Rapid Resolution of Suicidal Ideation After a Single Infusion of an *N*-Methyl-D-Aspartate Antagonist in Patients With Treatment-Resistant Major Depressive Disorder

Nancy DiazGranados, MD, MS; Lobna A. Ibrahim, MD; Nancy E. Brutsche, MSN; Rezvan Ameli, PhD; Ioline D. Henter, MA; David A. Luckenbaugh, MA; Rodrigo Machado-Vieira, MD, PhD; and Carlos A. Zarate Jr, MD

Objective: Suicidal ideation is a medical emergency, especially when severe. Little research has been done on pharmacologic interventions that could address this problem. Ketamine, an *N*-methyl-D-aspartate antagonist, has been reported to have antidepressant effects within hours. We examined the effects of a single dose of ketamine on suicidal ideation in subjects with treatment-resistant major depressive disorder (MDD).

Method: Thirty-three subjects with *DSM-IV*–diagnosed MDD received a single open-label infusion of ketamine (0.5 mg/kg) and were rated at baseline and at 40, 80, 120, and 230 minutes postinfusion with the Scale for Suicide Ideation (SSI), the Montgomery-Åsberg Depression Rating Scale, the Hamilton Depression Rating Scale, and the Beck Depression Inventory. The study was conducted between October 2006 and January 2009.

Results: Suicidal ideation scores decreased significantly on the SSI as well as on the suicide subscales of other rating instruments within 40 minutes; these decreases remained significant through the first 4 hours postinfusion ($P < .001$). Ten subjects (30%) had an SSI score ≥4 at baseline; all these scores dropped below 4 (9 dropped by 40 minutes and 1 by 80 minutes). For those patients with a starting score below 4 on the SSI, only 1 reached a score of 4. Depression, anxiety, and hopelessness were significantly improved at all time points ($P < .001$).

Conclusions: Suicidal ideation in the context of MDD improved within 40 minutes of a ketamine infusion and remained improved for up to 4 hours postinfusion. Future studies with ketamine in suicidal ideation are warranted due to the potential impact on public health.

Trial Registration: clinicaltrials.gov Identifier: NCT00088699

J Clin Psychiatry 2010;71(12):1605-1611

Submitted: *May 4, 2009; accepted July 14, 2009.*
Online ahead of print: *July 13, 2010 (doi:10.4088/JCP.09m05327blu).*
Corresponding author: *Carlos A. Zarate Jr, MD, 10 Center Drive, CRC, 7 Southeast Unit, Room 7-3465, Bethesda, MD 20892 (zaratec@intra.nimh.nih.gov).*

Individuals with serious psychiatric disorders commit suicide in disproportionate numbers, and the vast majority of patients who display suicidal behavior have major depressive disorder (MDD). Indeed, greater severity of depression has been associated with more suicide attempts.[1] In addition, anxiety and hopelessness seem to increase suicide risk in depressed patients.[1,2] Among 4,027 enrollees in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 16.5% reported previous suicide attempts.[1] When analyses controlled for age, gender, and depressive symptom severity, previous suicide attempters had more current general medical conditions ($P < .0001$), more current alcohol and substance abuse ($P < .001$), more work hours missed in the past week (26.2% versus 18.2%, $P < .0001$), and more current suicidal ideation (61.3% versus 45.5%, $P < .0001$) than nonattempters.[1] The results suggest that depression with suicidal behavior is a more severe form of the illness that requires more aggressive treatment.

Suicidal ideation or attempts in patients with MDD is a serious and emergent condition that requires immediate treatment. A recent study of patients who attempted suicide found that 74% said the decision-making period (ie, the period between decision and attempt) was very short—about 10 minutes or less.[3] While the identification of risk factors is central to suicide prevention, one crucial factor regards the timing of suicidal behavior. Studies have found that individuals with mood disorders are at greatest risk of death from any cause, including suicide, in the first 2 years after their diagnosis.[4] More specifically, studies have consistently identified the emergency department, the inpatient unit, time after discharge, and time after starting an antidepressant as time points during which individuals are particularly vulnerable to suicidal ideation.[5–9] These circumstances offer the possibility to intervene quickly and decisively to prevent suicidal behavior.

Data from the National Hospital Ambulatory Medical Care Survey indicate that between 1992 and 2001, emergency department visits for suicide attempts and self-injury increased by 47%, from 0.8 to 1.5 visits per 1,000 in the US population.[10] The risk of suicide attempts occurring in inpatient units is also a major concern and is the second most common sentinel event—defined as an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof—reported to the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).[6] Approximately 1,500 suicides occur in inpatient hospital units in the United States each year, and a staggering one-third of these take place while the patient is on 15-minute checks.[7,8] The JCAHO emphasized the need for around-the-clock observation for inpatients at high risk for suicide. However, there are no systematic studies or best-practice recommendations for patients in this situation.[6] Another time during which intervention with suicidal patients may

be possible is the time following discharge. In a 3-month case-control study of mortality in 238 psychiatric patients, Hunt and colleagues[5] found that 43% of suicides occurred within a month of discharge. The first week and the first day after discharge were periods of particularly high risk.[5]

Various therapeutic interventions to reduce suicide risk in serious psychiatric disorders are effective in long-term suicide prevention—most notably, lithium for the treatment of bipolar disorder[11] and, to a lesser extent, MDD,[12] as well as the atypical antipsychotic clozapine in schizophrenia.[13] Different types of psychotherapy have also been shown to effectively prevent suicidal behavior over the long term.[14–16] However, the acute pharmacologic management of suicidal risk in MDD remains comparatively underinvestigated.[17]

Emergency tranquilization with benzodiazepines and/or antipsychotic drugs is often recommended for patients at high risk of suicide[18]; indeed, the management of significant suicidal ideation in an emergency department setting is often done in the context of agitation. For example, a review[18] by the American College of Emergency Physicians found no class 1 studies for the emergency treatment of nonpsychotic agitation. With regard to atypical antipsychotic drugs, a recent controlled pharmacologic study[19] found that risperidone significantly reduced suicidal ideation in patients with MDD compared to placebo. The effects of risperidone augmentation were apparent at 2 weeks posttreatment and were sustained for the rest of the 8-week study.

The evidence regarding suicide risk and antidepressants has often appeared conflicting, a finding usually attributable to the delayed onset of action of antidepressants. Jick and colleagues[9] observed an increased risk of suicide during the first month of antidepressant treatment, particularly during the first 9 days; individuals showed similar rates of risk regardless of the chemical class of their antidepressant. In contrast, other studies[20,21] found that suicide attempt rates either did not change[20] or were significantly lower among patients who were treated with antidepressants (particularly selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants) compared to those not treated; this protective effect was seen across all adult age groups.[21] Another concern is that, in the United States, this issue has been clouded by the Food and Drug Administration's black box warning concerning the use of SSRIs in children, adolescents, and young adults. Regardless of the impact of antidepressants on suicide risk, the slow onset of action of antidepressants has prompted consideration of the use of electroconvulsive therapy (ECT) for severely depressed patients and as a treatment for suicidal ideation.[22]

In terms of the neurobiology of suicide, the most robust finding has involved multiple dimensions of serotonergic dysfunction including reduced central serotonin turnover and a polymorphism of the serotonin transporter.[23] Noradrenergic and dopaminergic system dysfunction has also been implicated in suicide. Comparatively, the direct role of the glutamatergic system in suicide has received little attention. However, 2 recent studies—the STAR*D[24] and the Munich Antidepressant Response Signature[25] projects—found a relationship between treatment-emergent suicidal ideation and the glutamate system, specifically identifying the involvement of the genes GRIA3 and GRIK2.[24,25] In postmortem studies, Nowak and colleagues[26] reported that the proportion of high-affinity, glycine-displaceable [^{3}H]CGP-39653 binding to glutamate receptors was reduced in patients who committed suicide compared with control subjects. However, another study[27] found no difference in the actual number of *N*-methyl-D-aspartate (NMDA) receptors in 9 brain regions of 22 suicide victims and age- and sex-matched controls compared using [^{3}H]MK-801 binding characteristics.

Notably, we previously reported that the NMDA antagonist ketamine resulted in a rapid antidepressant effect within hours as compared to placebo in a group of patients with treatment-resistant MDD.[28] In that study, we also noted that the Montgomery-Åsberg Depression Rating Scale (MADRS) suicide subscore improved rapidly (ie, earlier than previously reported in other pharmacologic studies). However, our previous study did not permit the inclusion of patients with significant suicidal ideation, thus minimizing the variance in suicide subscores.

On the basis of this previous study, we hypothesized that a single intravenous infusion of ketamine would bring about a rapid and clinically significant improvement in suicidal ideation within 230 minutes of the infusion. In order to assess this issue as carefully as possible, inpatients with treatment-resistant MDD currently experiencing a major depressive episode were included regardless of severity of suicidal ideation. Furthermore, we used a sensitive and specific scale to measure this construct: the Scale for Suicide Ideation (SSI).[29]

METHOD

Thirty-three patients aged 18 to 65 years participated in this inpatient study between October 2006 and January 2009. Participants fulfilled *DSM-IV* criteria for MDD and had no diagnosis of alcohol or substance abuse or dependence in the past 90 days, as determined by the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[30] All patients were in good health and had been unmedicated for at least 2 weeks prior to the ketamine infusion, as determined by medical history, physical examination, routine blood laboratories, electrocardiogram, urinalysis, and urine toxicology. Patients received a complete description of the study, and written informed consent was obtained. The study was approved by the Combined Neuroscience Institutional Review Board of the National Institutes of Health. Each subject was assigned a clinical research advocate (CRA) from the Human Subjects Protection Unit of the National Institute of Mental Health to monitor the consent process; in addition, CRAs monitored subjects during research participation from this initial consent throughout study participation.

Patients underwent a single infusion of ketamine hydrochloride (0.5 mg/kg), infused over 40 minutes, followed by double-blind random assignment to riluzole or placebo 6 hours postinfusion. Here we report only the results of the

© Copyright 2010 Physicians Postgraduate Press, Inc.

Table 1. Demographic and Course of Illness Characteristics at Baseline

Variable	Group With Baseline SSI Score > 3 (n = 10), Mean (SD)	Group With Baseline SSI Score < 4 (n = 23), Mean (SD)	Total (N = 33), Mean (SD)	High vs Low SSI Score, *P* Value
Age, y	49.3 (13.4)	45.0 (13.9)	46.3 (13.7)	.42
Age at onset, y	21.6 (10.4)	20.7 (12.3)	20.9 (11.7)	.85
Length of illness, y	28.8 (11.7)	24.3 (13.0)	25.5 (12.6)	.40
Length of current episode, mo	92.0 (123.4)	100.7 (148.3)	98.5 (140.3)	.88
Height, cm	174.3 (9.8)	174.2 (11.7)	174.2 (11.0)	.98
Weight, kg	90.8 (19.0)	95.7 (28.2)	94.2 (25.6)	.62
Body mass index, kg/m^2	29.8 (5.3)	31.2 (7.9)	30.8 (7.1)	.61
Clinical scale ratings at baseline				
Suicide				
SSI score	8.7 (7.0)	0.6 (0.9)	3.0 (5.4)	< .001
HDRS item score	2.3 (0.8)	0.5 (0.7)	1.1 (1.1)	< .001
MADRS item score	3.4 (1.0)	1.7 (0.9)	2.2 (1.2)	< .001
Depression				
HDRS score	24.5 (5.0)	18.7 (2.7)	20.5 (4.4)	< .001
MADRS score	36.8 (4.5)	31.6 (3.1)	33.2 (4.3)	< .001
Anxiety, HDRS subscale score	7.2 (2.3)	5.9 (1.2)	6.3 (1.7)	.04
BPRS score	36.7 (5.8)	35.4 (5.4)	35.8 (5.5)	.54
CADSS score	7.9 (12.7)	3.5 (5.2)	4.8 (8.3)	.16
	n (%)	n (%)	n (%)	*P* Value
Gender, male	6 (60)	14 (61)	20 (61)	.96
Education, college graduate	4 (50)[a]	14 (64)[a]	18 (60)[a]	.50
Mood disorder family history	8 (100)[a]	20 (87)	28 (90)[a]	.28
Hospitalization, lifetime	7 (70)	10 (43)	17 (52)	.16
Suicidal behavior				
Ideation				
Lifetime	9 (90)	11 (48)	20 (61)	.02
Admission	8 (80)	4 (17)	12 (36)	.001
Attempt				
Self	7 (70)	3 (13)	10 (30)	.001
Family history	4 (40)	8 (35)	12 (36)	.077

[a]For education, there were missing data for 2 individuals in the high SSI group and 1 in the low SSI group; for mood disorder family history, there were missing data for 2 individuals in the high SSI group.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CADSS = Clinician-Administered Dissociative States Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, SSI = Scale for Suicide Ideation.

open-label ketamine phase (up to 230 minutes postinfusion). This time point was chosen because previous studies have consistently found that 88% of all responders to ketamine reach response criteria by 230 minutes.[28,31,32] Ratings included the MADRS,[33] the 17-item Hamilton Depression Rating Scale (HDRS),[34] the Beck Depression Inventory (BDI),[35] the Clinician-Administered Dissociative States Scale (CADSS),[36] the Brief Psychiatric Rating Scale (BPRS),[37] and the SSI.[29] Ratings were obtained at baseline (60 minutes prior to the infusion) and at 40, 80, 120, and 230 minutes postinfusion. All items on each scale were used. High interrater reliability was obtained for both the MADRS (intraclass correlation coefficient = 0.88) and the SSI (intraclass correlation coefficient = 0.94).

Statistics

Linear mixed models were used to examine the course of outcome measures over time, in which time was a fixed within-subjects factor and a fixed intercept was included. Schwarz's Bayesian criteria were used to determine the best-fitting variance-covariance structure that was a first-order autoregressive model. A random intercept and random effect for subject did not add to the model, so they were not included. Bonferroni-adjusted post hoc tests were used to examine the change from baseline to each postinfusion time. Significance was evaluated at $P < .05$, 2-tailed.

Previous studies have identified a cutoff score > 3 as indicating significant suicidal ideation on the SSI; as a result, patients in this study were separated into groups with significant suicidal ideation (SSI > 3) and without significant suicidal ideation (SSI < 4) at baseline.[38] Youden's index—the optimal trade-off between sensitivity and specificity—was achieved for the SSI scale at a cutoff threshold of > 3, a score that is both clinically significant and an appropriate method for detecting significant suicidal ideation.[38] Kaplan-Meier survival analysis was used to examine the mean amount of time for patients with significant baseline ideation to reach minimal ideation (SSI < 4). For those without significant baseline ideation, survival analysis examined how long patients took to develop significant ideation (SSI > 3). The demographic characteristics of patients with and without suicidal ideation at baseline were examined with Student *t* tests for continuous measures and χ^2 tests for categorical ones.

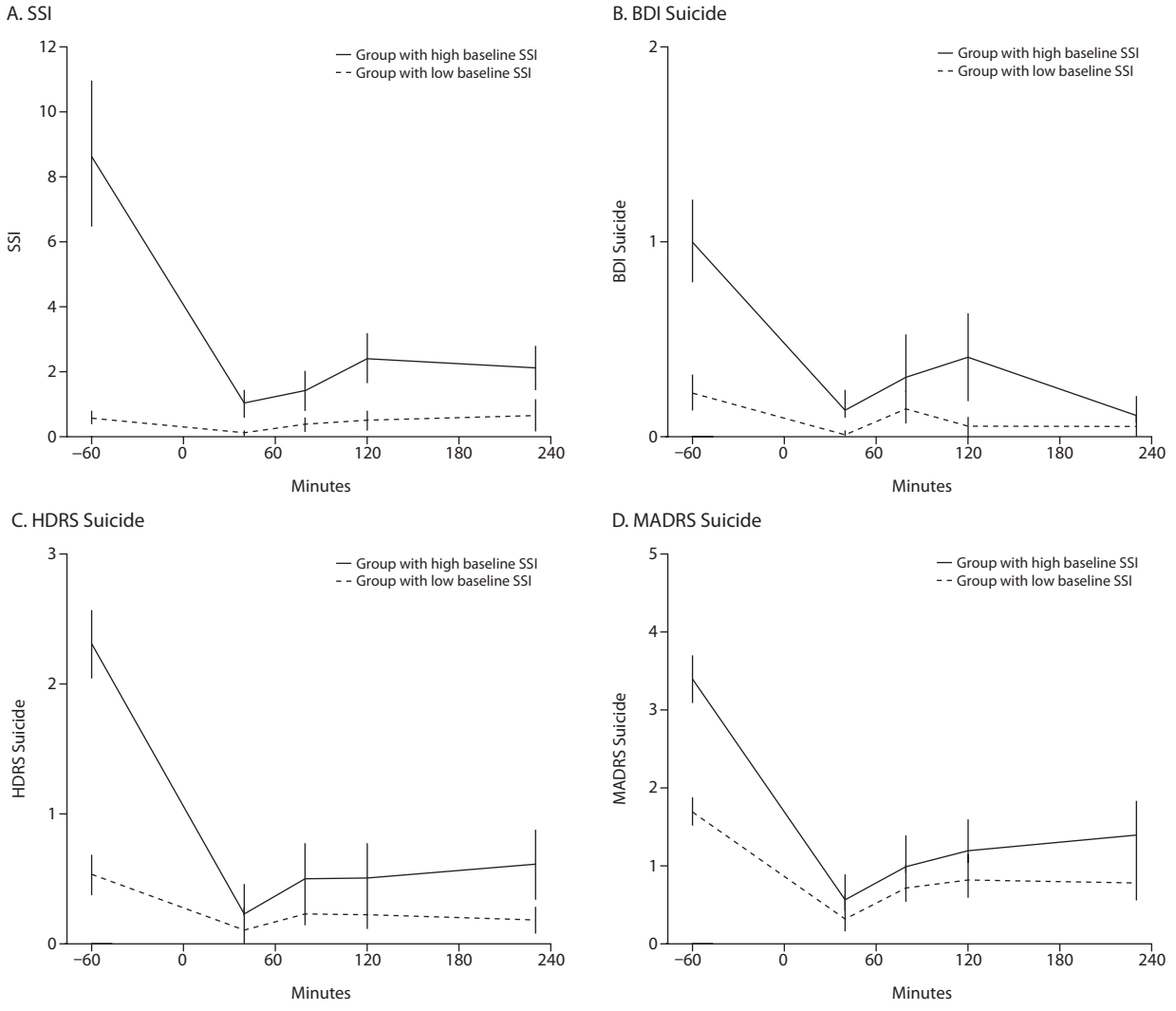
RESULTS

Table 1 shows demographic and clinical data for the full sample as well as for patients with (n = 10) and without (n = 23) clinically significant baseline SSI scores. Patients with greater suicidal ideation at baseline were significantly more likely to have higher MADRS and HDRS total scores, higher MADRS and HDRS suicide items, higher HDRS anxiety subscores, and higher rates of past suicidal ideation and attempts. Paired *t* tests indicated that the SSI scores did not change significantly from screening to baseline (a mean of 8.0 [SD = 4.1] days) for the total sample ($t_{23} = 1.39$, $P = .18$; mean change = −1.0 [SD = 3.7]), for the group with higher SSI scores at baseline ($t_4 = 0.70$, $P = .52$; mean change = −2.4 [SD = 7.6]), or for the group with lower SSI scores at baseline ($t_{18} = 1.58$, $P = .13$; mean change = −0.7 [SD = 1.9]), indicating that scores were relatively stable at baseline.

The linear mixed models with the full sample indicated significant improvement in all of the suicide scales following ketamine infusion (SSI: $F_{4,97} = 7.03$, $P < .001$; HDRS

© Copyright 2010 Physicians Postgraduate Press, Inc.

Figure 1. Course of Suicidal Ideation Within 230 Minutes of Ketamine Infusion in Patients With Treatment-Resistant MDD With and Without High Baseline Suicidal Ideation (N = 33)[a,b]



[a]High SSI score was defined as > 3; low SSI score was defined as < 4.
[b]The values presented are mean scores, with bars representing 1 standard error.
Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, SSI = Scale for Suicide Ideation.

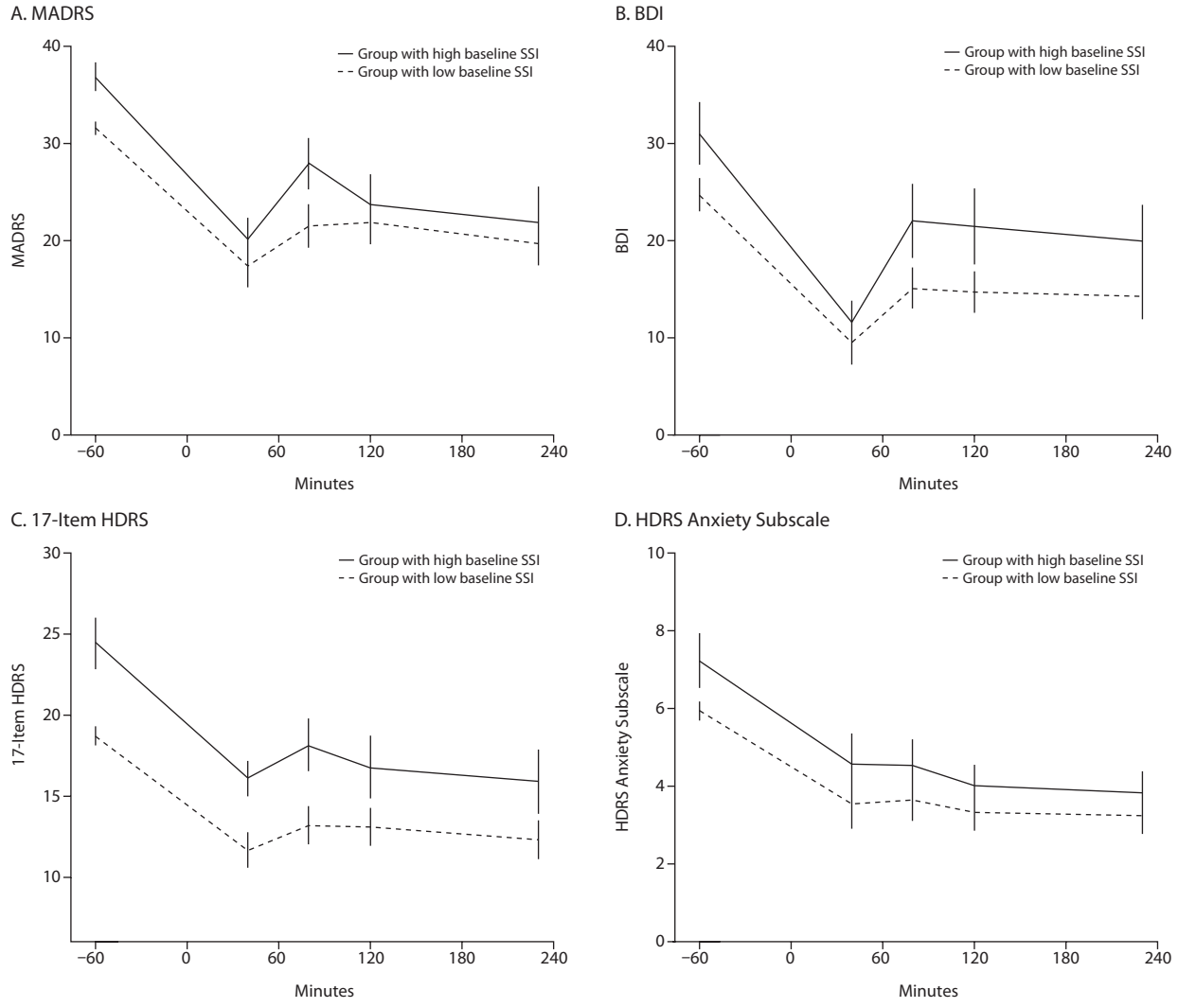
suicide item: $F_{4,106} = 17.25$, $P < .001$; MADRS suicide item: $F_{4,110} = 27.68$, $P < .001$; BDI suicide item: $F_{4,103} = 5.82$, $P < .001$) (Figure 1). On each scale, scores were significantly lower at 40 minutes and remained significantly lower at 230 minutes. The effect for the full sample was very large at 40 minutes ($d = 1.05$; 95% CI, 0.65–1.45) and moderate at 230 minutes ($d = 0.45$; 95% CI, 0.12–0.77).

In the subgroup with baseline SSI scores > 3, the effect size was $d = 2.36$ (95% CI, 1.56–3.16) at 40 minutes and $d = 1.27$ (95% CI, 0.62–1.92) at 230 minutes. At an SSI cutoff of > 4, the effect size was $d = 3.13$ (95% CI, 1.97–4.30) at 40 minutes and $d = 1.84$ (95% CI, 0.92–2.75) at 230 minutes. The same pattern was true for the depression and anxiety total scores (HDRS: $F_{4,117} = 29.57$, $P < .001$; MADRS: $F_{4,117} = 36.17$, $P < .001$; BDI: $F_{4,112} = 39.94$, $P < .001$; HDRS anxiety: $F_{4,115} = 15.10$, $P < .001$) (Figure 2), as well as for the hopelessness subscale score on the BDI ($F_{4,104} = 20.46$, $P < .001$).

All 10 patients (100%) with higher baseline SSI scores went below an SSI score of 4 within the first hours after the infusion; 9 of 10 (90%) went below a score of 4 within 40 minutes, and 1 within 80 minutes. The mean time needed to achieve an SSI score less than 4 was 44 minutes (SE = 4 minutes). Six of these patients (60%) reached SSI scores of zero during the first day, and 5 of these individuals achieved this reduction within 40 minutes; the remaining individual achieved this reduction within 80 minutes. For these patients, the mean time to achieve a score of zero was 120 minutes (SE = 29 minutes).

For patients with lower baseline SSI scores, only 1 of 23 patients (4%) went above an SSI score of 3 on the first day after infusion. This patient took 80 minutes to reach a score of 4 (from a baseline of 3). Furthermore, no serious adverse events occurred during the study. The adverse effects noted were comparable to those that occurred in our previous

Figure 2. Course of Depression and Anxiety Within 230 Minutes of Ketamine Infusion in Patients With Treatment-Resistant MDD With and Without High Baseline Suicidal Ideation (N = 33)[a,b]



[a]High SSI score was defined as > 3; low SSI score was defined as < 4.
[b]The values presented are mean scores, with bars representing 1 standard error.
Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, MDD = major depressive disorder, SSI = Scale for Suicide Ideation.

study, in which mild perceptual disturbances were observed in most patients only in the first hour after infusion.[28]

DISCUSSION

Thirty-three subjects with treatment-resistant *DSM-IV*–diagnosed MDD received a ketamine infusion as part of a clinical research protocol. Subjects with an SSI score of > 3, indicating substantial suicidal ideation, improved significantly within 230 minutes, as assessed by not only SSI total scores but also MADRS, HDRS, and BDI suicide items. In fact, the mean time necessary for these individuals to achieve an SSI score lower than 4 was 44 minutes. The effect size associated with ketamine use was very large, regardless of the cutoff used on the SSI scale (eg, > 3 or > 4).[39]

The rapidity of this improvement in suicidal ideation and the magnitude of the effect is especially notable given the treatment-resistant status of these patients; patients with more severe depression are at greater risk for more suicide attempts.[1] This group of patients had, on average, been ill for 26 years, and their current major depressive episode was, on average, of 8 years' duration; furthermore, 61% of the patients had a lifetime history of suicidal ideation, and 30% had a previous suicide attempt. In addition, anxiety and hopelessness, which are well-recognized risk factors for suicide, also improved significantly and rapidly during the course of the study. Rapidly modifying these risk factors could also impact the short-term risk of suicidal behavior.

Several factors need to be considered in interpreting these data. Although the sample size was relatively small, 4 different scales showed comparable improvement in suicidal ideation, and the effect sizes were very large. In addition, the drug was administered in an open-label fashion, which could have biased the reported response; however, it should be noted

that the improvements in suicidal ideation and depressive symptoms observed in the present study over the course of 230 minutes closely paralleled the improvement of depressive symptoms seen in our previous controlled study.[28] It is also possible that the results reflect a waxing and waning of suicidal ideation[40]; however, we think this possibility is unlikely because suicidal ideation in this treatment-resistant population of depressed patients was sustained over the course of 8 days prior to ketamine infusion (ie, it did not differ significantly from admission levels). Finally, it is important to note that the improvement in suicidal ideation observed here occurred in the context of severe depression. Whether ketamine rapidly reduces suicidal ideation in patients with a diagnosis other than MDD is unknown. In addition, the length of improvement remains unclear.

Suicide is one of the leading causes of death among young people worldwide—particularly among those with psychiatric disorders. In the past decade, an increased urgency has accompanied efforts at suicide prevention, leading to the identification of additional risk factors for suicide, as well as improved preventive strategies.[41] Suicidal ideation itself is a medical emergency that requires swift and careful treatment. Unfortunately, few currently available therapeutics can be used to immediately reduce suicidal ideation, often with tragic consequences. Relatedly, difficulties are also associated with treating individuals quickly enough to significantly reduce suicidal ideation; a key example of this is in the US military, in which the stress of multiple deployments and the difficulties associated with successfully treating soldiers in the field have made suicide a particularly urgent issue.[42]

It is clear that our preliminary results need to be interpreted with caution given the small group size and the open-label nature of the study. Nevertheless, the significant and often rapid response seen in some individuals who were refractory to many traditional antidepressants suggests that directly modulating the glutamatergic system may ultimately be effective in treating suicidal ideation. Due to the potentially significant impact on public health, further studies are needed to confirm these preliminary findings, and the continued examination of the role of the glutamatergic system in the pathophysiology and acute pharmacologic treatment of suicidal ideation is clearly warranted.

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

Author affiliation: Experimental Therapeutics, Mood and Anxiety Disorders Program, National Institute of Mental Health (NIMH), and Department of Human Health Services, Bethesda, Maryland.

Potential conflicts of interest: The authors declare that, except for income received from our primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. **Dr Zarate** is listed as a co-inventor on a patent for the use of ketamine in major depression and has assigned his patent rights on ketamine to the US government. None of the other investigators in this study have a possible conflict of interest, financial or otherwise.

Funding/support: This study was supported by the Intramural Research Program at NIMH and by NARSAD (Dr Zarate).

Previous presentation: Presented at the 64th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry; May 14–16, 2009; Vancouver, British Columbia, Canada.

REFERENCES

1. Claassen CA, Trivedi MH, Rush AJ, et al. Clinical differences among depressed patients with and without a history of suicide attempts: findings from the STAR*D trial. *J Affect Disord*. 2007;97(1–3):77–84.
2. Diefenbach GJ, Woolley SB, Goethe JW. The association between self-reported anxiety symptoms and suicidality. *J Nerv Ment Dis*. 2009; 97(2):92–97.
3. Deisenhammer EA, Ing CM, Strauss R, et al. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? *J Clin Psychiatry*. 2009;70(1): 19–24.
4. Gausset MF, Casadebaig F, Guillaud-Bataille JM, et al. Mortality of mentally ill patients: review of the literature. *Encephale*. 1992;18(1):93–100.
5. Hunt IM, Kapur N, Webb R, et al. Suicide in recently discharged psychiatric patients: a case-control study. *Psychol Med*. 2009;39(3):443–449.
6. Janofsky JS. Reducing inpatient suicide risk: using human factors analysis to improve observation practices. *J Am Acad Psychiatry Law*. 2009;37(1): 15–24.
7. Mills PD, DeRosier JM, Ballot BA, et al. Inpatient suicide and suicide attempts in Veterans Affairs hospitals. *Jt Comm J Qual Patient Saf*. 2008; 34(8):482–488.
8. Yeager KR, Saveanu R, Robers AR, et al. Measured response to identified suicide risk and violence: what you need to know about psychiatric patient safety. *Brief Treat Crisis Interv*. 2005;5(2):121–141.
9. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA*. 2004;292(3):338–343.
10. Larkin GL, Smith RP, Beautrais AL. Trends in US emergency department visits for suicide attempts, 1992–2001. *Crisis*. 2008;29(2):73–80.
11. Baldessarini RJ, Tondo L, Davis P, et al. Decreased risk of suicides and attempts during long-term lithium treatment: a meta-analytic review. *Bipolar Disord*. 2006;8(5 pt 2):625–639.
12. Guzzetta F, Tondo L, Centorrino F, et al. Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry*. 2007; 68(3):380–383.
13. Meltzer HY, Alphs L, Green AI, et al. International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: international suicide prevention trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82–91.
14. Linehan MM, Comtois KA, Murray AM, et al. Two-year randomized controlled trial and follow-up of dialectical behavior therapy vs therapy by experts for suicidal behaviors and borderline personality disorder. *Arch Gen Psychiatry*. 2006;63(7):757–766.
15. Fleischmann A, Bertolote JM, Wasserman D, et al. Effectiveness of brief intervention and contact for suicide attempters: a randomized controlled trial in five countries. *Bull World Health Organ*. 2008;86(9):703–709.
16. Brown GK, Ten Have T, Henriques GR, et al. Cognitive therapy for the prevention of suicide attempts: a randomized controlled trial. *JAMA*. 2005;294(5):563–570.
17. Ernst CL, Goldberg JF. Antisuicide properties of psychotropic drugs: a critical review. *Harv Rev Psychiatry*. 2004;12(1):14–41.
18. Lukens TW, Wolf SJ, Edlow JA, et al. American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Critical Issues in the Diagnosis and Management of the Adult Psychiatric Patient in the Emergency Department. Clinical policy: critical issues in the diagnosis and management of the adult psychiatric patient in the emergency department. *Ann Emerg Med*. 2006;47(1):79–99.
19. Reeves H, Batra S, May RS, et al. Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled pilot study. *J Clin Psychiatry*. 2008;69(8):1228–1236.
20. Simon GE, Savarino J, Operskalski B, et al. Suicide risk during antidepressant treatment. *Am J Psychiatry*. 2006;163(1):41–47.
21. Gibbons RD, Brown CH, Hur K, et al. Relationship between antidepressants and suicide attempts: an analysis of the veterans health administration data sets. *Am J Psychiatry*. 2007;164(7):1044–1049.
22. Patel M, Patel S, Hardy DW, et al. Should electroconvulsive therapy be an early consideration for suicidal patients? *J ECT*. 2006;22(2):113–115.
23. Currier D, Mann JJ. Stress, genes and the biology of suicidal behavior. *Psychiatr Clin North Am*. 2008;31(2):247–269.
24. Laje G, Paddock S, Manji HK, et al. Genetic markers of suicidal ideation emerging during citalopram treatment of major depression.

Am J Psychiatry. 2007;164(10):1530–1538.
25. Menke A, Lucae S, Kloiber S, et al. Genetic markers within glutamate receptors associated with antidepressant treatment-emergent suicidal ideation. *Am J Psychiatry*. 2008;165(7):917–918.
26. Nowak G, Ordway GA, Paul IA. Alterations in the *N*-methyl-D-aspartate (NMDA) receptor complex in the frontal cortex of suicide victims. *Brain Res*. 1995;675(1–2):157–164.
27. Holemans S, De Paermentier F, Horton RW, et al. NMDA glutamatergic receptors, labelled with [^{3}H]MK-801, in brain samples from drug-free depressed suicides. *Brain Res*. 1993;616(1–2):138–143.
28. Zarate CA Jr, Singh JB, Carlson PJ, et al. A randomized trial of an *N*-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63(8):856–864.
29. Beck AT, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*. 1979;47(2):343–352.
30. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders*. New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 2001.
31. Phelps LE, Brutsche NE, Moral JR, et al. Family history of alcohol dependence and initial antidepressant response to an *N*-methyl-D-aspartate antagonist. *Biol Psychiatry*. 2009;65(2):181–184.
32. Salvadore G, Cornwell BR, Colon-Rosario V, et al. Increased anterior cingulate cortical activity in response to fearful faces: a neurophysiological biomarker that predicts rapid antidepressant response to ketamine. *Biol Psychiatry*. 2009;65(4):289–295.
33. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
34. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
35. Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry*. 1974;7(0):151–169.
36. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). *J Trauma Stress*. 1998;11(1):125–136.
37. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10(3):799–812.
38. Holi MM, Pelkonen M, Karlsson L, et al. Psychometric properties and clinical utility of the Scale for Suicidal Ideation (SSI) in adolescents. *BMC Psychiatry*. 2005;5(1):8.
39. Sokero TP, Melartin TK, Rytsälä HJ, et al. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry*. 2003;64(9):1094–1100.
40. Zisook S, Trivedi MH, Warden D, et al. Clinical correlates of the worsening or emergence of suicidal ideation during SSRI treatment of depression: an examination of citalopram in the STAR*D study. *J Affect Disord*. 2009;117(1–2):63–73.
41. US Department of Health and Human Services. *National Strategy for Suicide Prevention: Goals and Objectives for Action*, Report No SMA 3517. Rockville, MD: US Department of Health and Human Services; 2001.
42. Kuehn BM. Soldier suicide rates continue to rise: military, scientists work to stem the tide. *JAMA*. 2009;301(11):1111–1113.

 © Copyright 2010 Physicians Postgraduate Press, Inc.