A Randomized, Double-Blind, Placebo-Controlled Pilot Trial of the Acute Antisuicidal and Antidepressant Effects of Intranasal (*R,S*)-Ketamine in Severe Unipolar and Bipolar Depression With and Without Comorbid Alcohol Use Disorder

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Abstract

Objective: Although individuals with a family history of alcohol use disorder (AUD) have a superior antidepressant response to ketamine, outcomes in patients with current AUD remain unclear. This study sought to investigate whether intranasal (IN) racemic (*R,S*)-ketamine had antisuicidal and antidepressant effects in unipolar and bipolar depression and whether comorbid AUD conferred superior antisuicidal outcomes for patients.

Methods: This was a double-blind, randomized, placebo-controlled trial (May 2018 to January 2022) of single-administration, fixed-dose (50 mg) IN (*R,S*)-ketamine (or saline comparator) in unmedicated inpatients meeting *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, criteria for a current major depressive episode (bipolar or unipolar), with current suicidal ideation (SI) and past attempt. Patients with and without comorbid AUD were enrolled. Change in Scale for Suicide Ideation score was the primary outcome measure, and change in Montgomery–Åsberg Depression Rating Scale score was the secondary outcome measure.

Results: No significant group × time effect was noted for SI ($F = 1.1$, $P = .36$). A statistical trend toward superior improvement in suicidality was observed in participants with comorbid AUD. The group × time interaction was significant for improvements in depression ($F = 3.06$, $P = .03$) and largely unaffected by comorbid AUD or primary mood disorder type. Within the ketamine group, a significant correlation was observed between improvement in depressive symptoms and SI for patients without comorbid AUD ($r = 0.927$, $P = .023$) that was absent in patients with AUD ($r = 0.39$, $P = .44$).

Conclusion: IN ketamine induced rapid antidepressant effects compared to placebo but did not significantly alter SI scores. The treatment was well tolerated. Continued investigation with IN ketamine as a practical alternative to current formulations is warranted.

Trial Registration: ClinicalTrials.gov identifier: NCT03539887.

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Primary mood and alcohol use disorders (AUD) comprise the vast majority of identified psychiatric diagnoses among suicide completers worldwide.[1,2] Glutamatergic dysfunction has been highlighted as a major point of convergence between mood disorders, alcohol dependence, and suicidality, holding significant potential for broadly applicable therapeutic interventions.[3,4] Ketamine may be one such agent. Notably, a family history of AUD is one of the most replicated clinical predictors of positive antidepressant response (and reduced dissociative side effects) to intravenous (IV) ketamine in patients with major

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Clinical Points

- Intranasal racemic (*R,S*)-ketamine rapidly reduced depressive symptoms but not suicidal ideation (SI). Changes in depression did not appear to be impacted by the presence or absence of comorbid alcohol use disorder (AUD). However, a nonsignificant trend was observed for superior antisuicidal responses in patients with comorbid AUD.
- Patients without comorbid AUD experienced highly correlated changes in depression and SI, whereas those with comorbid AUD experienced heterogeneous (uncorrelated) symptomatic trajectories in response to ketamine. This may imply baseline differences in glutamatergic signaling conferred by chronic alcohol use, resulting in variable response for specific symptoms.

depressive disorder (MDD) or bipolar depression (BD).[5–7] Recent positive outcomes have also been demonstrated using adjunctive ketamine to promote abstinence in patients with current AUD.[8–10]

Despite these observations, little direct research has investigated ketamine's antidepressant and antisuicidal effects in patients with current AUD diagnoses. To date, controlled studies using ketamine in patients with mood disorders or suicidal ideation (SI) comorbid with AUD (NCT01551329 and NCT02911597) have not posted results. Given the positive results seen separately in mood disorders and AUD (and a 40%–70% lifetime comorbidity of AUD in MDD/BD),[11,12] further clinical investigation is needed in patients experiencing both diagnoses simultaneously. Most importantly, understanding whether patients with current AUD respond to ketamine similarly to those with a family history of AUD (ie, heightened antidepressant response and blunted dissociative side effects) is particularly relevant given their higher risk of suicide completion.

Another key issue is that the current clinical utility of IV ketamine and intranasal (IN) esketamine is offset by inherent cost and access barriers.[13] This study sought to address these issues by using IN (*R,S*)-ketamine. To our knowledge, only 2 studies using this formulation to treat depression or SI have published results. The first study[14] demonstrated moderately positive antidepressant response to a single 50-mg IN administration of (*R,S*)-ketamine in patients with unipolar treatment-resistant depression. However, 80% of the participants continued taking other antidepressant medications and were essentially treated as outpatients (eg, they were discharged from a research unit several hours posttreatment). Most importantly, participants with BD, those with comorbid alcohol use, and/or those deemed at high risk for suicide were excluded, which arguably limits information regarding patients most in need of rapid antidepressant and antisuicidal intervention in naturalistic settings. The second randomized, controlled study[15] assessed the acute antisuicidal effects of a single 40-mg IN administration of ketamine in 30 participants presenting to the emergency department with active SI. However, participants were enrolled regardless of whether they had a primary psychiatric diagnosis (apart from exclusionary screening), and no prior history of suicide attempt was required. A third study[16] was halted after enrolling only 5 participants due to adverse events (see "Discussion" for details). Collectively, these initial studies suggest that IN ketamine has potential as a safe, practical alternative to other resource-intensive delivery methods, but that significant gaps in knowledge remain. For example, prior designs have yet to rigorously isolate the direct pharmacologic effects of IN (*R,S*)-ketamine therapy in participants, as most have continued additional treatments during the study (some of which have documented synergy with ketamine).[17,18] Furthermore, given the less stringent inclusion criteria in prior studies, it remains unclear whether outcomes translate to higher-acuity cohorts (hospitalized participants with formal mood disorder diagnoses, documented prior suicide attempt, etc).

This double-blind, randomized, placebo-controlled trial sought to assess the antisuicidal and antidepressant efficacy of single-administration IN ketamine in medication-free participants at high risk for suicide during acute inpatient psychiatric hospitalization. Efforts were made to enrich representation for participants with comorbid AUD. Both MDD and BD I and BD II participants were included. Our primary hypothesis was that IN ketamine would exert rapid antisuicidal effects that would be superior in participants with comorbid AUD; these antisuicidal effects would occur independently of IN ketamine's rapid antidepressant effects. A saline placebo was used rather than an active placebo (midazolam) due to the risk of increasing craving for alcohol and because midazolam might otherwise potentially confound other dimensional study outcomes and biomarkers (planned for future publication). Because prior studies observed only minimal dissociative side effects with this IN ketamine dose,[14] the risk of functional unblinding was low.

METHODS

This study (NCT03539887) was a double-blind, randomized, placebo-controlled trial assessing the acute antisuicidal and antidepressant effects of a single dose of 50 mg IN (*R,S*)-ketamine hydrochloride (Pfizer Pharmaceuticals, New York, NY, prepared by Greenpark Compounding Pharmacy, Houston, TX) vs 0.9% saline comparator. This dose was selected because prior studies used a similar dose.[14] A mucosal atomization device provided 5 IN applications of

solution (ie, 100 µL of 0.9% saline ± ketamine), separated by 3 minutes, over a total of 15 minutes. Each of 5 ketamine applications provided 10 mg of the study drug, for a total of 50 mg.

Eligible inpatients were enrolled between May 2018 and January 2022. Participants were males and females between the ages of 21 and 60 years experiencing current SI (Columbia-Suicide Severity Rating Scale [C-SSRS[19]] ≥ 4), had a lifetime history of suicide attempt, met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*), criteria for a current major depressive episode, had a Montgomery–Åsberg Depression Rating Scale (MADRS)[20] score ≥12, were medication-free, and were not taken off any maintenance medications for the purposes of enrollment.

Participants were allocated via simple random assignment in a 2:1 ratio to receive 50 mg of IN (*R,S*)-ketamine hydrochloride (two-thirds) or saline solution (one-third). Randomization was performed independent of diagnosis or other subject-level factors. Outcome measures were assessed at baseline and at 240 minutes, 24 hours, and 48 hours posttreatment. The Scale for Suicide Ideation (SSI)[21] and MADRS were used as primary and secondary outcome measures, respectively.

Participants with primary diagnoses of MDD or BD I/II as well as those with and without comorbid AUD were included in the study. Because this was an exploratory study with limited prior data from representative populations, enrollment was planned for 40 participants with approximately 50% representation from participants with AUD (defined using *DSM-IV-TR* criteria for current alcohol abuse without active intoxication/withdrawal [assessed via clinical assessment]) who had abstained from drinking for >5 days prior to admission (assessed via self-report). Lack of other substance use was confirmed by a negative urine toxicology screen. Due to recruitment limitations associated with the COVID-19 pandemic, the final cohort comprised 28 participants.

Patients with unstable medical conditions or significantly abnormal laboratory tests were excluded, as were pregnant or nursing women. Psychiatric exclusion criteria included any lifetime diagnosis of a *DSM-IV-TR* psychotic spectrum disorder, psychotic symptoms, personality disorder, or history of *DSM-IV* drug dependency or abuse (except for alcohol, caffeine, or nicotine dependence) within the preceding 3 months.

To monitor for treatment-related adverse events, patients were assessed by an independent evaluator (separate from the primary clinical rater) at 40 minutes post-ketamine. Inventories from this timepoint were not included in the final outcome analysis. Treatment-emergent mania and dissociation were assessed via the Young Mania Rating Scale (YMRS)[22] and the Clinician-Administered Dissociative States Scale (CADSS),[23] respectively. Significant hemodynamic changes (characterized as systolic or diastolic blood pressure >180/100 mm Hg or heart rate >110 beats per minute [bpm]) were also monitored as potential side effects.

All investigators, patients, and raters were blinded to group assignment. Treatments were prepared in identical vials by independent pharmacy staff using the same saline vehicle. Vials were labeled numerically by pharmacy staff following random sequence generation to conceal allocation from investigators and participants. The study was approved by the Institutional Review Board of The University of Texas Health Sciences Center (Houston, TX). All enrolled patients were admitted voluntarily as inpatients and provided written, informed consent regarding potential side effects, risks, and benefits of the treatment prior to study participation.

Statistical Analysis

Baseline characteristics between treatment groups were assessed using Student *t* tests and Fisher exact tests for continuous and categorical variables, respectively. The normality of continuous variables was verified by the Shapiro-Wilk test. Variables with nonparametric distribution were assessed using the Mann-Whitney U test (see Table 1). Changes in severity of depressive symptoms and SI over the study period and their association with variables potentially related to ketamine response (ie, age, sex, diagnosis, body mass index [BMI], illness duration, and episode duration) were analyzed using mixed-model regression fit by restricted maximum likelihood estimation. For each outcome measure, treatment group, timepoints, and group × time interaction were included as fixed effects with intercepts clustered by participants as random effects. Given the a priori hypothesis that the presence of comorbid AUD would differentially impact response to ketamine, separate models were constructed that added AUD and its group interaction as fixed effects.

Additionally, as part of an exploratory analysis, multivariate analysis of covariance (MANCOVA) was performed to assess co-occurring changes in dependent variables (MADRS and SSI) over the entire study period. Multivariate normality and equality of variance were confirmed by the Shapiro-Wilk and Levene tests, respectively. Absence of multicollinearity was determined by standard correlation ($r < 0.9$).[24] Treatment group, AUD, and their interaction were included as factors, and baseline MADRS and SSI scores were included as covariates. Based on these results, a partial correlation was assessed (again controlling for baseline symptom severity) between change in SI and depression in active treatment recipients with and without comorbid AUD. Statistical significance was set at $P < .05$ (2-tailed), and all statistical analyses were carried out using SPSS

Table 1.
Baseline Demographic Variables and Inventories

Factor	Placebo (N = 11)	Ketamine (N = 17)	Statistic
Self-identified sex			
Male	9 (82%)	12 (71%)	$P = .668$
Female	2 (18%)	5 (29%)	
Primary diagnosis			
MDD	6 (55%)	13 (76%)	$P = .409$
BD I/II	5 (45%)	4 (24%)	
Comorbid AUD	9 (82%)	8 (47%)	$P = .115$
Mean BMI, kg/m^2	29.5 ± 7.51	30.8 ± 7.09	$t = -0.431$ ($P = .670$)
Mean age, y	38.5 ± 13.8	39.0 ± 9.0	$U = 81$ ($P = .571$)
Mean prior medication trials	4.6 ± 4.3	3.0 ± 2.1	$t = 1.19$ ($P = .245$)
Self-identified race			
Caucasian	8 (73%)	11 (65%)	$P = .442$
African American	3 (27%)	3 (18%)	
Hispanic	0 (0%)	3 (18%)	
Education			
Did not graduate high school	4 (36%)	3 (18%)	$P = .137$
High school graduate or general equivalency	4 (36%)	2 (12%)	
Some undergraduate education	1 (9%)	8 (47%)	
Bachelor's or graduate degree	2 (18%)	4 (24%)	
Approximate illness duration, y			
≤1	0 (0%)	2 (12%)	$P = .297$
1–5	1 (9%)	3 (18%)	
5–10	1 (9%)	6 (35%)	
10–20	2 (18%)	2 (12%)	
≥20	6 (55%)	4 (24%)	
Baseline outcome measures			
Mean SSI (primary)	23.9 ± 5.22	21.8 ± 4.76	$t = 1.12$ ($P = .275$)
Mean MADRS (secondary)	36.9 ± 6.47	35.9 ± 6.98	$t = 0.369$ ($P = .715$)

Abbreviations: AUD = alcohol use disorder, BD = bipolar disorder, BMI = body mass index, MADRS = Montgomery–Åsberg Depression Rating Scale, MDD = major depressive disorder, SSI = Scale for Suicide Ideation.

software, version 26.0.0.0 (SPSS Inc, Chicago, IL), and Jamovi (version 2.3.2).

RESULTS

Four hundred twenty-eight participants were prescreened, and 29 were randomized to receive either ketamine or placebo (Figure 1). The final study sample comprised 28 patients; 1 participant did not receive allocated ketamine due to the available drug surpassing its expiration date. All participants who received either ketamine or placebo after randomization were included in the final analysis based on the intention-to-treat principle.

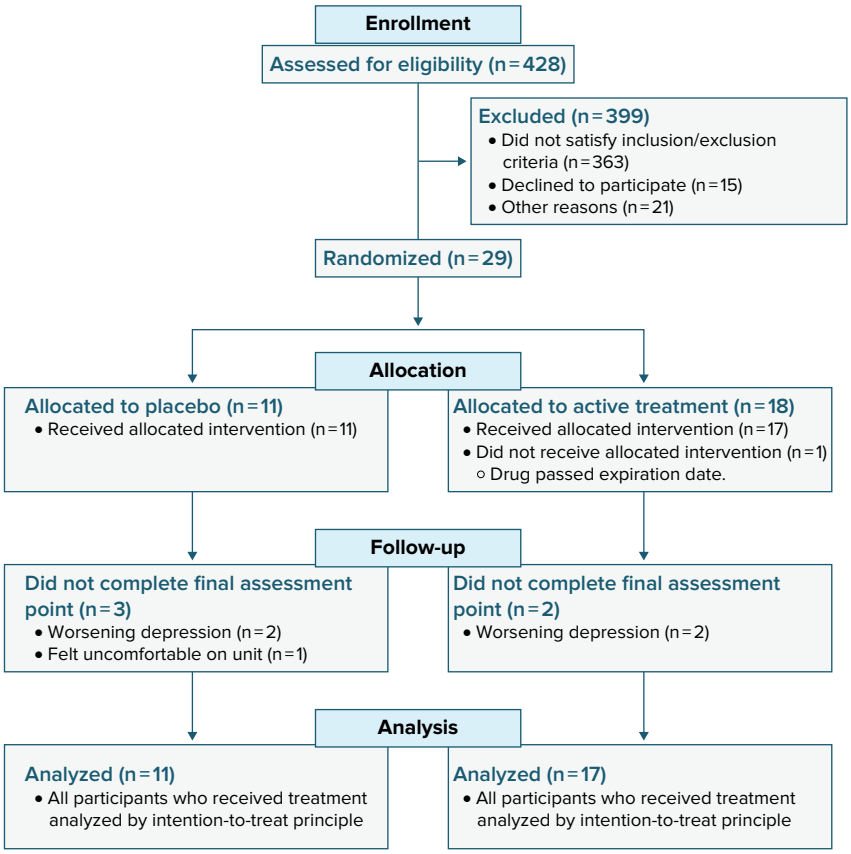
Baseline demographic variables are shown in Table 1. On average, study participants were severely depressed (mean MADRS score 36.3 ± 6.68) and had received 3–4 medications before taking part in this study. Baseline variables did not significantly differ between treatment and placebo groups.

In addition to their equal group distributions, covariates including primary mood diagnosis, age, sex, BMI, illness duration, and episode duration did not approach significance in preliminary models and were thus excluded from final constructs.

Overall, the group × time interaction for the primary outcome (SSI) was not significant (Figure 2A) ($F = 1.1$, $P = .362$). A nonsignificant trend was observed in the AUD × group interaction in the mixed model ($F = 1.99$, $P = .17$), and a significant AUD × group interaction was observed with the MANCOVA ($P = .009$, discussed below). Separate plots were included (Figure 2B–C) to communicate a trend toward enhanced antisuicidal response in patients with comorbid AUD.

With respect to depression improvement, both the group ($F = 5.81$, $P = .023$) and the group × time interaction ($F = 3.07$, $P = .033$) were statistically significant for the MADRS, favoring IN ketamine intervention. These results remained significant (and largely unchanged) with the inclusion of AUD and its group interaction ($F = 3.06$, $P = .033$) (Figure 3). Inventory subanalysis using the same model parameters for the single MADRS item 10 [regarding suicidal thoughts (MADRS-SI)] likewise yielded a significant

Figure 1.
CONSORT Diagram[25] Depicting Enrollment, Follow-up, and Final Analysis[a]



[a]All participants who received either ketamine or placebo (saline) were included in the final analysis by intention-to-treat principle.
Abbreviation: CONSORT = Consolidated Standards of Reporting Trials.

group × time interaction favoring IN ketamine ($F = 4.97$, $P = .003$).

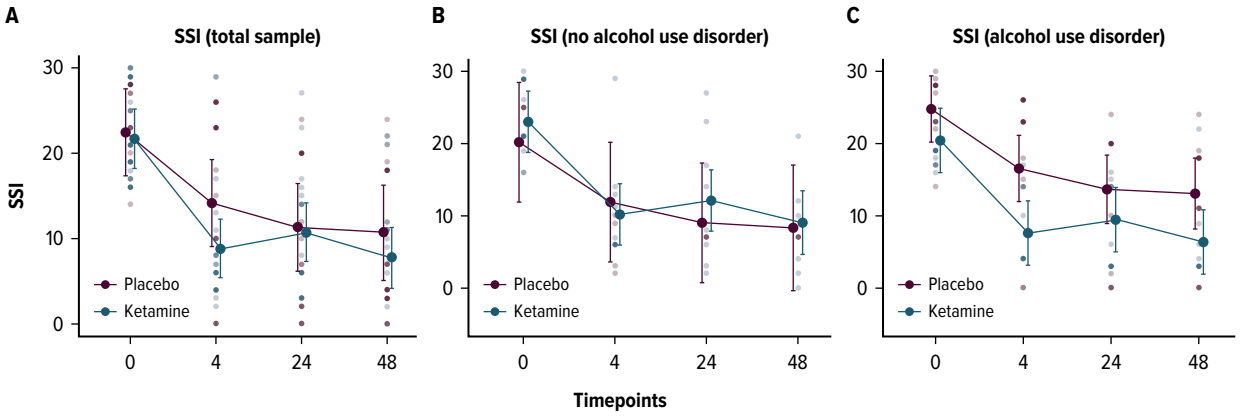
Significant individual patient variability was observed within outcome trajectories for both the SSI ($\partial = 20.6 \pm 4.54$, intraclass correlation coefficient [ICC] = 0.408) and the MADRS ($\partial = 68.6 \pm 8.28$, ICC = 0.479). Given the high degree of variability in response between the 2 outcome measures, an exploratory analysis was conducted to assess the correlation between primary and secondary outcomes over the entire study period. Using a multivariate structure (MANCOVA) allowed us to account for baseline severity of depression and SI while assessing both outcome variables (MADRS/SSI) simultaneously over the course of the study. All multivariate tests were significant for both treatment group ($F = 4.049$, $P = .038$) and treatment group × AUD interaction ($F = 6.467$, $P = .009$). As a preliminary test, this implies a significant difference in overall response to ketamine compared to placebo. The group × AUD interaction also implies a significant difference in combined antidepressant/antisuicidal response to ketamine based on the presence or absence of comorbid AUD.

To further elucidate the results of the MANCOVA, a partial correlation was conducted, again controlling for baseline severity of depression and SI in individual ketamine treatment recipients. There was a significant, strong correlation between change in SSI and MADRS scores over the duration of the study, but only among ketamine recipients without comorbid AUD (N = 9, $r = 0.927$, $P = .023$). For ketamine recipients with comorbid AUD, improvements in depression and suicide were not significantly correlated (N = 8, $r = 0.390$, $P = .44$).

IN ketamine treatment was generally well tolerated with no serious adverse events. Reported side effects were mild to moderate and most commonly included headache (ketamine:placebo = 4:1), dizziness (3:0), sluggishness/poor concentration (2:5), and a brief and

Figure 2.

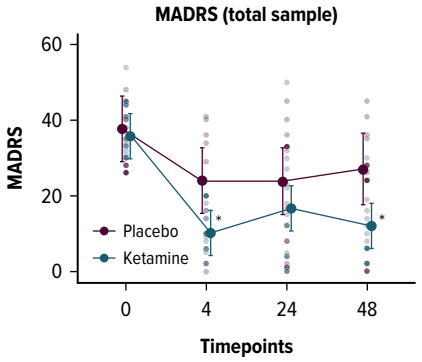
SSI Mixed-Model Regression Plot Separating Ketamine and Placebo for the Total Sample (A), Participants Without Comorbid AUD (B), and Only Participants with Comorbid AUD (C)[a]



[a]Timepoints correspond to baseline (0) and to 4 h, 24 h, and 48 h postinfusion. Error bars represent 95% confidence interval. Neither group ($P = .36$) nor group × time interaction ($P = .362$) was significant.
Abbreviations: AUD = alcohol use disorder, SSI = Scale for Suicide Ideation.

Figure 3.

MADRS Mixed-Model Regression Effects Plot Separating Ketamine and Placebo for Total Sample[a]



[a]Asterisks (*) indicate statistically significant fixed-effects parameter estimates for the group × time interaction at individual timepoints. Overall group × interaction was also statistically significant ($P = .033$). Error presented as 95% CI.
Abbreviation: MADRS = Montgomery–Åsberg Depression Rating Scale.

mild episode of hypertension (1:0). Minimal dissociative effects were observed across the study sample. Mean change in CADSS scores from baseline to 40 minutes after administration was −0.06 ± 6.70 for the ketamine group vs −1.00 ± 2.10 for the placebo group (Student *t* test = −0.449, $P = .657$). CADSS scores remained below this level in both groups for the remainder of the study. Likewise, no treatment-emergent mania was observed (total YMRS ≤ 10 for every patient at every timepoint). As with the other covariates mentioned above, change in CADSS score following ketamine treatment did not predict treatment response in any symptom domain (data not shown).

DISCUSSION

In this study, a 50 mg dose of IN (*R*,*S*)-ketamine rapidly improved depressive symptoms. No significant improvement was observed in the primary outcome measure (SSI) compared to placebo, despite a trend for superior response in the comorbid AUD group (Figure 2C). However, a significant response (group × time interaction) was observed for the single item MADRS-SI, which some studies have found to be a more sensitive metric to rapid post-ketamine changes in suicidal symptoms.[26] While this finding should not be interpreted as confirmation of our a priori hypothesis, it does highlight some of the inherent limitations of conventional psychometric instruments.

The present findings mirror those seen in Phase 3 IN esketamine trials for SI. In all 3 studies,[24–27] rapid improvements in depressive symptoms were observed without a significant impact on SI severity.[27–30] Conversely, single doses of IV (*R*,*S*)-ketamine have consistently reduced SI 4 hours (pooled $d = 1.16$) and 24 hours ($d = 0.95$) post-ketamine across trials.[31,32] Beyond the route of delivery, unique enantiomeric properties may contribute to this divergent antisuicidal response. For example, IV (*R*)-ketamine shows higher central nervous system uptake in vivo,[33] and IV (*S*)-ketamine is metabolized and eliminated more rapidly.[34,35] Such differences may be magnified by the

approximate 50% attenuation in bioavailability with IN (vs IV) (*R,S*)-ketamine administration.[36,37]

Among patients treated with ketamine in the present trial, those without comorbid AUD experienced more global, highly correlated improvements in both depressive symptoms and SI over the entire study. Conversely, patients with comorbid AUD experienced more variable, uncorrelated symptomatic trajectories. Though exploratory in nature, these findings suggest the possibility that baseline differences in glutamatergic function—whether incurred by genetic susceptibility, chronic alcohol overuse, or other means—may impart differential symptomatic responses to ketamine.

Several strengths of this study are noteworthy. As indicated by 2 recent meta-analyses,[38,39] the intensity of SI and prior suicidal behavior both appear to carry independent risk vis-à-vis completed suicide.[36,37] Thus, the stringent eligibility cutoffs used here (C-SSRS score ≥4 and a prior suicide attempt) capture a higher-risk stratum than previously assessed with IN ketamine. Likewise, the inclusion of both MDD and BD participants experiencing severe depression bolsters real-world applicability. Our study also prioritized risk assessment by using a separate, blinded rater to assess posttreatment adverse events. Consistent with prior IN ketamine (and esketamine) studies, we observed minimal emergence of dissociative side effects and only 1 episode of significant hypertension (transient). This may reflect less functional unblinding than seen with many IV ketamine studies (especially those that use inactive placebo), but the minimal dissociative and cardiovascular effects associated with IN ketamine may also reflect lower effective dosing.[40] For comparison, a pooled analysis of 3 studies (n = 84, 205 total IV ketamine infusions) found that approximately 30% of participants met the criteria for clinically significant hypertension used in this study (>180/100 mm Hg or heart rate >110 bpm). Furthermore, the plasma ketamine concentrations observed in the study by Lapidus and colleagues[14] (which also used a single 50 mg IN dose) were approximately half of those achieved in many 0.5 mg/kg IV trials (84 ng/mL at 40 minutes vs 100–200 ng/mL).[41,42] Conversely, an IN ketamine study that used a self-administered 100 mg fixed dose was suspended after enrolling 5 patients because of significant cardiovascular, psychotomimetic, and neurological side effects—in concert with much higher plasma ketamine levels (108–201 ng/mL).[16] Taken together, this suggests that variability in effective dosing may have contributed to some of the individual response heterogeneity in our sample. Given the limited available evidence with IN ketamine, the conservative 50 mg dose used here was selected to prioritize patient safety while still providing a reasonable opportunity to observe beneficial effects. Future studies may benefit from increased (or adjusted) dosing strategies.

Limitations of this study include the short duration, small sample size, and demographic homogeneity, necessitating further replication in larger samples. Given trends seen in the primary outcome, it is likely that our study was underpowered to detect a significant difference in antisuicidal response between participants with and without comorbid AUD. Though not statistically significant, there was also a large difference in the number of patients with comorbid AUD between groups (47% in the ketamine arm vs 82% in the placebo arm). This may also have contributed to a lack of separation in the primary outcome. Also, blood levels for ketamine (and its metabolites) were not collected, although an analysis with other suicide-related biomarkers is planned. Treatment resistance was also not formally assessed, though patients in the trial on average had failed to respond to several treatment regimens prior to study enrollment. The quantity of alcohol use was not assessed, precluding any dose-response analysis. However, prior research has raised questions regarding the reliability of self-reported past drinking behavior in similar populations.[43] Other alcohol-related metrics have been collected from this cohort and are planned for a forthcoming publication. Lastly, given the biological half-life of alcohol across various analytes (12–24 hours), it would not be possible to confirm abstinence for a full 5-day window. However, lack of alcohol consumption by self-report aligned with close clinical observation, which showed a complete lack of withdrawal/intoxication for at least 24 hours before drug administration (and throughout the study period) across the entire population.

In conclusion, IN ketamine induced rapid antidepressant (but not antisuicidal) effects in participants with severe depression at high risk for suicide. IN ketamine's antidepressant effects occurred independently of mood disorder diagnosis or comorbid AUD. Coimprovements in SI were not observed, though a trend toward enhanced reductions in SI in AUD participants was detected. In the ketamine group, those without comorbid AUD demonstrated highly correlated symptomatic improvement in depression and SI, whereas individual trajectories in AUD participants were more variable. Overall, the treatment was well tolerated with minimal adverse effects, suggesting its potential as an alternative rapid-acting antidepressant, particularly in lower-resource settings. Future correlative studies designed to assess underlying transdiagnostic constructs are warranted to fully elucidate therapeutic response to IN ketamine.

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