ORIGINAL ARTICLE

A Randomized Trial of an *N*-methyl-D-aspartate Antagonist in Treatment-Resistant Major Depression

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Context: Existing therapies for major depression have a lag of onset of action of several weeks, resulting in considerable morbidity. Exploring pharmacological strategies that have rapid onset of antidepressant effects within a few days and that are sustained would have an enormous impact on patient care. Converging lines of evidence suggest the role of the glutamatergic system in the pathophysiology and treatment of mood disorders.

Objective: To determine whether a rapid antidepressant effect can be achieved with an antagonist at the *N*-methyl-D-aspartate receptor in subjects with major depression.

Design: A randomized, placebo-controlled, double-blind crossover study from November 2004 to September 2005.

Setting: Mood Disorders Research Unit at the National Institute of Mental Health.

Patients: Eighteen subjects with *DSM-IV* major depression (treatment resistant).

Interventions: After a 2-week drug-free period, subjects were given an intravenous infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on 2 test days, a week apart. Subjects were rated at baseline and at 40, 80, 110, and 230 minutes and 1, 2, 3, and 7 days postinfusion.

Main Outcome Measure: Changes in scores on the primary efficacy measure, the 21-item Hamilton Depression Rating Scale.

Results: Subjects receiving ketamine showed significant improvement in depression compared with subjects receiving placebo within 110 minutes after injection, which remained significant throughout the following week. The effect size for the drug difference was very large (d=1.46 [95% confidence interval, 0.91-2.01]) after 24 hours and moderate to large (d=0.68 [95% confidence interval, 0.13-1.23]) after 1 week. Of the 17 subjects treated with ketamine, 71% met response and 29% met remission criteria the day following ketamine infusion. Thirty-five percent of subjects maintained response for at least 1 week.

Conclusions: Robust and rapid antidepressant effects resulted from a single intravenous dose of an *N*-methyl-D-aspartate antagonist; onset occurred within 2 hours postinfusion and continued to remain significant for 1 week.

Trial Registration: clinicaltrials.gov Identifier: NCT00088699.

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THE TREATMENT OF DEPRESsion was revolutionized about a half century ago by the serendipitous discovery of monoamine oxidase inhibitors and tricyclic antidepressants. Since then, the availability of a host of newer medications with better adverse-effect profiles has greatly increased our ability to safely treat a significant percentage of patients. However, the newer medications are largely "me too" drugs in as much as they exert their primary biochemical effects by increasing the intrasynaptic levels of monoamines. Unfortunately, these medications take weeks to achieve their full effects and in the meantime, patients continue to suffer from their symptoms and risk self-harm as well as harm to their personal and professional lives. Indeed, the lag period in onset of action of several weeks of traditional antidepressants is recognized as a major limitation, resulting in considerable morbidity and high risk of suicidal behavior especially in the first 9 days after starting antidepressant treatment.[1] Pharmacological strategies that have rapid onset of antidepressant effects within hours or even a few days and that are sustained would therefore have an enormous impact on public health.

A very useful "initiation and adaptation" paradigm for understanding the delayed therapeutic actions of antidepressants has been an important line of research for several years now[2]; more recent versions of this paradigm have focused attention away from monoaminergic systems to adaptive changes in other systems.[3] This paradigm posits that the effect of acute drug administration is mediated via an initial direct target protein perturbation (eg, binding to a monoamine transporter, thereby inhibiting monoamine reuptake); with repeated administration, the same initial event, over time, leads to enduring adaptive changes in critical neuronal networks, thereby resulting in stable long-term antidepressant effects. Thus, this paradigm posits that the delay in the therapeutic actions of existing pharmacologic agents is due to the fact that they initially act on substrates that are considerably upstream of targets that are ultimately responsible for the antidepressant effects. In this context, the major systems that have been postulated to mediate the delayed adaptive effects of antidepressants are neurotrophic signaling cascades and the glutamatergic system.[4,5] These systems should not necessarily be viewed as separate, and the interested reader is referred to several excellent reviews on the link between neurotrophins and glutamate systems[5-7]; herein we discuss the role of the glutamatergic system, most notably the *N*-methyl-D-aspartate (NMDA) system, in the actions of antidepressants.[8-11]

N-methyl-D-aspartate receptor antagonists have antidepressant effects in many animal models of depression, including the application of inescapable stressors, forced-swim, and tail suspension–induced immobility tests; in learned helplessness models of depression; and in animals exposed to a chronic mild stress procedure.[12-17] A single dose of the NMDA antagonist ketamine hydrochloride in male Wistar rats interferes with the induction of behavioral despair for up to 10 days after its administration.[18] Additionally, repeated administration of different classes of antidepressants—in a time frame consistent with the delayed therapeutic effects—brings about alterations in the expression of NMDA subunit messenger RNA[19] and radioligand binding to these receptors in regions of the brain implicated in the pathophysiology of depression.[8]

Although clearly not unequivocal, several lines of evidence from diverse studies also suggest that dysfunction of the glutamatergic system may play an important role in the pathophysiology of depression.[20,21] Notably, a recent study by Sanacora et al[22] showed glutamate levels in the occipital cortex to be significantly elevated in 29 medication-free subjects with unipolar major depression as compared with 28 age- and sex-matched healthy controls. Together, these data support the hypothesis of regional alterations in glutamatergic signaling in mood disorders.

Finally, in clinical trials, the glutamatergic modulators lamotrigine and riluzole (both inhibitors of glutamate release) were found to have antidepressant properties.[23-25] Based on the preclinical and preliminary clinical studies, we have postulated that the NMDA receptor complex may mediate the delayed therapeutic effects of traditional monoaminergic-based antidepressants and, furthermore, that directly targeting the NMDA receptor would bring about rapid antidepressant effects. Indeed, in a preliminary study of 8 subjects with major depression, it was reported that a single dose of the noncompetitive NMDA receptor antagonist ketamine resulted in a rapid and short-lived antidepressant effect.[26] Therefore, the objective of the present double-blind trial was to determine if ketamine exerts rapid antidepressant effects in a relatively refractory population and, furthermore, if the effects of a single dose of ketamine are sustained.

METHODS

PATIENT SELECTION

Subjects were recruited from referrals from local inpatient psychiatric units or through advertisements placed in the local newspapers of the Washington, DC, metropolitan area; the Internet; and local and national referrals from physicians. Men and women, aged 18 to 65 years, who were inpatients with a diagnosis of major depressive disorder recurrent without psychotic features as diagnosed by means of the Structured Clinical Interview for Axis I *DSM-IV* Disorders–Patient Version[27] were eligible to participate. Patients with a *DSM-IV* diagnosis of bipolar disorder or who had a history of antidepressant- or substance-induced hypomania or mania were excluded. All subjects were studied at the National Institute of Mental Health Clinical Research Center in Bethesda, Md, between November 2004 and September 2005. Subjects were required to have a score of 18 or higher on the 21-item Hamilton Depression Rating Scale (HDRS)[28] at screening and at the start of ketamine/placebo infusions and to have previously failed at least 2 adequate antidepressant trials (adequacy of antidepressant trials was determined with the Antidepressant Treatment History Form).[29]

All subjects were in good physical health as determined by medical history, physical examination, blood laboratory results, electrocardiogram, chest radiography, and urinalysis and toxicology findings. Subjects were free of comorbid substance abuse or dependence for at least 3 months, had a negative urine toxicology screen, and were judged clinically not to be a serious suicide risk. Comorbid Axis I anxiety disorder diagnoses were permitted if they did not require current treatment. Final selection was made by consensus of the investigator team.

The study was approved by the National Institute of Mental Health institutional review board. All subjects provided written informed consent before entry into the study. Informed consents and ongoing study participation were monitored by the Central Office for Recruitment and Evaluation at the National Institute of Mental Health.

The study was initially planned to include 22 patients; however, interim analysis with the data collected indicated a very large effect even if the remaining data indicated no response.

STUDY DESIGN

Following a 2-week drug-free period, 18 subjects with major depressive disorder (*DSM-IV* criteria) received intravenous infusions of saline solution and 0.5 mg/kg of ketamine hydrochloride (Abbott Laboratories, North Chicago, Ill), 1 week apart, using a randomized, double-blind crossover design. Patients were randomly assigned to the order in which they received the 2 infusions via a random-numbers chart. Study solutions were supplied in identical 50-mL syringes, containing either 0.9% saline or ketamine with the additional volume of saline

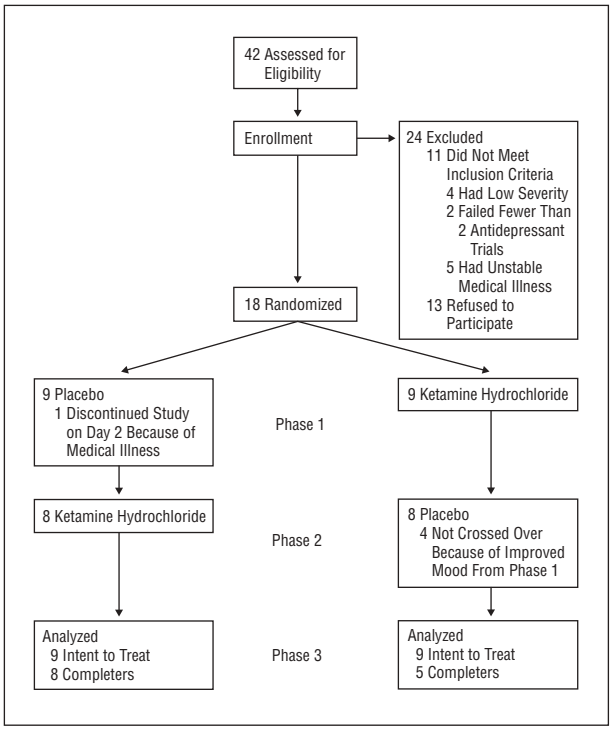

Figure 1. Enrollment, randomization, withdrawals, and completion of the 2 treatment phases (n=18).

to total 50 mL. Ketamine forms a clear solution when dissolved in 0.9% saline. The infusions were administered over 40 minutes via an infusion pump (Baxter, Deerfield, Ill) by an anesthesiologist in the perianesthesia care unit.

OUTCOME MEASURES

Subjects were rated 60 minutes prior to the infusion and at 40, 80, 110, and 230 minutes, as well as 1, 2, 3, and 7 days, after the infusion. Rating scales included the 21-item HDRS, which was the primary outcome measure, and the secondary outcome measures: the Beck Depression Inventory (BDI),[30] Brief Psychiatric Rating Scale (BPRS) positive symptoms subscale,[31] Young Mania Rating Scale (YMRS),[32] and the visual analog scale.[33] Raters (research nurses, a physician, and a psychologist), who trained together to establish reliability, performed patient ratings. High interrater reliability for the HDRS (intraclass correlation coefficient=0.81) and the YMRS (intraclass correlation coefficient=0.91) were obtained. Clinical response was defined as a 50% or greater decrease in the HDRS score from baseline and remission was defined as an HDRS score of 7 or lower.[34]

STATISTICAL ANALYSES

A fixed-effects linear mixed model was used to examine the differences between ketamine and placebo treatment over 9 points from baseline to 7 days. A compound symmetry covariance structure appeared to be the best fit to the data. Restricted maximum likelihood estimation was used to analyze incomplete data. Significant effects were examined with simple effects tests. The Cohen d shows the size of effect for the ketamine-placebo difference at the indicated points. Secondary analysis included examination of the individual items of the HDRS. Significance was evaluated at $P<.05$, 2-tailed. Following the Shapiro-Wilk test and visual examination of the data, no cells deviated substantially from normality.

Three sets of linear mixed models were run to fully understand the influence of the active treatment. One set of analysis included only those who completed both phases of the study (completers analysis). Subjects who did not receive both treatment conditions were not included in this analysis. A second set included all available data (intent-to-treat analysis). A third set of statistics was performed on the first test condition only. In this case, the drug effect was a between-subjects factor instead of a within-subjects factor. Secondary analysis of individual items was performed only with completers.

To evaluate the proportion of responders and remitters at each point, a McNemar test was used at each point for the completers and the results were Bonferroni corrected for the number of points examined.

Carryover was examined using a linear mixed model with the same structures as the primary analysis where drug was a within-subjects factor, treatment order was a between-subjects factor, and only the baseline measure for each phase was used. The intent-to-treat sample was used for this analysis since baseline data for both phases were available.

RESULTS

PATIENTS

Forty-two subjects were screened, of which 18 subjects who met *DSM-IV-TR* criteria for major depressive disorder with a major depressive episode were randomized. Twenty-four subjects were excluded as they did not meet inclusion/exclusion criteria (n=11) or refused to participate (n=13) (**Figure 1**). Seventeen subjects received ketamine and 14 received placebo. Four subjects did not receive placebo after ketamine infusion because they maintained a response for 7 days and 1 subject discontinued the study for medical reasons after a placebo infusion (Figure 1).

Subjects' demographic and clinical characteristics are summarized in the **Table**. There were 12 women and 6 men, and the mean±SD age was 46.7±11.2 years. Sixty-one percent had a lifetime comorbid anxiety diagnosis; 39%, a lifetime diagnosis of any substance abuse or dependence; and 28%, a lifetime diagnosis of alcohol abuse or dependence. The mean±SD length of illness was 23.7±12.5 years, the mean±SD duration of the current depressive episode was 33.6±37.4 months, and the mean±SD number of lifetime episodes of depression was 6.6±4.7. The mean±SD number of lifetime antidepressant trials (not including augmentation trials) was 5.7±3.4, and 4 subjects had previously received electroconvulsive therapy. All subjects except for 1 had failed an adequate antidepressant trial for the current major depressive episode.

EFFICACY

Using only those who completed both phases of the study, the linear mixed model with the HDRS showed significant main effects for drug ($F_{1,203}=58.24$; $P<.001$) and time ($F_{8,203}=9.48$; $P<.001$) and an interaction between drug and time ($F_{8,203}=4.15$; $P<.001$). Simple effects tests indicated significant improvement for ketamine over placebo at 110 minutes through 7 days. The effect size for the drug difference was very large (d=1.46 [95% confidence interval,

Table. Demographic and Clinical Characteristics

Participant/ Sex/Age, y	Length of Illness, y	Current Episode, mo	No. of Previous Episodes	Failed Medication and Somatic Treatments*	Lifetime Diagnosis of Any Substance Abuse or Dependence†	Lifetime Diagnosis of Alcohol Abuse or Dependence	Peak Change in BPRS[31] Positive Symptoms Subscale Score While Taking Ketamine Hydrochloride	% Change in HDRS Score (Day 1)‡	
								Ketamine	Placebo
1/F/43	24	4	10	SSRI (2); MAOI; AAP (2); BZD (3)	No	No	+9	–90	NA
2/M/46	29	144	2	SSRI (3); SNRI; BUP; OAD (4); AAP; LAM; stimulant; BZD	No	No	+2	–85	–15
3/F/35	20	11	20	SSRI; BUP; TCA; OAD (2); AAP; LAM; BZD (3)	Yes	No	+5	–78	NA
4/F/43	24	24	4	SSRI (3); SNRI; BUP; OAD (2); lithium; LAM; stimulant (2)	No	No	+7	–78	+11
5/F/45	27	9	1	SSRI (3); BZD	Yes	Yes	–1	–74	+14
6/F/56	38	24	10	SSRI (3); BUP; TCA (2); VPA; BZD (2)	Yes	Yes	+7	–64	–18
7/F/57	44	60	9	SSRI (3); BUP; MAOI; OAD (2); AAP (3); lithium; LAM; stimulant; BZD (3); ECT	Yes	Yes	+3	–61	0
8/F/19	3	8	4	SSRI (3); BUP; stimulant	No	No	0	–57	–27
9/F/48	33	60	9	SSRI (4); BUP; OAD; VPA; stimulant; BZD	Yes	No	+8	–55	NA
10/M/45	14	1	6	SSRI (4); TCA; OAD (3); stimulant; BZD (3); ECT	Yes	Yes	+2	–54	+25
11/M/28	16	17	4	SSRI (2); SNRI; TCA; OAD; AAP (2); lithium; LAM; BZD (3)	No	No	–1	–50	–41
12/F/46	13	4	9	SSRI (2); BUP; TCA (2)	No	No	+6	–50	0
13/M/55	22	4	9	SSRI (2); BUP; AAP; lithium; BZD (2)	No	No	–2	–39	NA
14/F/62	6	12	4	SSRI (3); OAD (2); BZD	No	No	+3	–39	–10
15/F/60	47	55	3	SSRI (2); TCA; BZD (2)	No	No	+1	–36	–26

(*continued*)

0.91-2.01]) after 24 hours and moderate to large (d=0.68 [95% confidence interval, 0.13-1.23]) after 1 week. The percentage change in HDRS scores from baseline to day 1 for each subject is listed in the Table. **Figure 2** shows the generalized least squares means and standard errors for the completer analysis. The intent-to-treat analysis had similar effects (drug, $F_{1,260}=34.08$; $P<.001$; time, $F_{8,257}=8.92$; $P<.001$; drug × time, $F_{8,257}=5.29$; $P<.001$). Notably, participants receiving ketamine were better than those receiving placebo within 2 hours (110 minutes) and remained better through 7 days (Figure 2).

Looking at possible carryover effects with the intent-to-treat sample, a linear mixed model looking at the baseline measures showed a significant main effect for drug ($F_{1,16}=6.25$; $P=.02$) and a significant interaction ($F_{1,16}=5.05$; $P=.04$) but no main effect for order ($F_{1,16}=1.54$; $P=.23$). Participants who received placebo first had similar baseline measures for the first and second phases (mean±SD HDRS score, 24.4±6.9 vs 24.9±6.8) ($F_{1,16}=0.03$; $P=.86$), but those who received ketamine first had much lower baseline measures in the second phase (mean±SD HDRS score, 24.9±6.9 vs 17.2±6.9) ($F_{15}=11.80$; $P=.004$).

To examine data relatively independent of carryover effects, only the first-phase data were used in an additional analysis. Results were similar to those of the completers and intent-to-treat analysis. There were significant main effects for drug ($F_{1,16}=10.44$; $P=.005$) and time ($F_{8,126}=8.25$; $P<.001$) and a significant interaction between drug and time ($F_{1,126}=4.66$; $P<.001$). Scores were

Table. Demographic and Clinical Characteristics (cont)

Participant/ Sex/Age, y	Length of Illness, y	Current Episode, mo	No. of Previous Episodes	Failed Medication and Somatic Treatments‡	Lifetime Diagnosis of Any Substance Abuse or Dependence*	Lifetime Diagnosis of Alcohol Abuse or Dependence	Peak Change in BPRS[31] Positive Symptoms Subscale Score While Taking Ketamine Hydrochloride	% Change in HDRS Score (Day 1)†	
								Ketamine	Placebo
16/M/59	7	84	3	SSRI (2)	No	No	+3	–29	–38
17/M/50	31	60	3	SSRI (4); BUP; TCA (3); MAOI; OAD (7); VPA; stimulant (3); BZD; AAP; lithium; ECT	No	No	+1	–17	–20
18/F/44	29	24	10	SSRI; SNRI; TCA; OAD; AAP; stimulant; ECT	Yes	Yes	NA	NA	+8
All (12 women, 6 men; mean ± SD age, 46.7 ± 11.2 years), mean ± SD§	23.7 ± 12.5	33.6 ± 37.4	6.6 ± 4.7	5.7 ± 3.4‖¶	7 Yes/11 No	5 Yes/13 No	+3.1 ± 3.4	–56.2 ± 20.4	–9.8 ± 20.1

Abbreviations: AAP, atypical antipsychotic; BPRS, Brief Psychiatric Rating Scale; BUP, bupropion; BZD, benzodiazepine; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale; LAM, lamotrigine; MAOI, monoamine oxidase inhibitor; NA, not applicable; OAD, other antidepressants (eg, nefazodone hydrochloride, trazodone hydrochloride, pramipexole dihydrochloride); SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; VPA, valproic acid.

*The numbers in parentheses indicate the number of separate trials for that class of medication.

†Lifetime substance abuse column also includes subjects with lifetime alcohol abuse/dependence.

‡"–" indicates a decrease in HDRS scores (improvement of depression) and "+" indicates an increase in HDRS scores (worsening of depression).

§Unless otherwise indicated.

‖Number of antidepressant trials not including augmentation strategies.

¶All subjects except for 1 had failed an adequate antidepressant trial for the current depressive episode.

lower for participants receiving ketamine by 80 minutes, and the difference remained significant through the seventh day.

Using the completers with the BDI, there were significant main effects for drug ($F_{1,200}=50.57$; $P<.001$) and time ($F_{8,200}=5.82$; $P<.001$) and a trend-level interaction between drug and time ($F_{8,200}=1.90$; $P=.06$). The patient ratings showed that ketamine seemed to improve depression at 40 minutes through 7 days. Additionally, there were significant changes in the visual analog scale depression scores (drug, $F_{1,198}=59.88$; $P<.001$; time, $F_{8,198}=4.70$; $P<.001$; drug × time, $F_{8,198}=1.92$; $P=.058$). Similar to the BDI, ketamine improved mood at 40 minutes through 7 days.

On the individual HDRS symptoms, 7 of 20 symptoms had significant time × drug interactions; loss of insight was not tested since none of the participants had this symptom. Depressed mood, guilt, work and interests, and psychic anxiety improved significantly. The earliest improvements were at 40 minutes for depressed mood and guilt. Depersonalization or derealization was worse from 40 to 110 minutes. Motor retardation and gastrointestinal symptoms were worse at 40 minutes, but at day 1, motor retardation was better for participants receiving ketamine than those receiving placebo. An additional 7 symptoms showed only a significant main effect for drug; symptoms improved for participants receiving ketamine for suicide, insomnia, general somatic symptoms, genital symptoms, and hypochondriasis. At baseline, no symptoms were different between the ketamine and placebo phases.

Figure 3 shows the proportion of responders (Figure 3A) and remitters (Figure 3B) at each point for the intent-to-treat sample. One day after infusion, 12 (71%) of the 17 subjects treated with ketamine met response criteria as compared with 0 (0%) of 14 subjects treated with placebo. Five (29%) of 17 participants receiving ketamine met remission criteria 1 day after infusion, while none (0%) receiving placebo reached remission at the same point. Six subjects (35%) maintained response to ketamine for at least 1 week; 2 of these maintained response at least 2 weeks. By contrast, no subject receiving placebo responded at 1 or 7 days. For completers, McNemar tests showed significantly more responders to ketamine on days 1 and 2, but after Bonferroni correction, only day 1 was significant. The number of remitters was not significant at any point.

The BPRS positive symptoms subscale scores[35] were worse for participants receiving ketamine than those receiving placebo only at 40 minutes (drug, $F_{1,200}=4.23$; $P=.04$; time, $F_{8,200}=9.31$; $P<.001$; drug × time, $F_{8,200}=6.89$; $P<.001$) (Figure 2). Similarly, YMRS scores were worse (higher score) for participants receiving ketamine than those receiving placebo at 40 minutes only, but they were significantly better from days 1 to 2 (drug, $F_{1,201}=3.08$; $P=.08$; time, $F_{8,201}=3.54$; $P<.001$; drug × time, $F_{8,201}=4.68$; $P<.001$) (Figure 2).

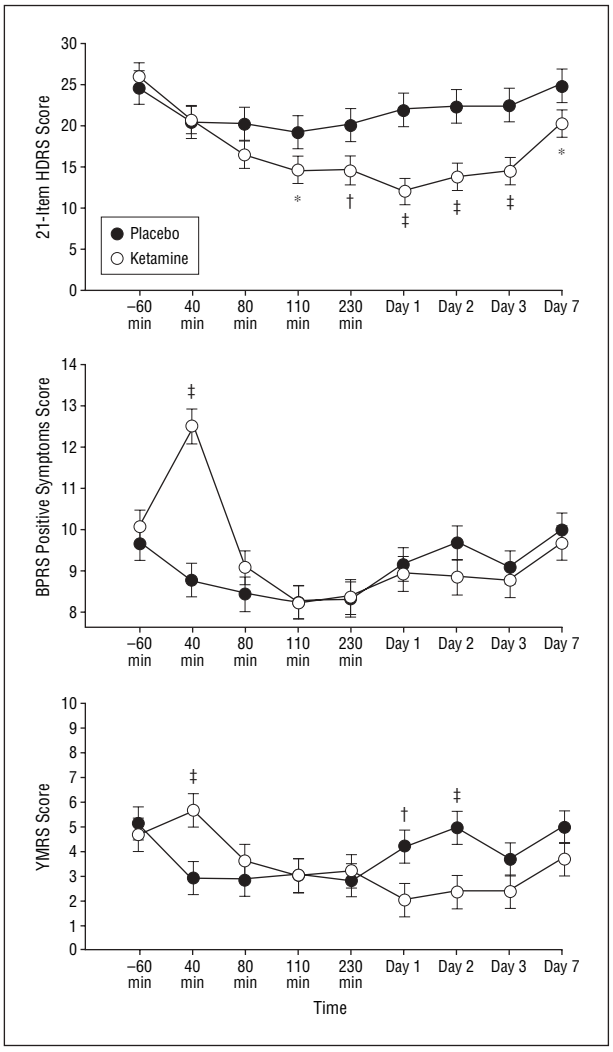

Figure 2. Change in the 21-item Hamilton Depression Rating Scale[28] (HDRS), Brief Psychiatric Rating Scale[31] (BPRS) positive symptoms subscale, and Young Mania Rating Scale[32] (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the completer analysis. * indicates $P<.05$; †, $P<.01$; ‡, $P<.001$.

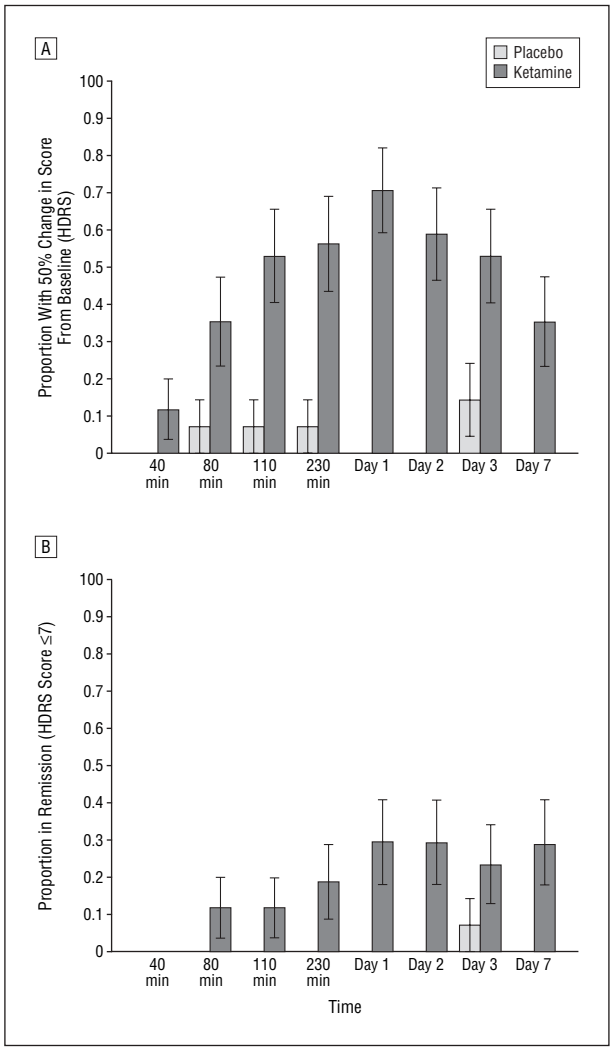

Figure 3. A, Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale[28] [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B, Proportion of remitters (HDRS score ≤7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18).

There was a trend for an inverse relationship between the percentage change in HDRS score at day 1 and the peak percentage change in BPRS positive symptoms subscale score ($r=-0.46$; $P=.06$). None of the other factors listed in the Table predicted a response to ketamine.

ADVERSE EVENTS

Adverse effects occurring more commonly in participants taking ketamine than those taking placebo were perceptual disturbances, confusion, elevations in blood pressure, euphoria, dizziness, and increased libido. Adverse effects occurring more frequently with placebo than ketamine were gastrointestinal distress, increased thirst, headache, metallic taste, and constipation. The majority of these adverse effects ceased within 80 minutes after the infusion. In no case did euphoria or derealization/depersonalization persist beyond 110 minutes (Figure 2). No serious adverse events occurred during the study.

COMMENT

We found a robust, rapid (hours), and relatively sustained (1 week) response to a single dose of the NMDA antagonist ketamine. Improvement in mood ratings for the course of the week was greater with ketamine than placebo; this difference was statistically significant for the 21-item HDRS (from 110 minutes through 7 days) and the self-rated BDI (from 40 minutes through 7 days). To our knowledge, there has never been a report of any other drug or somatic treatment (ie, sleep deprivation, thyrotropin-releasing hormone, antidepressant, dexamethasone, or electroconvulsive therapy)[36-39] that results in such a dramatic rapid and prolonged response with a single administration. In reviews of antidepressant trials in major depression, response rates at week 8 were 62% for bupropion hydrochloride, 63% for selective serotonin reuptake inhibitors, and 65% for venlafaxine.[40,41] In the present study involving treatment-resistant subjects, these response rates were obtained the day after the ketamine infusion.

In contrast to the dramatic effects observed in this study, a previous controlled study did not show the low- to moderate-affinity, noncompetitive NMDA antagonist memantine, administered orally, to have antidepressants effects.[42] While it is likely that higher-affinity NMDA antagonists are necessary for antidepressant effects to occur, intravenous administration may also be an important factor.

Ketamine in contrast to memantine has (1) higher affinity for the NMDA receptor, (2) much slower open-channel blocking/unblocking kinetics, (3) a different type of channel closure (ie, "trapping block" as opposed to "partial trapping" properties),[43] and (4) different NMDA subunit selectivity.[44-46] Such differences might explain the antidepressant properties observed with ketamine in the present trial.

When comparing our results with the preliminary study by Berman et al,[26] we confirmed the finding of rapid antidepressant response with ketamine. The larger sample size of our study permitted us to obtain additional information regarding the time of onset, course of response, and degree of improvement with ketamine. Compared with the previous study, we were able to (1) detect an earlier onset of antidepressant effect after infusion (110 minutes by objective ratings and 40 minutes by self-report, postinfusion, vs 230 minutes); (2) find a more prolonged antidepressant effect of ketamine, which remained significant up to 7 days postinfusion (the previous study collected ratings only until day 3); and (3) better characterize the magnitude of response and remission obtained over the course of 7 days. The Berman et al study group[26] reported that 4 of 8 patients obtained 50% or greater decreases in HDRS score during the 3-day follow-up period. In our study, we found 71% response and 29% remission rates on day 1 (Figure 2 and Figure 3), and 35% of subjects were able to maintain response for at least 1 week. The relatively prolonged antidepressant effect that occurred with ketamine (about 1 week) is remarkable considering its short half-life, which is approximately 2 hours for ketamine[47] and 5 hours for norketamine; the latter metabolite is 7 to 10 times less potent than ketamine.[48] Blood levels of ketamine or its metabolites were not collected in this study. As a result, this study cannot rule out the possibility that differences in drug metabolism may have contributed in part to the current findings.

Although these results are provocative, they may not be generalizable to all populations with depression. The subjects in this study were a refractory subgroup who were relatively late in their course of illness (Table), and as such, their neurobiology and pharmacological responses may be different from those with a less severe or shorter course of illness.

Several factors need to be considered in interpreting these data. Although the sample size was relatively small, 3 different types of analysis showed the significance of ketamine over placebo, and the effect sizes of this study were very large at day 1 and moderate to large at day 7. Consistent with all of the published randomized, placebo-controlled studies with ketamine, we also found short-lived perceptual disturbances[26,49,50]; such symptoms could have affected study blind. Hence, limitations in preserving study blind may have biased patient reporting by diminishing placebo effects, thereby potentially confounding results. One potential study design in future studies with ketamine might be to include an active comparator such as intravenous amphetamine (a dopamine agonist), which also produces psychotogenic effects.[51]

However, the time of onset and course of antidepressant response (relatively prolonged) after receiving only 1 dose of ketamine was nearly identical for each subject; this pattern suggests that there was indeed a true drug effect. The improvement associated with ketamine infusion reflects a lessening of core symptoms of depression and is disconnected from ketamine-induced euphoria and psychotomimetic symptoms. In support, the antidepressant effect of ketamine became significant on the HDRS at 110 minutes after a return of BPRS positive symptoms subscale scores and YMRS scores to baseline (Figure 2). However, although BPRS positive symptoms subscale scores returned to baseline within 110 minutes, the change in BPRS positive symptoms subscale scores from baseline to the 110-minute point trended to predict a greater percentage change (decrease) in HDRS scores at day 1. As a result, future research should explore a wider range of ketamine doses and rates of administration and determine if the presence or intensity of euphoric or psychomimetic effects are necessary for rapid antidepressant effects to occur. The dose of 0.5 mg/kg chosen for the present study is reported to be sufficient to test the validity of the concept of the NMDA receptor antagonism with ketamine. The dose of ketamine used in our study was based on (1) in vitro data of NMDA blockade, (2) its mood-enhancing effects in healthy volunteers, and (3) its antidepressant effects in a pilot study of patients with major depression.[26,50]

While ketamine is believed to be relatively selective for NMDA receptors, the possibility that these intriguing results are mediated by interactions with other receptors cannot entirely be ruled out.[52] However, ketamine binds to the NMDA receptor with an affinity that is several-fold higher than that for other sites,[53-56] and behaviors induced by NMDA receptor antagonists are not blocked by opiate, cholinergic, or monoamine receptor antagonists,[57] providing indirect evidence that ketamine's behavioral effects are mediated by its interaction with the phenylcyclidine site. In vitro studies have found that ketamine only reduces non-NMDA voltage-gated potassium currents at much higher than reported in patients anesthetized with ketamine.[58] This suggests that low doses of ketamine enhance selectivity for the phenylcyclidine site. Nevertheless, more selective NMDA antagonists will need to be tested in patients with major depression. Several NR2B subunit–selective antagonists are currently being developed for ischemic brain injury.[59]

In conclusion, the results of the present study support the hypothesis that directly targeting the NMDA receptor complex may bring about rapid and relatively sustained antidepressant effects. This line of research holds considerable promise for developing new treatments for depression with the potential to alleviate much of the morbidity and mortality associated with the delayed onset of action of traditional antidepressants. Future studies need to be carried out in an attempt to develop strategies for

maintaining the rapid antidepressant response obtained with ketamine long-term.

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