* (15) reported a larger dissociative effect 40 min after IV administration of ketamine (mean CADSS score of 14.7 points; 95% CI, 10.6–18.8). A similar pattern was observed for psychotic-like effects measured using the Brief Psychiatric Rating Scale–Positive Subscale (11,15). We also observed comparatively small changes in hemodynamic parameters. No patient met protocol criteria for interventions. Studies of IV ketamine in patients with depression have reported relatively greater changes in hemodynamic parameters (mean systolic BP increase of 19.0 mm Hg vs. 7.6 mm Hg in our study at +40 min relative to baseline) (15). The reduced magnitude of acute behavioral and hemodynamic changes observed in the present study may be consistent with the lower blood levels achieved compared with prior studies with IV administration of ketamine, as discussed earlier.

The bioavailability of ketamine administered via an intranasal route has been reported to be 25%–50% (35). A study in healthy volunteers comparing administration methods found ketamine bioavailability of 45% with intranasal administration, higher than bioavailability with sublingual, oral, or rectal administration, and found no significant differences in pharmacokinetics between preparations, including injection (36). Additionally, this study found conversion to norketamine was more similar between intranasal and injection than the other administration methods, suggesting that first-pass metabolism is relatively absent with intranasal administration. The area under the ketamine and norketamine plasma concentration-time curves in that study was lowest for intranasal administration but was found to increase almost linearly with doses from 25–50 mg (36). In previous studies of IV administration of ketamine in patients with depression, peak norketamine blood levels of approximately 20–50 ng/mL were reported (30,31). In line with these findings, the mean norketamine level in our study was 46 ng/mL at 40 min.

We selected a ketamine dose of 50 mg largely based on a previous study using a similar design and the same dose in patients with a chronic pain disorder (23). Based on an expected bioavailability of intranasal ketamine of 25%–50% (35), our dose may be approximately equivalent to .15–.34 mg/kg administered intravenously. Although this dose is lower than the standard intravenous dose of .5 mg/kg frequently used in studies of ketamine and depression, we reasoned that this dose was appropriate from a safety perspective given that the administration period in the current study is shorter (20 min vs. ≥40 min in IV studies). Much more research is required to determine the optimal dose, duration, frequency, and route of administration of ketamine for depression.

Regarding our study sample, some participants had lower levels of treatment resistance compared with prior studies because we required only a single antidepressant treatment failure in the current episode. Some authors have defined TRD as failure to respond to a single treatment (37), although published studies of IV ketamine have frequently required a minimum of two to three treatment failures (11,15). Despite a wider range, our sample as a whole was highly treatment

resistant with an average of 4.1 ± 3.9 antidepressant failures; this compares with 5.7 ± 3.4 and 5.1 ± 2.0 in previous studies (11,15). Other pertinent clinical characteristics, including duration of illness, length of current depressive episode, and history of electroconvulsive therapy, are not appreciably different compared with prior studies (11,15).

The current study has several limitations. We allowed ongoing treatment with psychotropic medication at stable doses, including antidepressant medications. Our augmentation approach makes it difficult to distinguish an intrinsic effect of ketamine from benefits resulting from the combination of ketamine with other antidepressant agents. However, this augmentation design more likely reflects the potential clinical use of ketamine in treatment-refractory populations should it gain approval for this indication. This approach enabled us to gather preliminary data to address concerns about risks of ketamine administration in patients with depression who are currently taking other psychotropic medications (38). We used a crossover design, which can result in carry-over effects, including subjects whose response to the first treatment prevents them from completing the second treatment. In our study, 2 of 20 patients were unable to complete all study procedures (1 patient in each randomization group). The relatively small sample size is also a limitation. The use of saline as a placebo control in ketamine treatment studies is a limitation because the integrity of the blind may be compromised. The very low levels of treatment-emergent psychotomimetic and dissociative symptoms observed in the current study may have helped to mitigate this limitation. The use of a single dose and a single drug administration in the current study does not address important questions related to optimal dosing and the longer term safety or efficacy of this intervention.

In conclusion, patients with MDD who were treated with intranasal administration ketamine experienced rapid improvement of depressive symptoms and limited adverse effects. To our knowledge, this study represents the first controlled investigation of intranasal administration of an *N*-methyl-D-aspartate antagonist for patients with depression. Although these findings are suggestive of efficacy and of a favorable tolerability profile, much more research is required before the true efficacy and safety of this intervention can be assessed. It is hoped that future studies designed to optimize dosing and identify relapse prevention strategies and biomarkers of treatment response will provide additional needed data to maximize benefit for patients and minimize side effects.

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ClinicalTrials.gov: Intranasal Ketamine in Treatment-Resistant Depression; http://clinicaltrials.gov/ct2/show/NCT01304147; NCT01304147.

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