Rapid and Sustained Reductions in Current Suicidal Ideation Following Repeated Doses of Intravenous Ketamine:

Secondary Analysis of an Open-Label Study

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ABSTRACT

Background: Ketamine rapidly reduces thoughts of suicide in patients with treatment-resistant depression who are at low risk for suicide. However, the extent to which ketamine reduces thoughts of suicide in depressed patients with *current* suicidal ideation remains unknown.

Methods: Between April 2012 and October 2013, 14 outpatients with *DSM-IV*–diagnosed major depressive disorder were recruited for the presence of current, stable (≥ 3 months) suicidal thoughts. They received open-label ketamine infusions over 3 weeks (0.5 mg/kg over 45 minutes for the first 3 infusions; 0.75 mg/kg over 45 minutes for the last 3). In this secondary analysis, the primary outcome measures of suicidal ideation (Columbia-Suicide Severity Rating Scale [C-SSRS] and the Suicide Item of the 28-item Hamilton Depression Rating Scale [$HDRS_{28}$-SI]) were assessed at 240 minutes postinfusion and for 3 months thereafter in a naturalistic follow-up.

Results: Over the course of the infusions (acute treatment phase), 7 of 14 patients (50%) showed remission of suicidal ideation on the C-SSRS Ideation scale (even among patients whose depression did not remit). There was a significant linear decrease in this score over time ($P < .001$), which approached significance even after controlling for severity of 6-item Hamilton Depression Rating Scale ($HDRS_6$) core depression items ($P = .05$). Similarly, there were significant decreases in the C-SSRS Intensity ($P < .01$) and $HDRS_{28}$-SI ($P < .001$) scores during the acute treatment phase. Two of the 7 patients who achieved remission during the acute treatment phase (29%) maintained their remission throughout a 3-month naturalistic follow-up.

Conclusions: In this preliminary study, repeated doses of open-label ketamine rapidly and robustly decreased suicidal ideation in pharmacologically treated outpatients with treatment-resistant depression with stable suicidal thoughts; this decrease was maintained for at least 3 months following the final ketamine infusion in 2 patients.

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Someone dies by suicide nearly every 40 seconds.[1] Thoughts of suicide increase the risk for an eventual suicide attempt[2]; interventions that prevent and treat suicidal ideation are a public health priority.[3] In patients with depression, the lifetime risk for a suicide attempt is approximately 20 times that of the general population,[4,5] even among those who receive adequate treatment.[6,7]

Several interventions, such as lithium,[8,9] clozapine (which is approved by the US Food and Drug Administration for the prevention of suicide),[10] electroconvulsive therapy,[11] and cognitive behavioral therapy,[12] have antisuicidal properties and were recently reviewed.[13] These treatments can take weeks to months to take effect and have unpleasant side effects/monitoring schedules and/or limited availability (due to a lack of adequately trained professionals and facilities for administration).[11] There is certainly a need for effective antisuicidal treatments that are rapidly acting, empirically validated, and easily implemented.

Intravenous infusions of subanesthetic ketamine doses (typically, 0.5 mg/kg over 40 minutes) rapidly and robustly reduced suicidal ideation in patients with treatment-resistant unipolar[14–17] and bipolar[18] depression. Ketamine also outperformed the active comparator midazolam in significantly decreasing both explicit (measured by rating scales) and implicit (measured by the Implicit Association Test [IAT]) cognitions linked to suicidal behaviors in unmedicated patients with treatment-resistant depression.[19] However, these studies[14–19] did not recruit patients specifically for their endorsement of suicidal thoughts. In contrast, a few small studies and case reports[20–22] *have* examined the effects of ketamine on patients with a significant risk for suicide. Although these small reports are promising, many questions remain about the utility and stability of ketamine for suicidal thoughts.

In sum, the use of subanesthetic ketamine rapidly decreases measures of suicidal ideation in patients with treatment-resistant depression.[14–17,19,23] However, several critical unknowns remain: (1) the efficacy of ketamine's antisuicidal properties (in addition to ongoing antidepressant pharmacotherapy) in outpatients with treatment-resistant depression recruited for the endorsement of current thoughts of suicide and (2) the extent to which repeated/escalated doses of ketamine affect implicit (as measured by the IAT) and explicit (as measured by rating scales) measures

Clinical Points

- Rapidly acting, sustained treatment options for patients with treatment-resistant depression and suicidal thoughts are currently limited.
- Ketamine is an emerging treatment for suicidal ideation.

of suicidal ideation in this group. This secondary data analysis explores these unknowns in an outpatient sample of medicated patients with treatment-resistant depression and current thoughts of suicide.

METHODS

Previously, our methods were described in detail in Cusin et al.[24] The following sections provide a summary.

Participants

This study was approved by the Partners Human Research Committee, in accordance with the ethical principles of the Declaration of Helsinki, and is registered at ClinicalTrials.gov (NCT01582945). Between April 2012 and October 2013, patients aged 18–65 years were screened at Massachusetts General Hospital after providing written informed consent. All patients met *DSM-IV* criteria for a primary diagnosis of moderate-to-severe major depressive disorder (MDD; as diagnosed by the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders [SCID-II])[25] plus a score of ≥ 20 on the 28-item Hamilton Depression Rating Scale ($HDRS_{28}$).[26,27] Treatment-resistant depression was defined as ≥ 3 failed antidepressant trials of adequate dose and duration during the current depressive episode (assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire[28]). All patients were on a stable antidepressant treatment regimen for ≥ 4 weeks prior to enrollment; if dose changes were required during infusions, the participant was disenrolled. All patients endorsed current suicidal ideation (for ≥ 3 months) at screening or baseline on the Columbia-Suicide Severity Rating Scale (C-SSRS)[29] and per the $HDRS_{28}$ Suicide Item ($HDRS_{28}$-SI; a score of ≥ 2 indicating passive death wish and/or current suicidal ideation). No severity cutoff score for suicidal ideation was required on the C-SSRS for inclusion; rather, the presence of *any* suicidal ideation endorsement (based on binary "yes/no" responses) was adequate.

Study Design and Treatment

In the pretreatment phase, patients were screened by a trained study doctor. After the initial screening visit, patients were seen in the clinic twice more within the next month before entering the acute treatment phase of active ketamine infusions. The purpose of the first 3 visits was to (1) verify that patients met inclusion criteria for the study and (2) verify that patients remained on a stable antidepressant medication regimen prior to receiving the ketamine infusions (≥ 28 days). The third visit (ie, the last visit before the active phase) was considered as the baseline.

In the acute treatment phase, patients received 2 ketamine infusions per week for 3 weeks. Specifically, a single infusion of intravenous ketamine (0.5 mg/kg) was administered over 45 minutes for the first 3 infusions; the dose was increased to 0.75 mg/kg for the last 3 infusions. After the acute treatment phase, patients entered the follow-up (naturalistic) phase. Patients were assessed once every 2 weeks for 3 months, for a total of 6 additional visits. Changes in pharmacotherapy and psychotherapy were allowed in the follow-up phase.

Throughout the entire study—pretreatment, acute treatment, and follow-up phases—patients were evaluated a total of 15 times.

Outcome Measures

The primary *explicit* outcome measures for suicidal ideation were scores of the $HDRS_{28}$-SI and C-SSRS Ideation and Intensity, which were administered at all visits. C-SSRS Ideation refers to the presence of suicidal thoughts, as rated on a 5-point ordinal scale: 1 = wish to be dead, 2 = nonspecific active suicidal thoughts, 3 = suicidal thoughts with methods, 4 = suicidal intent, and 5 = suicidal intent with plan. C-SSRS Intensity refers to the intensity of suicidal ideation, as rated on a 5-point ordinal scale for 5 separate items: frequency, duration, controllability, deterrents, and reason for ideation. Suicidal ideation remission was defined as C-SSRS Ideation = 0.

The *implicit* measure of suicidal ideation was obtained via the IAT. The IAT is a brief computer-based task that measures the patient's reaction times to automatic mental associations about various topics.[30] The Death/Suicide IAT (IAT-D) is a specific version of the IAT that has been described in detail elsewhere.[31] IAT-D scores, which were used in the analyses, were calculated as follows: ([mean reaction time during Death = Me block] – [mean reaction time during Life = Me block]/[standard deviation of reaction time across all trials]).

In the acute treatment phase, all implicit and explicit suicide measures were administered at the end of each study visit, at approximately 240 minutes postinfusion. The Clinician-Administered Dissociative States Scale (CADSS)[32] was administered at baseline (preinfusion), as well as at 60 and 120 minutes following the end of the infusion to assess dissociative side effects. Side effects and vital signs were monitored before, during, and for 120 minutes after each infusion.

Statistical Analysis

Demographic variables were compared using frequencies and χ^2 for categorical variables and *t* tests for continuous variables.

For the analysis of the suicide measures, the intent-to-treat (ITT) model was utilized for all analyses to include all patients. A mixed-effect model with repeated measures (MMRM) approach was used to model the effects of treatment for all efficacy analyses, adjusting for

baseline severity. Random coefficient models were also used. Baseline severity was defined as the last visit of the pretreatment phase, prior to the first infusion of the acute treatment phase. Efficacy analyses of changes in suicidal thoughts were measured with the C-SSRS Ideation, C-SSRS Intensity, $HDRS_{28}$-SI, and IAT-D scores. Because of the difference in time frames between the acute treatment and follow-up phases (ie, 6 visits over 3 weeks in the acute treatment phase vs 6 visits over 12 weeks in the follow-up phase), separate analyses were run for each phase.

Additional statistics were done to covary for 6-item Hamilton Depression Rating Scale ($HDRS_6$) symptoms (ie, depressed mood, work and interests, general somatic symptoms, psychic anxiety, guilt feelings, and psychomotor retardation), as these "core" symptoms are sensitive to antidepressant activity[33] (ie, the rapid change expected with ketamine); acute treatment phase findings were additionally covaried for the CADSS (because dissociation has been suggested to mediate ketamine's antidepressant response),[34] as well as for changes in sleep and anxiety (as measured by the HDRS sleep items and HDRS Anxiety/Somatization Factor Score,[35] respectively). All tests were conducted with a significance level of $P < .05$ (2-sided),* using STATA SE Version 12 statistical software (StataCorp LP, College Station, Texas).

RESULTS

Demographics

Fourteen patients were enrolled into the acute treatment phase. Twelve of 14 patients (85.7%) completed all 6 infusions. One patient discontinued after the second infusion because of intolerable side effects (ie, unpleasant feelings and mild dissociative symptoms during the infusions), and the other patient discontinued after the fourth infusion due to scheduling conflicts. Other clinical and demographic information is outlined in Table 1. For a full discussion of antidepressant findings, see Cusin et al.[24] Briefly, the ITT response and remission rates at the end of the final infusion were 35.7% (5/14 patients) and 14.3% (2/14 patients), respectively; all but 1 responder relapsed within 2 weeks of the final infusion.[24]

Explicit Measures of Suicide (Acute Treatment Phase)

Results for measures of explicit suicidal ideation in the acute treatment phase are presented in Table 2. There was a significant decrease in C-SSRS Ideation scores over time in the MMRM (coefficient = −0.27; $P < .001$; Figure 1A), suggesting that the C-SSRS Ideation score decreased by an average of −0.27 per patient after each infusion. Furthermore, this decrease approached significance after controlling for the $HDRS_6$ core depression items (coefficient = −0.12; $P = .050$), suggesting that −0.12 of the −0.27 decrease in C-SSRS Ideation scores observed was *independent* of acute decreases in core depression symptoms. For changes in the C-SSRS Ideation scores, there was no significant effect of dose ($P = .58$) or dissociation

Table 1. Demographic and Illness Characteristics of 14 Outpatients With Major Depressive Disorder

Variable	n	%	
Gender, female	11	78.6	
Education, completed college	12	85.7	
Marital status, never married	6	42.9	
History of failed ECT	6	42.9	
Significant suicidal ideation (baseline)	14	100	
Past suicide attempts	2	14.3	
	Mean	SD	Range
Age, y	50.0	7.8	38 to 62
Age at onset, y	16.9	8.4	7 to 36
Length of current depressive episode, mo	21.0	4.2	18 to 24
No. of lifetime depressive episodes	4.0	2.8	2 to 6
No. of failed antidepressant trials	8.6	5.3	3 to 19
Average ketamine dose (infusion 1–3) in mg/kg	29.0	16.2	25.0 to 56.0
Average ketamine dose (infusion 4–6) in mg/kg	43.5	24.3	37.4 to 84.0
Mean C-SSRS Ideation score (baseline)	2.3	1.3	1 to 4
Mean C-SSRS Intensity score (baseline)	12.1	3.8	5 to 17
Mean $HDRS_{28}$-SI score (baseline)	2.1	0.62	1 to 3[a]
Mean IAT-D score (baseline)	−0.65	0.35	−0.17 to −1.2

[a]For inclusion, all patients must have had an $HDRS_{28}$-SI score ≥ 2 at screening and/or baseline.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, ECT = electroconvulsive therapy, $HDRS_{28}$-SI = 28-item Hamilton Depression Rating Scale-Suicide Item, IAT-D = Death/Suicide Implicit Association Test, SD = standard deviation.

Table 2. MMRM Analyses Predicting Key Outcome Measures From the Number of Ketamine Infusions During the Acute Treatment Phase

Outcome Measure of Suicide	Coefficient[a]	SE	*Z*	*P*	95% CI
C-SSRS Ideation	−0.27	0.05	−5.03	<.001[b]	−0.38 to −0.17
C-SSRS Ideation (controlled for $HDRS_6$ change)	−0.12	0.06	−1.96	.05	−0.23 to −0.00
C-SSRS Intensity	−1.10	0.40	−2.73	<.01[b]	−1.89 to −0.31
C-SSRS Intensity (controlled for $HDRS_6$ change)	−0.27	0.38	−0.72	.47	−1.01 to 0.47
$HDRS_{28}$-SI	−0.22	0.06	−4.06	<.001[b]	−0.33 to −0.12
$HDRS_{28}$-SI (controlled for $HDRS_6$ change)	−0.07	0.06	−1.17	.24	−0.18 to 0.05
IAT-D[c]	+0.05	0.03	2.20	.03[c]	0.01 to 0.09
IAT-D (controlled for $HDRS_6$ change)	−0.01	0.02	−0.70	.49	−0.05 to 0.02

[a]The coefficient represents the change in the outcome measure for each additional infusion (eg, −0.27 indicates score dropped 0.27 points for each additional infusion). Although changes of −0.27 may seem small, this is actually a clinically significant change on the C-SSRS Ideation measure, which is measured on a scale of 0–5.

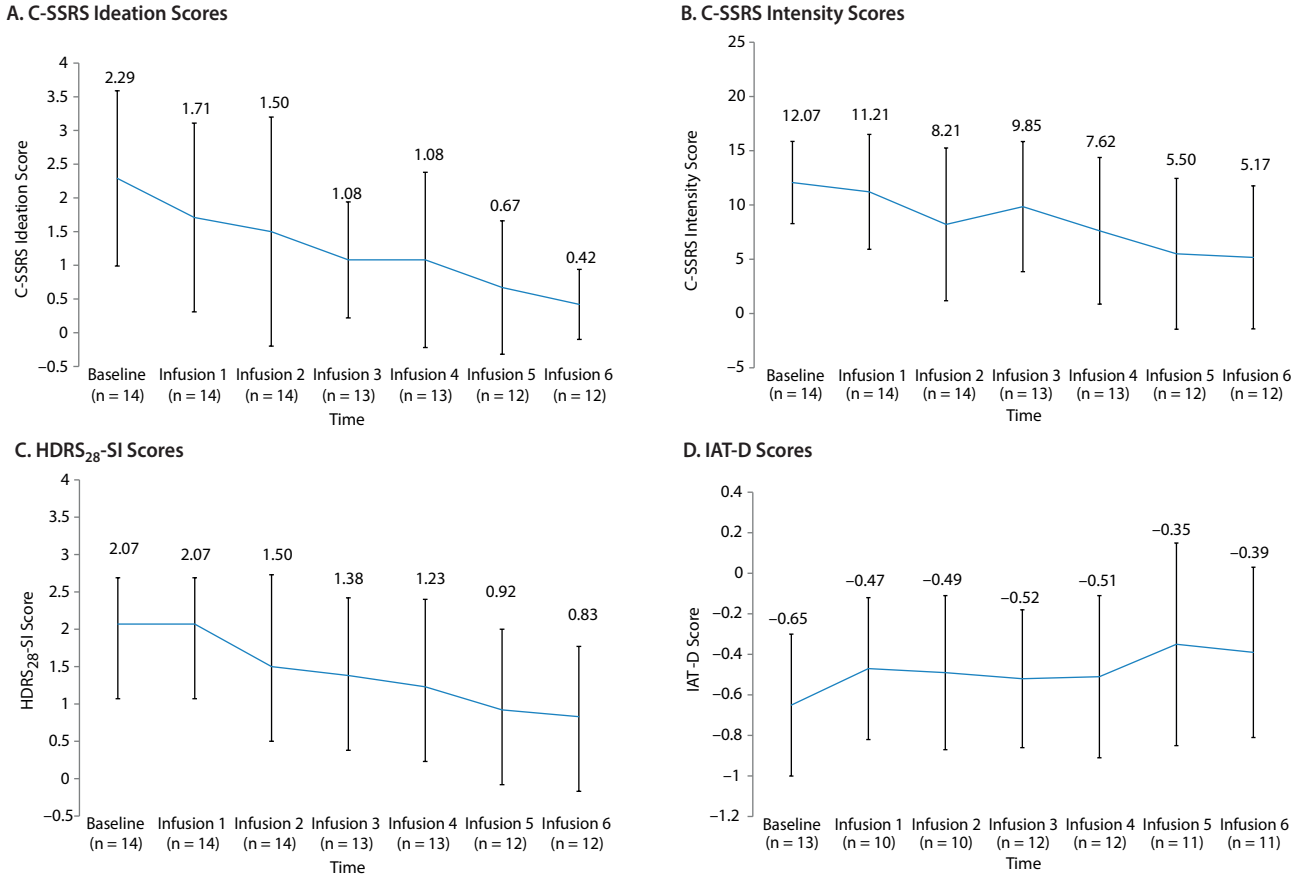
[b]Significance at $P < .05$.

[c]For the IAT-D score, +0.05 indicates that the score increased 0.05 points for each additional infusion. This increase in scores during the infusions indicated increased implicit thinking about dying (vs living).

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, $HDRS_6$ = 6-item Hamilton Depression Rating Scale, $HDRS_{28}$-SI = 28-item Hamilton Depression Rating Scale Suicide Item, IAT-D = Death/Suicide Implicit Association Test, MMRM = mixed-effect model with repeated measures.

*We did not adjust *P* levels for multiple comparisons because with a sample size of N = 14, our statistical power would have been reduced below 25% for a large effect size if tested at $P < .01$.

Figure 1. Mean Change in Scores During the Acute Treatment Phase



Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale, $HDRS_{28}$-SI = 28-item Hamilton Depression Rating Scale-Suicide Item, IAT-D = Death/Suicide Implicit Association Test.

($P = .28$) over and above infusion number. Similar to the C-SSRS Ideation scores, there was a significant decrease in the C-SSRS Intensity scores over time in the MMRM (coefficient = −1.10; $P < .01$; Figure 1B). This decrease was no longer significant after including the $HDRS_6$ core depression items ($P = .47$), indicating that decreases in $HDRS_6$ core depression items mediated the decrease in C-SSRS Intensity. For changes in the C-SSRS Intensity scores, there was no significant effect of dose ($P = .67$) or dissociation ($P = .42$) over and above infusion number.

Prior to the infusions, 10 patients had an $HDRS_{28}$-SI = 2, and 4 had an $HDRS_{28}$-SI = 3 at screening and/or baseline. There was a significant decrease in $HDRS_{28}$-SI scores over time in the MMRM (coefficient = −0.22; $P < .001$; Figure 1C). This decrease was no longer significant when controlling for change in $HDRS_6$ core depression items ($P = .24$), indicating that decreases in $HDRS_6$ core depression items mediated $HDRS_{28}$-SI decreases. For decreases in $HDRS_{28}$-SI, there was no significant effect of dose ($P = .63$). However, there was a significant effect of dissociation, over and above infusion number (coefficient = +0.14; $P = .02$), suggesting that $HDRS_{28}$-SI scores increased (worsened) as dissociation increased.

Implicit Measure of Suicide (Acute Treatment Phase)

In the acute treatment phase, there was a significant change in IAT-D scores over time in the MMRM (coefficient = +0.05; $P = .03$; Figure 1D), indicating that IAT-D scores increased by 0.05 at each infusion (suggesting patients were responding *faster* to words associated with "death" and "me"). This increase was no longer significant after controlling for $HDRS_6$ depression items ($P = .49$). There was no significant effect of dose ($P = .96$) or dissociation ($P = .15$) over and above infusion number.

Sleep and anxiety, as measured by HDRS subscales, had no significant effects on any measures in the acute treatment or follow-up phases.

Follow-Up Phase

There were too few patients in the follow-up phase (n = 11) to permit meaningful inferential statistics. Therefore, descriptive statistics are presented (Tables 3 and 4), following the recommendations of the C-SSRS Scoring and Data Analysis Guide, Version 2.0 (February 2013). Of the 7 patients (50%) who achieved C-SSRS suicidal ideation remission (ie, C-SSRS Ideation = 0) at the end of the acute

Table 3. Shift-Table to Demonstrate Changes in C-SSRS Suicidal Ideation Scale From Baseline During Acute Phase[a]

C-SSRS Ideation Score at Baseline	C-SSRS Ideation Score at Endpoint During Acute Phase (N = 14)						
	0	1	2	3	4	5	Total
1	4	2	0	0	0	0	6
2	0	1	0	0	0	0	1
3	2	3	0	0	0	0	5
4	1	0	0	0	0	0	1
5	0	0	0	0	0	1	1

[a]These analysis methods are recommended for this scale by the Columbia research group.
Abbreviation: C-SSRS = Columbia-Suicide Severity Rating Scale.

Table 4. Shift-Table to Demonstrate Changes in C-SSRS Suicidal Ideation Scale From End of Acute Phase Through the Follow-Up Phase[a]

C-SSRS Ideation Score at Beginning of Follow-Up Phase	Maximum C-SSRS Ideation Score During Follow-Up (n = 11)						
	0	1	2	3	4	5	Total
0	2	1	0	1	2	0	6
1	0	1	1	3	0	0	5

[a]These analysis methods are recommended for this scale by the Columbia research group.
Abbreviation: C-SSRS = Columbia-Suicide Severity Rating Scale.

treatment phase, 2 patients (29%) maintained remission at the end of the follow-up period; both also achieved depression remission ($HDRS_{28} < 7$) at the end of the acute treatment phase. The data suggest that decreases in suicidal ideation during the acute phase were maintained for some patients during the follow-up phase.

Finally, of the 7 total patients with remission of suicidal ideation at the end of the acute phase, only 2 had also achieved depression remission at the same time point.

DISCUSSION

In this study, we found that repeated doses of ketamine rapidly decreased explicit measures of suicidal ideation in medicated outpatients with treatment-resistant depression and current suicidal thoughts, independent of escalating doses. Seven patients (50%) met criteria for suicidal ideation remission at the end of the infusions, as opposed to only 2 patients (29%) who met criteria for depression remission at the same time point. Furthermore, remission of suicidal ideation was maintained for at least 3 additional months in 2 patients. Finally, implicit measures of suicidal ideation increased throughout the infusions.

Regarding suicidal ideation, C-SSRS Ideation scores decreased by −0.27 points after each infusion. Since the baseline C-SSRS Ideation score was 2.3 (for reference, 2 = nonspecific active suicidal thoughts), this would predict an average final score (after 6 infusions) of 0.7 (for reference, 1 = death wish; the actual average final score was 0.4). Given (1) the length (≥ 3 months) of participants' ongoing suicidal ideation and (2) the lack of currently available antisuicidal agents, this steady decrease in suicidal ideation within 3 weeks is noteworthy. C-SSRS Intensity scores also decreased throughout the infusions, which is in line with the decrease in C-SSRS Ideation scores, because intensity scores are not measured in the absence of ideation. Furthermore, this decrease in intensity of suicidal ideation is important, since patients who do not meet criteria for suicidal ideation *remission* may still experience a clinically important *improvement* in suicidal ideation.

Changes in suicidal ideation on the C-SSRS Ideation score, when controlled for $HDRS_6$ scores, approached significance. Furthermore, 50% of patients met criteria for suicidal ideation remission, compared to only 29% meeting criteria for depression remission. These findings suggest that decreases in suicidal ideation may be somewhat independent from ketamine's antidepressant effects and are in line with a previous post hoc analysis that showed that decreases in suicidal ideation were related to, but not completely dependent on, decreases in depression and anxiety in patients with treatment-resistant depression (although patients in that study were specifically excluded for suicidal ideation).[36] Additionally, although dissociation may mediate ketamine's antidepressant response,[34] increased dissociation in our sample led to increases on the $HDRS_{28}$-SI—suggesting different mechanisms for ketamine's antidepressant and antisuicidal properties. Perhaps the antisuicidal effects are enacted at the level of reward circuitry, whereas the antidepressant effects are mediated by actions at the prefrontal cortex. Although depression is a risk factor for suicidal ideation, distinct neurobiological signatures may explain differences between depression and suicidal thinking.

Ketamine's antisuicidal effect may have advantages over currently available treatments. Unlike electroconvulsive therapy, repeated subanesthetic doses of ketamine are not associated with memory impairments.[37] Although 1 small (N = 23) 8-week study[38] demonstrated the rapid (within 2 weeks) antisuicidal effects of risperidone augmentation over placebo, no follow-up phase was completed in this sample, and the long-term side effects of antipsychotic use (eg, metabolic syndrome) are of significant concern. Furthermore, in our study, ketamine's initial antisuicidal effects occurred within 4 hours of infusion and persisted for up to 3 months in 2 patients after the infusions. Despite ketamine's short half-life (approximately 2.5 hours), its antisuicidal (and antidepressant) effects are sustained well beyond the elimination of the drug, in some patients.

In contrast to explicit measures, scores on the implicit measure *increased* with ketamine. Previous studies[16,19] that found decreases in implicit suicidal ideation after ketamine excluded patients with suicidal risk. Only 6 of 12 patients (50%) of Price and colleagues'[16] IAT subsample endorsed "significant" Montgomery-Asberg Depression Rating Scale-Suicide Item (MADRS-SI) scores ≥ 4, with 5 of 6 patients endorsing MADRS-SI = 4 (indicating "probably better off dead" and/or nonspecific suicidal thoughts). In their second study,[19] the mean baseline MADRS-SI was only 1.61 (note, 0 = "Enjoys life," 2 = "Weary of life, only fleeting suicidal thoughts"). The authors concluded that the clinical utility of

the IAT as an index of suicidality is "mixed," as "Death = Me" associations were unrelated to suicidal ideations at baseline. In contrast, 71% of our sample (n = 10) had $HDRS_{28}$-SI = 2 prior to ketamine, indicating *at least* passive death wishes. Suicidal thinking in our other 4 patients was even more serious; therefore, 100% of our sample endorsed clinically significant suicidal thoughts. Given the increase in IAT scores in our sample, we, too, question the utility of implicit suicide measures in this population. Also of note, fewer patients completed the IAT at each visit compared to the explicit measures; many patients expressed frustration and dislike of the implicit task. Nonetheless, because of our small sample size (with limited power to detect small to moderate changes), we must emphasize the need for larger future studies to test the reliability of IAT scores following ketamine.

One of the main strengths of this study is that we studied ketamine's antisuicidal effects in patients recruited *specifically* for the presence of suicidal ideation—a reason for exclusion in previous well-characterized ketamine studies.[14,15,19] Furthermore, 7 of 14 patients (50%) were taking concomitant benzodiazepines, which may actually attenuate ketamine's antidepressant effects,[39] thereby making our preliminary significant findings of potential interest.

Several limitations should be considered. First, this was an open-label trial of repeated-dose ketamine, with no placebo group. Therefore, we cannot assess the extent to which multiple, escalating doses have an antisuicidal advantage over a single dose. Second, patients remained on antidepressant medications; changes were allowed in the naturalistic follow-up phase. Therefore, we cannot rule out the possibility that improvements in suicidal ideation were due to augmenting effects of ketamine, rather than ketamine alone. Third, given our small sample size, larger studies are needed in a broader sample of suicidal patients (eg, suicidal patients in the emergency room or inpatient unit). Fourth, there were no preinfusion suicide or mood ratings on the mornings of the infusions. Therefore, our ratings at 240 minutes postketamine could reflect immediate changes from the most recent infusions, instead of changes between infusions.

In conclusion, ketamine provides promise for the rapid treatment of suicidal ideation in medicated outpatients with treatment-resistant depression and suicidal thoughts. Larger controlled studies (including more serious/acute patients in the emergency room) are necessary to study ketamine's antisuicidal effects and the relationship between antisuicidal and antidepressant effects.

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Drug names: clozapine (Clozaril, FazaClo, and others), ketamine (Ketalar and others), lithium (Lithobid and others), risperidone (Risperdal and others).

Potential conflicts of interest: **Dr Mischoulon** has received research support from the Bowman Family Foundation, Fisher Wallace, Nordic Naturals, Methylation Sciences, and PharmoRx Therapeutics; has received honoraria for speaking from the Massachusetts General Hospital Psychiatry Academy; and has received royalties from Lippincott Williams & Wilkins for the published book *Natural Medications for Psychiatric Disorders: Considering the Alternatives*. **Dr Alpert** has received research support from Abbott, Alkermes, Lichtwer Pharma GmbH, Lorex, Aspect Medical Systems, Astra-Zeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Eli Lilly, Forest, GlaxoSmithKline, J&J Pharmaceuticals, National Institutes of Health, National Alliance for Research on Schizophrenia & Depression (NARSAD), Novartis, Organon, PamLab, Pfizer, Pharmavite, Roche, Sanofi/Synthelabo, Solvay, and Wyeth-Ayerst; has participated in advisory boards/consulting at Eli Lilly, PamLab, and Pharmavite; has received speakers' honoraria from Eli Lilly, Xian-Janssen, Organon, MGH Academy, Reed Medical Education, Primedia, Nevada Psychiatric Association, American Society of Clinical Psychopharmacology, and the American Psychiatric Association; and has received editorial fees from Belvoir Publishing. **Dr Fava** has received consultant fees from Abbott, Affectis Pharmaceuticals AG, Alkermes, Amarin Pharma, Aspect Medical Systems, AstraZeneca, Auspex, Avanir, AXSOME Therapeutics, Bayer AG, Best Practice Project Management, BioMarin, Biovail, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Cerecor, CNS Response, Compellis, Cypress, DiagnoSearch Life Sciences (P) Ltd, Dinippon Sumitomo Pharma, Dov, Edgemont, Eisai, Eli Lilly, EnVivo, ePharmaSolutions, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, GenOmind, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenis, Janssen, Jazz, Johnson & Johnson Pharmaceutical R & D, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, MSI Methylation Sciences, Naurex, Neuralstem, Neuronetics, NextWave, Novartis AG, Nutrition 21, Orexigen Therapeutics, Organon, Otsuka, Pamlab, Pfizer, PharmaStar, Pharmavite, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa, Puretech Ventures, PsychoGenics, Psylin Neurosciences, RCT Logic (formerly Clinical Trials Solutions), Rexahn, Ridge Diagnostics, Roche, Sanofi-Aventis US, Sepracor, Servier Laboratories, Schering-Plough, Solvay, Somaxon, Somerset, Sunovion, Supernus, Synthelabo, Takeda, Tal Medical, Tetragenex, TransForm, Transcept, and Vanda; has received grant/research support from Abbott, Alkermes, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir, BioResearch, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clintara, Covance, Covidien, Eli Lilly, EnVivo, Euthymics Bioscience, Forest, Ganeden Biotech, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D, Jed Foundation, Johnson & Johnson Pharmaceutical R & D, Lichtwer Pharma GmbH, Lorex, Lundbeck, MedAvante, Methylation Sciences, NARSAD, National Center for Complementary and Alternative Medicine, National Institute of Drug Abuse, National Institute of Mental Health, Neuralstem, Novartis AG, Organon, PamLab, Pfizer, Pharmacia-Upjohn, Pharmaceutical Research Associates, Pharmavite, PharmoRx Therapeutics, Phototherapeutics, Reckitt Benckiser, Roche, RCT Logic (formerly Clinical Trials Solutions), Sanofi-Aventis US, Shire, Solvay, Stanley Medical Research Institute, Synthelabo, and Wyeth-Ayerst; has served on speakers or advisory Boards for Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Avanir, AXSOME Therapeutics, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon, CME Institute/Physicians Postgraduate Press, Eli Lilly, Forest, GlaxoSmithKline, Imedex, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst Laboratories; has equity holdings in Compellis and PsyBrain; holds a patent for Sequential Parallel Comparison Design, which is licensed by MGH to Pharmaceutical Product Development; has a patent application for a combination of ketamine plus scopolamine in major depressive disorder licensed by MGH to Biohaven; holds copyright for the MGH Cognitive & Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs & Symptoms, and SAFER; and has received royalties from Lippincott Williams & Wilkins, Wolters Kluwer, and World Scientific Publishing. **Drs Ionescu**, **Taylor**, **Akeju**, **Baer**, **Nyer**, **Cassano**, **Brown**, **Nock**, and **Cusin** and **Mss Swee** and **Pavone** have no conflicts of interest to disclose.

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