BRIEF REPORT

# Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression

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**Background:** Intravenous ketamine has shown rapid antidepressant effects in early trials, making it a potentially attractive candidate for depressed patients at imminent risk of suicide. The Implicit Association Test (IAT), a performance-based measure of association between concepts, may have utility in suicide assessment.

**Methods:** Twenty-six patients with treatment-resistant depression were assessed using the suicidality item of the Montgomery-Asberg Depression Rating Scale (MADRS-SI) 2 hours before and 24 hours following a single subanesthetic dose of intravenous ketamine. Ten patients also completed IATs assessing implicit suicidal associations at comparable time points. In a second study, nine patients received thrice-weekly ketamine infusions over a 12-day period.

**Results:** Twenty-four hours after a single infusion, MADRS-SI scores were reduced on average by 2.08 points on a 0 to 6 scale ($p < .001$; $d = 1.37$), and 81% of patients received a rating of 0 or 1 postinfusion. Implicit suicidal associations were also reduced following ketamine ($p = .003$; $d = 1.36$), with reductions correlated across implicit and explicit measures. MADRS-SI reductions were sustained for 12 days by repeated-dose ketamine ($p < .001$; $d = 2.42$).

**Conclusions:** These preliminary findings support the premise that ketamine has rapid beneficial effects on suicidal cognition and warrants further study.

**Key Words:** Implicit association test, ketamine, suicide

Current treatment options for severe mood disorders are limited by the slow time course of change in suicidal thoughts. For instance, in major depressive disorder (MDD) patients receiving thrice-weekly electroconvulsive therapy, suicidal thoughts persisted in 62% of patients after 1 week of treatment and 39% after 2 weeks (1). Furthermore, conventional antidepressant treatment may produce slower and less robust response in patients with moderate to high suicide risk than in nonsuicidal patients, a pattern observed by an elderly MDD sample (2).

Treatment of acute suicidality is further constrained by inaccuracies in patients' explicit reports of suicidal thoughts (3,4). The Implicit Association Test (IAT) (5) may be useful as a behavioral measure of suicidal cognition, as the task is reliable (6) and resistant to attempts to intentionally control its outcome (7). Furthermore, when socially taboo cognitions are assessed (e.g., prejudicial attitudes), the IAT is a superior predictor of future behavior relative to explicit measures (8). Variants of the IAT assessing suicide- and self-injury-related cognition have shown promise in discriminating between self-injurious and noninjurious adolescents (9), suicidal and nonsuicidal adolescents (3), and adult suicide attempters and nonattempters presenting to a psychiatric emergency department (10).

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Received Feb 4, 2009; revised Apr 14, 2009; accepted Apr 28, 2009.

Early evidence suggests that a single subanesthetic dose of intravenous (IV) ketamine, a glutamate-modulating agent, acutely reduces depressive symptoms in approximately 70% of MDD patients 24 hours after infusion (11–13). We tested ketamine's impact on suicidal cognition in a sample of adults with treatment-resistant depression (TRD). We hypothesized that ketamine would yield rapid, correlated reductions in explicit and implicit suicidal indices. Furthermore, we expected that rapid initial reductions in explicit suicidality would be sustained through repeated ketamine infusions.

## Methods and Materials

Twenty-six TRD patients were recruited via media advertisement or clinician referral. Treatment resistance was defined as two or more failed, adequate antidepressant trials in the current episode, as determined by the Antidepressant Treatment History Form (14). *Diagnostic and Statistical Manual of Mental Disorders-Text Revision* (DSM-IV-TR) diagnoses of MDD were established by Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-I/P). Eligible participants had moderate to severe depression (Inventory of Depressive Symptomatology score ≥32) (15); were psychotropic medication-free for ≥2 weeks before infusion (4 weeks for fluoxetine); were free of substance abuse/dependence for ≥6 months; denied lifetime use of ketamine and phencyclidine (PCP); had no lifetime history of psychotic disorder, mania, or hypomania; and had no clinically unstable medical or neurological conditions. Patients whom research team psychiatrists deemed unsafe for study participation due to highly active suicidality were excluded.

Patients were admitted to a private hospital room for a 28-hour period for racemic ketamine hydrochloride infusion (.5 mg/kg diluted in saline, administered over 40 minutes by IV pump [12]) and cardiorespiratory monitoring. Patients were assessed for depressive symptoms using the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-administered measure that includes a single suicidality item (Table 1)

0006-3223/09/$36.00
doi:10.1016/j.biopsych.2009.04.029

**Table 1.** Montgomery-Asberg Depression Rating Scale Scoring Guidelines for Item 10: Suicidal Thoughts

| Score | Description |
|---|---|
| 0 | "Enjoys life or takes it as it comes." |
| 1 | (None provided) |
| 2 | "Weary of life. Only fleeting suicidal thoughts." |
| 3 | (None provided) |
| 4 | "Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention." |
| 5 | (None provided) |
| 6 | "Explicit plans for suicide when there is an opportunity. Active preparation for suicide." |

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(16). Ratings were completed 150 minutes before and 24 hours after infusion. Montgomery-Asberg Depression Rating Scale raters held graduate degrees and achieved high interrater reliability both during training and when co-rating a random sample of videotaped study interviews (intraclass correlation coefficients [ICCs] ≥.96). The time frame for postinfusion MADRS was modified to reflect the period since last assessment. Ketamine's antidepressant effects in this sample (not including suicidality analysis) have been reported previously (13).

A subset of patients ($n$ = 12)[1] completed the IAT and the 21-item self-report Beck Scale for Suicidal Ideation (BSI) (17) at baseline. Ten patients repeated these measures 24 hours postinfusion[2] (see Supplement 1 for a flowchart of study events).

A distinct subset of single-dose ketamine responders ($n$ = 10)[3] enrolled in a subsequent study of repeated-dose IV ketamine. Detailed methods, tolerability, and antidepressant effects will be reported separately (M. aan het Rot, unpublished data, February 2009). Following a day 1 infusion identical to that described above, patients were assessed for 24-hour antidepressant response (MADRS ≤50% of baseline score). Responders (9 of 10 participants) then received up to five additional infusions (days 3, 5, 8, 10, and 12) identical to the first, except that patients were assessed and discharged 4 hours postinfusion.

Table 2 presents clinical and demographic characteristics of the three samples. All participants provided informed consent. The Mount Sinai School of Medicine Institutional Review Board approved procedures.

### IAT

Two recently developed variants of the IAT (IAT-Death, assessing the strength of association between words related to "Death" and "Me"; and IAT-Escape, assessing associations between "Escape" and "Me") were selected based on the hypothesis that individuals contemplating suicide would be characterized by greater self-identification with death (relative to life) and escape (relative to stay). Preliminary evidence suggests these associations are stronger in suicide attempters than nonattempters (10). Implicit Association Tests were administered and scored in accordance with recommended procedures (18) and followed a design described in detail in previous self-injury IAT studies (9) (Supplement 2). D-scores for "Escape = Me" and "Death = Me" were calculated for each participant, where D = ([mean reaction time (RT) during Escape = Me (or Death = Me) block] – [mean RT during Stay = Me (or Life = Me) block] ÷ [SD of RT across all trials]).

### Statistical Analysis

A composite suicidality index ($SI_{composite}$) was calculated by summing $z$ scores on the BSI and MADRS suicidality item (MADRS-SI). Change scores for all measures were calculated as 24-hour value – baseline value. Baseline and postketamine scores were compared by paired $t$ tests, with effect sizes calculated as Cohen's $d$ (19), and by repeated-measures analysis of covariance (ANCOVA). Due to violation of Small's test for multivariate normality in several baseline measures, baseline correlations were calculated nonparametrically with Spearman's rho. Correlations for change scores were calculated using Pearson's r. Two-tailed alpha level was set at .05, unadjusted.

## Results

A single infusion of ketamine reduced scores on the MADRS-SI by an average of 2.08 points on a 0 to 6 scale [$t(25)$ = 6.42, $p < .001$; $d$ = 1.37], with 81% of patients achieving a rating of 0 or 1 at 24 hours postinfusion (Figure 1, Table 3). Of the 13 patients with clinically significant suicidal ideation at baseline (MADRS-SI scores ≥4), 8 (62%) received a rating of 0 or 1 at 24 hours postinfusion and 3 (23%) endorsed fleeting suicidal thoughts (ratings of 2 or 3), while 2 (15%) remained at or above a rating of 4. With change scores in nonsuicide-related MADRS items ($MADRS\text{-}total_{nonSI}$) entered as a covariate, repeated-measures ANCOVA of baseline and 24-hour MADRS-SI scores was not significant [$F(1,24)$ = .38, $p$ = .54], suggesting ketamine's antisuicidal effects were mediated by depression reduction.

In the TRD subsample completing baseline IATs ($n$ = 12), stronger Escape = Me implicit associations were associated with greater MADRS-SI scores (rho = .60; $p$ = .04) and marginally with $SI_{composite}$ scores (rho = .57; $p$ = .052) but not with nonsuicide-related depression severity ($MADRS\text{-}total_{nonSI}$: rho = .24; $p$ = .46). Baseline Death = Me associations were unrelated to other measures ($p$s > .34). In patients who repeated the measures 24 hours postinfusion ($n$ = 10), there was a reduction in Escape = Me associations [$t(9)$ = 3.76; $p$ = .006; $d$ = 1.37] (Figure 2) and in BSI [$t(9)$ = 3.15; $p$ = .012] and MADRS-SI [$t(9)$ = 5.24; $p < .001$]. Death = Me associations were not significantly changed [$t(9)$ =.658; $p$ = .52]. Escape = Me reductions were correlated with reductions in BSI ($r$ = .65; $p$ = .042), $SI_{composite}$ ($r$ = .64; $p$ = .048), and MADRS-SI at the trend level ($r$ = .57; $p$ = .09) but not with nonsuicide-related depression ($MADRS\text{-}total_{nonSI}$) changes ($r$ = −.03; $p$ = .94). Death = Me changes showed a trend-level association with BSI changes only ($r$ = .60; $p$ = .06). Most zero-order correlations were maintained or increased after controlling for change in $MADRS\text{-}total_{nonSI}$ and baseline $SI_{composite}$ (Table 4).

In patients who subsequently enrolled in the repeated-dose ketamine study ($n$ = 10), the first infusion again significantly reduced MADRS-SI scores [2.8-point mean decrease; $t(9)$ = 5.47, $p < .001$; $d$ = 2.17], with 90% of patients receiving a 24-hour rating of 0 (Figure 1, Table 3). Acute reductions were maintained throughout the 12-day treatment period by the nine patients receiving repeated infusions [baseline to day 12 mean decrease = 2.89; $t(8)$ = 5.12, $p$ = .001; $d$ = 2.42], with no patient scoring >2 at any postbaseline assessment (completed before and after each infusion).

## Discussion

These preliminary findings support the premise that a single subanesthetic dose of IV ketamine has rapid effects on suicidal

[1]Implicit Association Test and BSI data were collected from patients enrolled during the latter half of the enrollment period only.

[2]Time constraints prevented postinfusion data collection in two patients.

[3]Three participants in the repeated-dose study were also participants in the IAT subsample.

**Table 2.** Baseline Descriptive and Clinical Characteristics of Full Sample Treated with Single Infusion Intravenous Ketamine, Subsample Who Subsequently Completed the Repeated Infusions Study, and IAT Subsample Who Completed Additional Implicit and Explicit Measures of Suicidality at Baseline

| | Single Infusion Sample ($n$ = 26) | IAT Subsample ($n$ = 12) | Repeated Infusions Subsample ($n$ = 10) |
|---|---|---|---|
| Age, Mean (SD), Years | 48.2 (11.8) | 50.1 (10.3) | 51.4 (14.6) |
| Female, Number (%) | 10 (39%) | 5 (42%) | 5 (50%) |
| Non-Hispanic Caucasian, Number (%) | 18 (69%) | 8 (67%) | 7 (70%) |
| IQ, Mean (SD) | 115.0 (10.3) | 118.7 (10.2) | 115.7 (11.8) |
| Median Household Annual Income | $15,000–24,999 | $10,000–14,999 | $15,000–24,999 |
| Time Since Illness Onset, Mean (SD), Years | 29.3 (13.3) | 29.7 (10.5) | 29.6 (13.0) |
| Age of Onset, Mean (SD), Year | 18.5 (12.2) | 20.4 (11.2) | 20.9 (15.4) |
| Number of Episodes, Mean (SD) | 1.9 (1.7) | 2.3 (2.1) | 2.1 (1.7) |
| Duration of Current Episode ≥ 2 Years, Number (%) | 26 (100%) | 12 (100%) | 10 (100%) |
| Number of Failed Antidepressant Trials in Current Episode, Mean (SD) | 6.0 (4.1) | 6.8 (3.9) | 7.1 (4.2) |
| History of Suicide Attempts, Number (%) | 5 (19%) | 3 (25%) | 1 (10%) |
| Clinically Significant Suicidal Ideation (MADRS-SI Score ≥ 4), Number (%) | 13 (50%) | 6 (50%) | 6 (60%) |
| MADRS-SI = 4 | 10 (38.5%) | 5 (41.7%) | 5 (50%) |
| MADRS-SI = 5 | 3 (11.5%) | 1 (8.3%) | 1 (10%) |
| MADRS-SI = 6 | 0 | 0 | 0 |

IAT, Implicit Association Test (5); IQ, intelligence quotient; MADRS-SI, Montgomery-Asberg Depression Rating Scale Suicidality Item (16).

cognition in TRD and that acute improvements in suicidality can be sustained through repeated ketamine infusions. Confidence intervals for MADRS-SI suggested moderate to very large effects, despite small sample sizes.

An IAT assessing the association between Me and Escape was related to explicit suicidal ideation at baseline and showed sensitivity to therapeutic change, an important criterion if the IAT is to have utility as a clinical assessment tool. Associations

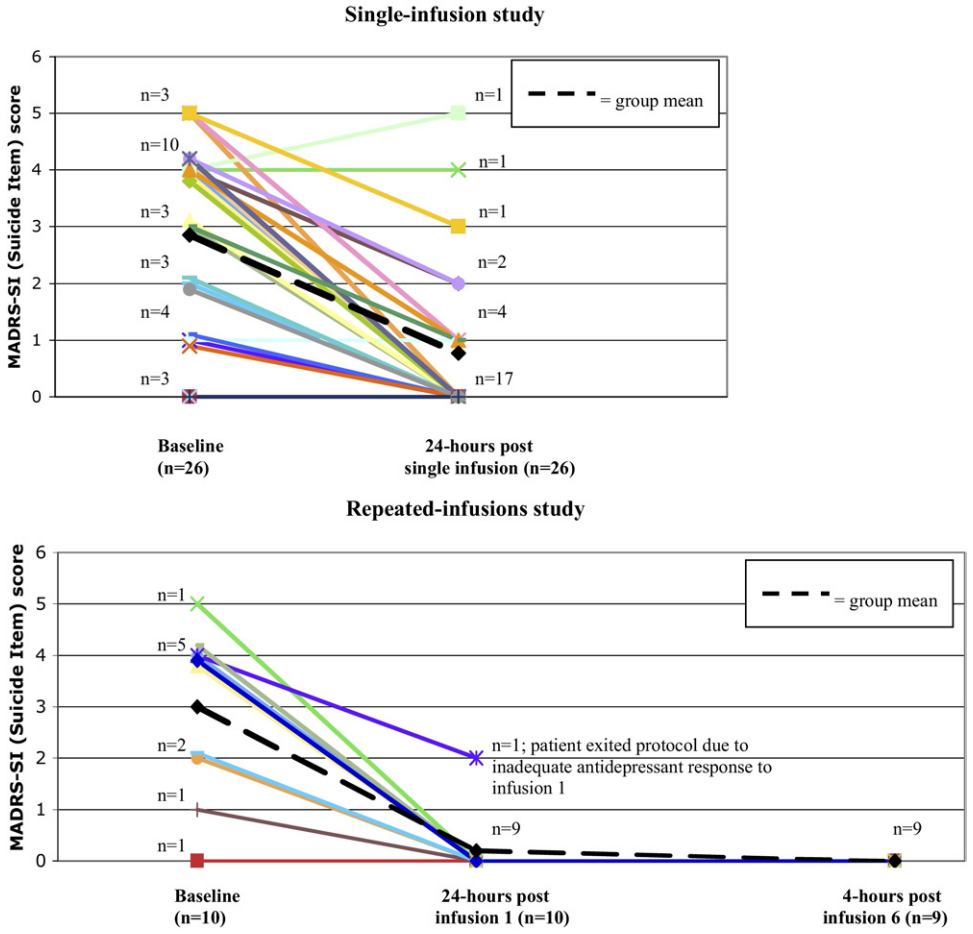


**Figure 1.** Individual patient scores on the Montgomery-Asberg Rating Scale-Suicide Item at baseline (day 1, 150 minutes before infusion), 24 hours following a single subanesthetic infusion of ketamine (day 2), and 4 hours following the final repeated infusion (day 12 of study; Panel 2 only).

**Table 3.** Ketamine Effects on Explicit and Implicit Suicidality

| Measure | Single Infusion Study ($n = 26$) Mean (SD) | Effect Size: Cohen's *d* (95% CI) | IAT Subsample ($n = 10$) Mean (SD) | Effect Size: Cohen's *d* (95% CI) | Repeated Infusions Study ($n = 10$) Mean (SD) | Effect Size: Cohen's *d* (95% CI) |
|---|---|---|---|---|---|---|
| MADRS Total | | | | | | |
| Baseline | 36.92 (5.41) | | 37.80 (5.8) | | 32.70 (6.43) | |
| Postinfusion 1 | 14.85 (13.14)[a] | $d = 2.11$ (1.25–2.97) | 9.40 (8.9)[a] | $d = 3.79$ (1.21–6.37) | 8.10 (4.63)[a] | $d = 4.43$ (.89–7.97) |
| Postinfusion 6 | — | — | — | — | 5.11 (3.66)[a,d] | $d = 5.98$ (1.52–10.44) |
| MADRS-SI | | | | | | |
| Baseline | 2.85 (1.6) | | 2.90 (1.7) | | 3.00 (1.63) | |
| Postinfusion 1 | .77 (1.4)[a] | $d = 1.37$ (.79–1.95) | .40 (.97)[a] | $d = 1.67$ (.70–2.64) | .20 (.63)[a] | $d = 2.17$ (.75–3.59) |
| Postinfusion 6 | — | — | — | — | .00 (.00)[a,d] | $d = 2.42$ (1.20–3.63) |
| BSI | | | | | | |
| Baseline | — | — | 8.00 (9.3) | | — | — |
| Postinfusion 1 | — | — | 3.3 (7.8)[c] | $d = .53$ (.18–.87) | — | — |
| IAT: Escape = Me | | | | | | |
| Baseline | — | — | −.04 (.31) | | — | — |
| Postinfusion 1 | — | — | −.53 (.40)[b] | $d = 1.36$ (.38–2.34) | — | — |
| IAT: Death = Me | | | | | | |
| Baseline | — | — | −.48 (.63) | | — | — |
| Postinfusion 1 | — | — | −.28 (.43) (ns) | $d = -.38$ (−1.56–.79) | — | — |

Postinfusion 1 ratings taken on day 2, 24 hours after a single infusion. Postinfusion 6 ratings taken on day 12, 4 hours after the 6th repeated dose infusion. Baseline and postinfusion scores compared by paired *t* tests; baseline to postinfusion effect size (*d*) calculated from means, SDs, and precorrelation/postcorrelation coefficients (20).

BSI, Beck Scale for Suicidal Ideation (17); CI, confidence interval; IAT, implicit association test (5); MADRS, Montgomery-Asberg Depression Rating Scale (16); MADRS-SI, MADRS-Suicidality Item; ns, not significant; TRD, treatment-resistant depression.

[a] $p < .001$.
[b] $p < .01$.
[c] $p < .05$.
[d] $n = 9$ for day 12 assessments.

between Me and Death did not change as predicted, suggesting that the implicit representation of suicide in TRD might more closely relate to the concept of escape than to death itself. Death = Me associations were low at baseline, possibly limiting room for improvement. Prospective studies in high-risk samples should test whether the IAT can improve prediction of suicide risk in clinical settings, where motivation to conceal suicidal thoughts may exist (4). The IAT might also be useful in revealing psychological mechanisms of change. For instance, mediational analysis in larger samples could test the hypothesis that ketamine reduces depressed mood in suicidal patients, thereby decreasing implicit desire to escape from an unbearable emotional state, leading to downstream reductions in explicit suicidal thoughts.

The rapid onset and maintenance of improvement we observed suggests that IV ketamine, administered in the hospital setting with appropriate safety monitoring, may offer an attractive therapy for acutely suicidal depressed patients. Whether high-risk patients with markedly active suicidality will respond similarly remains an open question. Controlled studies are needed to establish whether ketamine is efficacious in such samples and whether decreased suicidality, once achieved, can be maintained through alternative pharmacological or psychos-

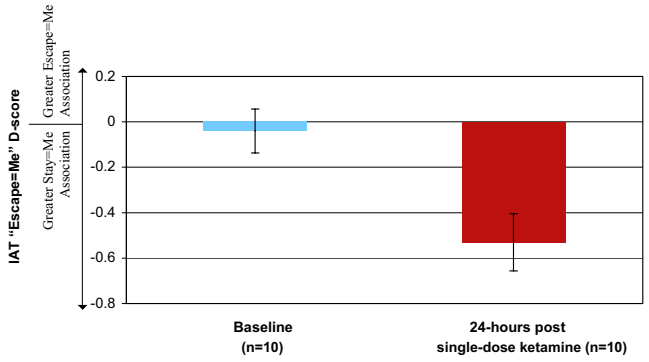


**Figure 2.** Mean IAT Escape *D* scores (±SEM) representing the strength of association between words related to "Me" and words related to "Escape" at baseline and 24 hours following a single subanesthetic infusion of ketamine. *D* scores calculated as *D* = ([mean response latency during Escape/Me block − mean response latency during Escape/not Me block] ÷ SD of response latency across all trials). More positive *D* score indicates stronger implicit self-identification with words related to "Escape," in comparison with words related to "Stay." IAT, Implicit Association Test.

**Table 4.** Partial Correlations Between Change Scores (24 Hour − Baseline) in Implicit and Explicit Suicidality Measures, Controlling for Change in Other Depressive Symptoms (MADRS, Excluding Suicidality Item)

| | MADRS-SI | BSI | $SI_{composite}$ |
|---|---|---|---|
| IAT: Escape = Me | .74 ($p = .022$) | .72 ($p = .028$) | .78 ($p = .014$) |
| IAT: Escape = Me, adding baseline $SI_{composite}$ as an additional covariate | .64 ($p = .086$) | .60 ($p = .118$) | .71 ($p = .048$) |
| IAT: Death = Me | .34 ($p = .366$) | .69 ($p = .038$) | .55 ($p = .122$) |
| IAT: Death = Me, adding baseline $SI_{composite}$ as an additional covariate | .31 ($p = .460$) | .80 ($p = .016$) | .65 (.078) |

BSI, Beck Scale for Suicidal Ideation (17); IAT, Implicit Association Test (5); MADRS, Montgomery-Asberg Depression Rating Scale (16); MADRS-SI, MADRS-Suicidality Item; $SI_{composite}$, composite suicidality index: sum of *z* scores on BSI and MADRS-SI.

ocial interventions. Given that all three datasets analyzed here were obtained from a single group of TRD patients, these findings require independent replication.

*This work was supported by National Institutes of Health Grants F31 MH081468 (RBP), K23-MH-069656 and MO1-RR-00071 (SJM) and NARSAD (SJM, DSC). Registered at http://ClinicalTrials.gov as trial numbers NCT00419003, "Research Study for Major Depressive Disorder: Investigation of Glutamate Medications" and NCT00548964, "Continuation Intravenous Ketamine in Major Depressive Disorder."*

*We thank Marije aan het Rot, Kate Collins, Kimberly Hunter, Michele Gonen, James Murrough, M.D., Andrew Perez, M.D., David Reich, M.D., all additional members of the Mood & Anxiety Disorders Program, and the staff of the Mount Sinai General Clinical Center for their assistance with the study.*

*Ms. Price and Dr. Nock report no biomedical financial interests or potential conflicts of interest. Dr. Mathew has received lecture or consulting fees from AstraZeneca and Jazz Pharmaceuticals and has received research support from Alexza Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, and Novartis Pharmaceuticals. Dr. Charney discloses consultant activities with Unilever, UK Central Resources, Limited in the past 2 years. Drs. Charney and Mathew have been named as an inventor on a use-patent of ketamine for the treatment of depression. If ketamine were shown to be effective in the treatment of depression and receive approval from the Food and Drug Administration for this indication, Dr. Charney and the Mount Sinai School of Medicine could benefit financially. Dr. Mathew has relinquished his claim to any royalties and will not benefit financially if ketamine is approved for this use.*

*Supplementary material cited in this article is available online.*

1. Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, *et al.* (2005): Relief of expressed suicidal intent by ECT: A consortium for research in ECT study. *Am J Psychiatry* 162:977–982.
2. Szanto K, Mulsant BH, Houck P, Dew MA, Reynolds CF 3rd (2003): Occurrence and course of suicidality during short-term treatment of late-life depression. *Arch Gen Psychiatry* 60:610–617.
3. Nock MK, Banaji MR (2007): Prediction of suicide ideation and attempts among adolescents using a brief performance-based test. *J Consult Clin Psychol* 75:707–715.
4. Busch KA, Fawcett J, Jacobs DG (2003): Clinical correlates of inpatient suicide. *J Clin Psychiatry* 64:14–19.
5. Greenwald AG, McGhee DE, Schwartz JL (1998): Measuring individual differences in implicit cognition: The implicit association test. *J Pers Soc Psychol* 74:1464–1480.
6. Cunningham WA, Preacher KJ, Banaji MR (2001): Implicit attitude measures: Consistency, stability, and convergent validity. *Psychol Sci* 12:163–170.
7. Banse R, Seise J, Zerbes N (2001): Implicit attitudes towards homosexuality: Reliability, validity, and controllability of the IAT. *J Exp Psychol* 48:145–160.
8. Greenwald AG, Poehlman TA, Uhlmann EL, Banaji MR (in press): Understanding and using the Implicit Association test. III. Meta-analysis of predictive validity. *J Pers Soc Psychol*.
9. Nock MK, Banaji MR (2007): Assessment of self-injurious thoughts using a behavioral test. *Am J Psychiatry* 164:820–823.
10. Nock MK, Deliberto TL, Dour HJ, Banaji MR, Park J, Finn C (2008): Measuring implicit associations about suicide. Paper presented at: Annual Convention of the Association for Behavioral and Cognitive Therapies; November 13–16, 2008; Orlando, FL.
11. Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, *et al.* (2006): A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 63: 856–864.
12. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, *et al.* (2000): Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry* 47:351–354.
13. Mathew SJ, Murrough JW, Aan Het Rot M, Collins KA, Reich DL, Charney DS (2009): Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial. *Int J Neuropsychopharmacol* 17:1–12.
14. Sackeim HA (2001): The definition and meaning of treatment-resistant depression. *J Clin Psychiatry* 62(suppl 16):10–17.
15. Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH (1996): The Inventory of Depressive Symptomatology (IDS): Psychometric properties. *Psychol Med* 26:477–486.
16. Montgomery SA, Asberg M (1979): A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134:382–389.
17. Beck AT, Steer RA (1991): *Manual for the Beck Scale for Suicide Ideation*. San Antonio, TX: Psychological Corporation.
18. Nosek BA, Greenwald AG, Banaji MR (2005): Understanding and using the Implicit Association Test. II. Method variables and construct validity. *Pers Soc Psychol Bull* 31:166–180.
19. Cohen J (1988): *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates.