Effect of Baseline Anxious Depression on Initial and Sustained Antidepressant Response to Ketamine

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ABSTRACT

Objective: Patients with anxious depression are typically more difficult to treat with monoaminergic antidepressants compared to those with nonanxious depression. Although novel research has shown that the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine has rapidly acting, relatively sustained effects in treating depression, we predicted that, consistent with the existent literature on traditional antidepressants, patients with anxious depression would have a poorer antidepressant response.

Method: Twenty-six inpatients with treatment-resistant major depressive disorder (MDD) (*DSM-IV* criteria) received a single infusion of ketamine (0.5 mg/kg over 40 minutes) from January 2006–March 2013 and were followed for 28 days. A post hoc analysis compared treatment response and relapse using the Montgomery-Asberg Depression Rating Scale (MADRS) in patients with anxious versus nonanxious depression. Anxious depression was defined as MDD plus a Hamilton Depression Rating Scale anxiety/somatization factor score ≥ 7.

Results: Both anxious and nonanxious depressed patients responded positively to ketamine. A linear mixed model controlling for baseline with the MADRS revealed a significant group main effect ($P = .03$) and group-by-time interaction ($P = .01$). Post hoc tests indicated that patients with anxious depression had significantly fewer depression symptoms compared to those with nonanxious depression at days 1 through 5, 9 through 12, 15 through 17, and 25, with no significant group differences in dissociative ($P = .62$) or psychotic ($P = .41$) side effects. Regarding responders, patients with anxious depression relapsed significantly later than those with nonanxious depression (median ± SE = 19.0 ± 17.9 vs 1.0 ± 0.0 days to relapse, respectively; $\chi^2 = 9.30$; $P = .002$).

Conclusions: Unexpectedly, patients with anxious depression responded better to ketamine than those with nonanxious depression, with longer time to relapse and no side effect differences. This finding gives promise for the role of novel glutamatergic medications for the treatment of those with anxious depression, a traditionally difficult-to-treat subgroup of depressed patients.

Trial Registration: ClinicalTrials.gov identifier: NCT00088699

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Dimensionally defined anxious depression captures common symptoms of anxiety within depression, but does not necessarily require the diagnosis of an anxiety disorder. Defined in this fashion, dimensional anxious depression is clinically relevant, accounting for approximately 50% of patients with unipolar major depressive disorder (MDD).[1,2] Indeed, increasing importance for recognizing anxious symptoms within a primary diagnosis of depression is evidenced by the recent addition of an anxious distress specifier for MDD in the *Diagnostic and Statistical Manual for Mental Disorders*, Fifth Edition (*DSM-5*).[3]

Although anxious depression has a unique clinical profile compared to other subtypes of depression,[4] some,[2,5–8] but not all,[9–13] studies have shown that it is less likely to respond to traditional (ie, monoaminergic) antidepressants and cognitive therapy. The heterogeneity of *anxious depression* definitions throughout the literature may explain such inconsistencies, making comparisons across various studies difficult.[14] Nonetheless, even when response and remission are achieved in treating patients with anxious depression with traditional antidepressants and cognitive therapy, these effects are often not sustained.[2,7,8,15,16] Moreover, several studies suggest that baseline anxious depression may put patients at greater risk of side effect burden.[2,8,15,17,18]

Of important note, previous treatment studies have focused on the use of monoaminergic antidepressants. However, new literature has emerged that implicates the importance of the glutamatergic system for treating depression.[19] In particular, ketamine, a noncompetitive glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been found to have rapid, robust, and relatively sustained antidepressant effects[20–23] and is safe for use at subanesthetic levels in selected clinical psychiatric research settings.[24]

Despite the high prevalence of anxious depression, there is a dearth of literature examining ketamine's antidepressant effect on this specific patient population. As reviewed above, given that patients with dimensional anxious depression may be more difficult to treat with traditional monoaminergic antidepressants, with longer time to response, shorter time to relapse, and greater risk for side effect burden, we hypothesized that they would demonstrate poorer treatment outcomes over the course of a month when given the novel glutamatergic antidepressant ketamine.

METHOD

Patient Selection

Following approval by the Combined Neuroscience Institutional Review Board of the National Institutes of Health,

Clinical Points

- Patients with anxious depression are often more difficult to treat than those with nonanxious depression when using traditional antidepressants.
- Treatment-resistant patients with anxious depression responded better to a single infusion of the novel antidepressant ketamine compared to those with nonanxious depression, as demonstrated by lower depression scores and longer time to relapse, with no differences in side effect profiles.

adult men and women aged 18–65 years were admitted between January 2006 and March 2013 to the inpatient mood disorders unit at the Clinical Research Center of the National Institute of Mental Health (NIMH) in Bethesda, Maryland (ClinicalTrials.gov identifier: NCT00088699). Recruitment was conducted via advertisements in local newspapers, local inpatient psychiatric units, nationwide physician referrals, and Internet sources. All patients provided written informed consent and were assigned a clinical research advocate from the NIMH Human Subjects Protection Unit to monitor the consent process and research participation for the duration of the study. All patients had a current diagnosis of treatment-resistant MDD without psychotic features based on *DSM-IV* criteria, lasting at least 4 weeks in duration, as confirmed by both clinician interview and the Structured Clinical Interview for Axis I *DSM-IV* Disorders–Patient Version (SCID-P).[25] Treatment resistance was defined as failure of at least 2 adequate antidepressant trials, as guided by the modified antidepressant treatment history form.[26]

Prior to entering the study, all patients were in good physical health as determined by extensive medical history, physical examination, laboratory assessment, electrocardiogram, urinalysis, and toxicology screening. Comorbid Axis I anxiety disorders were permitted, insofar as they were not the primary focus of treatment for the 12 months prior to screening. The following anxiety disorders were permitted as secondary psychiatric diagnoses: generalized anxiety disorder, panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder, social phobia, and anxiety disorder not otherwise specified. All patients had a total score ≥ 22 on the Montgomery-Asberg Depression Rating Scale (MADRS)[27] at both admission and baseline (defined as 60 minutes prior to ketamine infusion), indicating at least moderate depression, with no greater than a 25% decrease in MADRS total score between the 2 time points. Exclusion criteria included patients with a comorbid substance abuse or dependence disorder (excluding caffeine or nicotine) in the 3 months prior to screening, positive urine toxicology screen, history of antidepressant-induced or substance-induced hypomania or mania, serious unstable medical disorders or conditions, or concomitant treatment with psychotropic medications or electroconvulsive therapy in the 2 weeks prior to ketamine infusion (5 weeks for fluoxetine). Women could not be pregnant or nursing. In addition, patients could not have prior use of ketamine, riluzole, or phencyclidine.

Study Design and Sample Size

Patients (N = 51) received a single open-label intravenous infusion of a subanesthetic dose of ketamine hydrochloride (0.5 mg/kg) delivered over 40 minutes. Six hours following the infusion, patients were randomized in a double-blind fashion to either riluzole or placebo in an effort to assess the safety and efficacy of add-on riluzole to ketamine following a single infusion of ketamine. Overall results from this study have been previously published.[28] Since this study, additional subjects were recruited. Here, however, we report only the results of patients randomized to placebo (up to 28 days postinfusion; N = 26). This was done in order to examine response to ketamine only, as a way of eliminating possible confounding effects of riluzole on ratings of anxiety and depression.

Anxious Depression Definition

Patients were divided into anxious (n = 15) and nonanxious (n = 11) depression. Anxious depression was defined as a baseline score (60 minutes prior to ketamine infusion) ≥ 7 on the Hamilton Depression Rating Scale (HDRS) anxiety somatization factor score, plus a current *DSM-IV* diagnosis of MDD. This factor score, derived from a factor analysis of the HDRS,[29] has been deemed useful for systematically monitoring anxious features of depression in both clinical and research settings, making it a valuable tool for translating research findings into clinical practice.[30] Additionally, several analyses from the large real-world Sequenced Treatment Alternatives to Relieve Depression study employed this definition for anxious depression, finding it useful for distinguishing anxious and nonanxious patients in terms of clinical differences, sociodemographic variables, and treatment outcomes.[1,2,4]

Main Outcome Measures

Patients were rated at baseline (60 minutes prior to ketamine infusion); at 40, 80, 120, and 230 minutes postinfusion; and daily for the 28 days following the infusion. Rating scales utilized included the MADRS[27] and the HDRS.[31] The Hamilton Anxiety Rating Scale (HARS)[32] was also obtained at baseline, at 230 minutes postinfusion, and on days 1, 3, 7, 14, 21, and 28. Ratings were completed by research nurses and a psychologist who trained together to establish reliability. High interrater reliability was established for all 3 scales: MADRS (intraclass correlation coefficient [ICC] = 0.90), HDRS (ICC = 0.75), and HARS (ICC = 0.86). In most cases, the same rater stayed consistent for each individual patient throughout the study. Response was defined as ≥ 50% decrease in total MADRS score. Relapse was defined as < 25% improvement from baseline for at least 2 consecutive days after reaching response. Time to relapse was counted from the first day of the consecutive relapse days, making the minimum time to relapse 1 day.

Psychotomimetic and dissociative symptoms were measured using the Brief Psychiatric Rating Scale (BPRS)[33] and the Clinician Administered Dissociative States Scale (CADSS),[34] respectively.

Table 1. Demographic and Illness Characteristics in Anxious and Nonanxious Depressed Patients

	Total (N = 26)		Anxious Depression (n = 15)		Nonanxious Depression (n = 11)		
Characteristic	n	%	n	%	n	%	*P* (2-tailed)
Gender (female)	9	34.6	5	33.3	4	36.3	.87
Unemployed	19	73.1	11	73.3	8	72.7	.46
Education (completed college)	20	76.9	11	73.3	9	81.8	.94
Lifetime diagnosis of anxiety disorder	15	57.7	10	66.7	5	45.5	.2
Family history mood disorder	20	76.9	12	80.0	8	72.7	.66
	Mean	SD	Mean	SD	Mean	SD	*P* (2-tailed)
Age, y	49.4	12.6	46.8	12.9	53.0	12.2	.23
Age at onset, y	21.3	13.0	19.3	12.1	23.9	14.3	.39
Length of illness, y	28.5	14.1	27.7	11.7	29.5	17.4	.77
Length of current depressive episode, mo	97.4	139.3	111.6	161.0	78.1	107.4	.56
Total lifetime antidepressant trials	8.2	4.4	8.6	5.1	7.5	3.3	.55
No. of previous episodes	14.1	32.0	15.9	35.2	11.9	28.9	.76
Suicide attempts	0.6	1.3	0.8	1.6	0.3	0.7	.31
Hospital admissions	1.7	1.5	1.6	1.4	1.8	1.8	.73
MADRS score (baseline)	33.5	5.6	33.8	6.1	32.7	5.1	.64
HDRS score (baseline)	21.3	4.3	22.5	4.9	19.6	2.8	.09
HDRS anxiety somatization factor score (baseline)	6.9	1.9	8.0	1.6	5.4	0.9	<.001*
HARS score (baseline)	21.2	3.4	22.2	3.6	20.0	2.9	.14

Abbreviations: HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale.
Symbol: * = statistically significant at $P < .05$.

Statistical Analysis

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

Factorial linear mixed models were used to compare the groups over time on measures of depression and anxiety. These models used a compound symmetry covariance structure with restricted maximum likelihood estimation. One set of models included baseline values as a covariate, and a second set included baseline as a separate time point. Bonferroni simple effects tests were used post hoc to examine omnibus effects.

Kaplan-Meier survival analysis was used with a log rank test to compare the time to response and the time to relapse for the groups. Significance was determined at $P < .05$, 2-tailed.

RESULTS

Fifteen (58%) of 26 patients met criteria for anxious depression. Demographic information for patients is shown in Table 1. No significant demographic differences were found between the 2 groups.

Baseline mean MADRS scores did not significantly differ between anxious and nonanxious depressed patients (Table 1; 33.8 ± 6.1 vs 32.7 ± 5.1, respectively; $P = .64$), indicating moderate to severe depression in both groups. Neither baseline total HDRS (22.5 ± 4.9 vs 19.6 ± 2.8, $P = .09$) nor baseline total HARS (22.2 ± 3.6 vs 20.0 ± 2.9, $P = .14$) scores differed between anxious and nonanxious patients, respectively. As expected, baseline HDRS anxiety somatization factor scores significantly differed between anxious and nonanxious depressed patients (8.0 ± 1.6 vs 5.4 ± 0.9, $P < .001$).

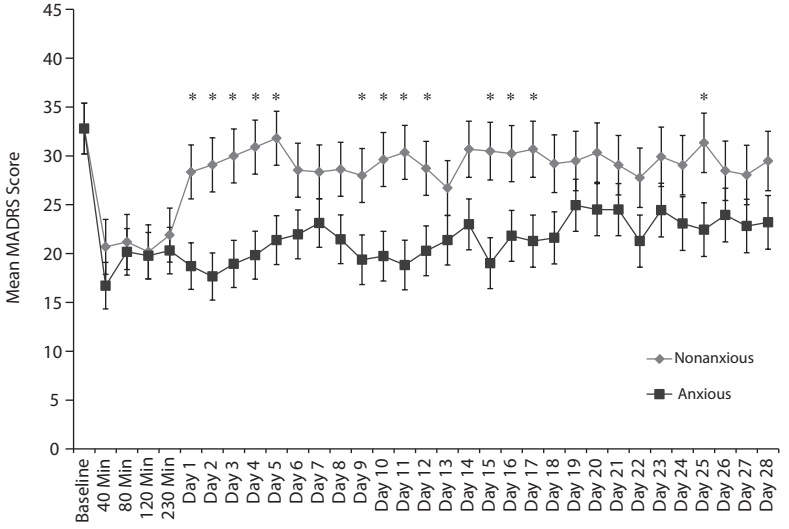
A linear mixed model controlling for baseline with the MADRS revealed a significant group main effect ($F_{1,23} = 5.62$, $P = .03$) and group-by-time interaction ($F_{31,560} = 1.73$, $P = .01$). Post hoc tests indicated that patients with anxious depression had significantly lower depression scores compared to those with nonanxious depression at days 1 through 5, 9 through 12, 15 through 17, and 25 (Figure 1A). The biggest difference was at day 2 when there was a large effect ($d = 0.76$). All significant time points had at least moderate differences ($d > 0.51$). Similar analysis with the HDRS showed a significant main effect of group ($F_{1,23} = 6.80$, $P = .02$), but no significant interaction between group and time ($F_{31,560} = 1.39$, $P = .08$). This result suggested overall less depression during the 28 days following infusion (Figure 1B) in the anxious group. No overall statistically significant difference was found between anxious and nonanxious depressed patients on HARS scores (group: $F_{1,20} = 4.03$, $P = .058$; group by time: $F_{6,95} = 0.67$, $P = .67$; Figure 1C).

A second set of mixed models included baseline as a time point to examine whether each patient group improved from baseline. A priori comparisons at each postbaseline measure were compared to baseline separately for the 2 groups within the context of the full mixed model. Bonferroni comparisons were used to adjust for the number of time points. With the MADRS and HDRS, the anxious group had scores significantly lower than baseline from 40 minutes to day 28 (corrected *P* values < .05). The nonanxious group had scores significantly lower than baseline from 40 to 230 minutes (corrected *P* values < .05), but not at any other subsequent time points (*P* values > .20). For the HARS, the anxious group had significantly less anxiety from 230 minutes through day 28 (*P* values > .007) with the exception of day 14 ($P = .26$), but the nonanxious group had less anxiety at 230 minutes ($P = .004$) and day 1 ($P = .04$) only (other times: *P* values > .52).

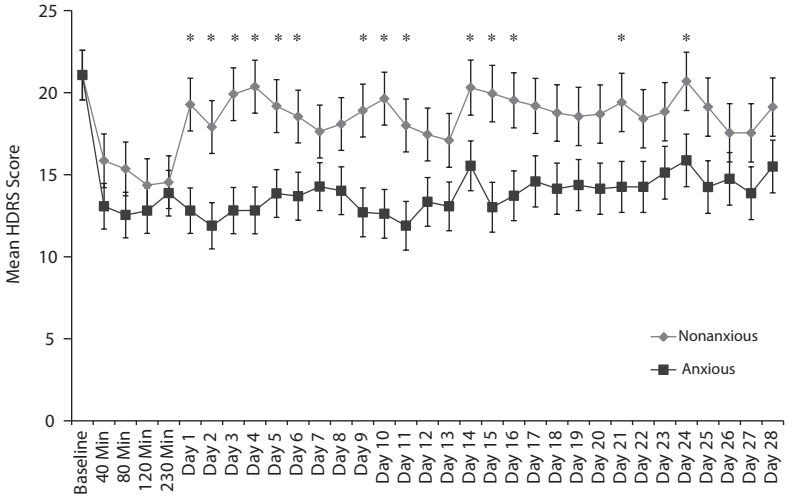
Following the infusion, 18 of 26 patients achieved response, defined as a ≥ 50% decrease in total MADRS

Figure 1. Mean Scores[a] in Anxious Versus Nonanxious Depressed Patients at Baseline Through Day 28 Postinfusion

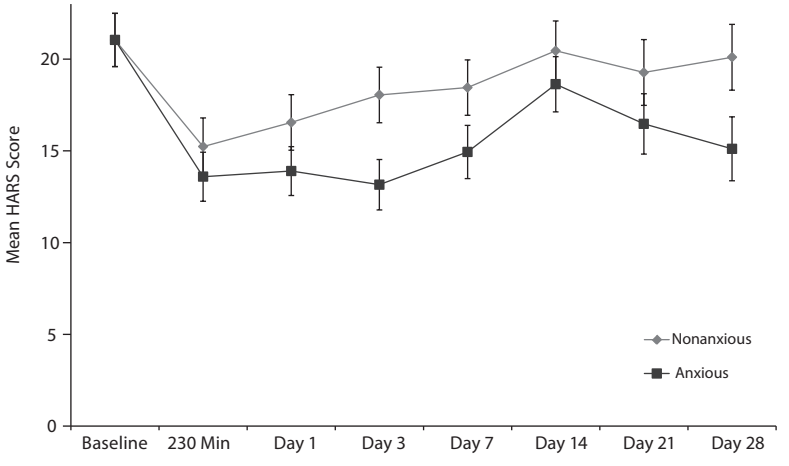
A. Montgomery-Asberg Depression Rating Scale (MADRS)



B. Hamilton Depression Rating Scale (HDRS)



C. Hamilton Anxiety Rating Scale (HARS)



[a]Values covaried for baseline.
Symbol: * = significance at $P \leq .05$.

score. Specifically, 9 of 15 (60%) patients with anxious depression and 9 of 11 (82%) with nonanxious depression met criteria for response at some point during the trial ($\chi^2 = 1.42$; $P = .23$; odds ratio [OR] = 3.00; 95% CI, 0.37–29.38). Anxious and nonanxious patients did not differ in time to response (median ± SE = 120.0 ± 3,250.6 vs 40.0 ± 0.0 minutes, respectively; $\chi^2 = 1.84$; $P = .17$).

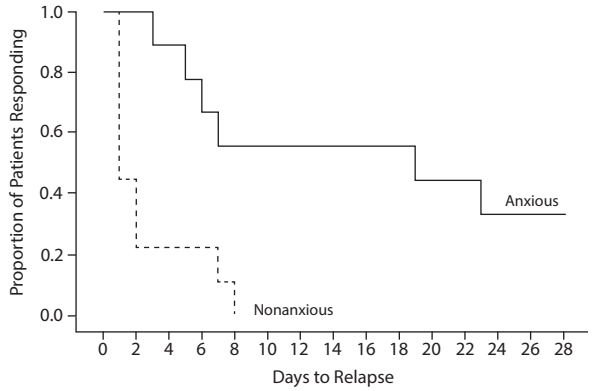
Of the 18 total responders, 15 (83%) relapsed within 4 weeks. Specifically, 6 of 9 (67%) patients with anxious depression and all (100%) of the patients with nonanxious depression met criteria for relapse. The patients with anxious depression relapsed (median ± SE = 19.0 ± 17.9 days) significantly later than those with nonanxious depression (1.0 ± 0.0 days, $\chi^2 = 9.30$, $P = .002$, Figure 2).

To determine whether group differences could be due to side effects, linear mixed models were run with measures of dissociative (CADSS) and psychotic symptoms (BPRS). These models showed no significant main effect of group (CADSS: $F_{1,5} = 0.28$, $P = .62$; BPRS: $F_{1,23} = 0.70$, $P = .41$) or interaction between group and time (CADSS: $F_{22,157} = 0.73$, $P = .80$; BPRS: $F_{9,183} = 1.16$, $P = .32$). Thus, there was no difference in these side effects by anxious depressive grouping.

DISCUSSION

In this post hoc investigation of unmedicated patients with treatment-resistant MDD, we provide evidence that patients with dimensionally defined anxious depression had significantly lower scores on depression scales, exhibited similar time to response, and had longer time to relapse compared to patients with nonanxious depression in the 28 days following a single infusion of the glutamatergic NMDA-receptor antagonist ketamine. Although both groups of depressed patients showed improvements in depressive symptoms following ketamine administration with similar time to response, those with anxious depression had significantly greater improvements in depression symptoms compared to their nonanxious counterparts starting at day 1 postinfusion, an improvement that remained relatively sustained, as evidenced by MADRS and HDRS results. In addition, those with anxious depression took significantly longer to relapse based on MADRS scores. Furthermore, no differences in dissociative or psychotic side effects were found between those with anxious and nonanxious depression. The results differ from previous antidepressant research with

Figure 2. Kaplan-Meier Survival Curves for Unipolar Depressed Patients Following a Single Infusion of Ketamine[a]



[a]Day to relapse based on MADRS scores. Median ± SE day on which patients with anxious depression relapsed (19.0 ± 17.9 days) was significantly longer than the median ± SE day on which patients with nonanxious depression relapsed (1.0 ± 0.0 days, $\chi^2 = 9.30$, $P = .002$).

monoaminergic and therapy-based treatments that implicate anxious depression as a more difficult-to-treat subtype of depression.[2,7,8,15,16]

Interestingly, ketamine initially improved anxiety symptoms as measured by the HARS at 230 minutes postinfusion, regardless of anxiety status. Similarly, the HDRS anxiety somatization factor score has been shown to improve following ketamine administration in adults with treatment-resistant depression, both with and without high levels of suicidal ideation (as delineated by a baseline score >3 on the Scale for Suicidal Ideation).[35] In addition, one 28-day trial of open-label oral ketamine for hospice patients with depression and anxiety symptoms (based on ratings from the Hospital Anxiety and Depression Scale) showed a significant decrease in depression and anxiety symptoms that led to improved quality of life.[36] Given that there were no overall significant group differences in anxiety scores between the 2 cohorts in our current study, but there were significant group differences in depression scores, baseline anxious depression might represent a clinically relevant subtype of major depression that may serve as a useful clinical biomarker for predicting greater postketamine improvements in depressive, but not anxious, symptoms.

Of important note, the original ketamine study from which these data were extracted did not show a difference between the riluzole or placebo groups with regard to antidepressant response for 28 days following a single ketamine infusion.[28] All patients in this study were treated as a homogenous group of depressed patients, as is often the case with research concerning drug discovery and development. Here, however, we report on separation within the placebo group when depressed patients are dichotomized into anxious versus nonanxious subtypes. For further information, see Supplementary Material. This, again, speaks for the importance of subtyping in psychiatry. Indeed, in order to properly explore the usefulness of subtyping within psychiatric disorders, as well as the discovery of clinical predictors of response to current and experimental medications, further prospective research is imperative.[37]

The exact reason for this superior antidepressant response to ketamine in the anxious depression group remains unclear. A recent preclinical study showed that repeated ketamine administration (20 mg/kg injected twice daily) for 15 days in male adolescent rats resulted in sustained antidepressant and anxiolytic responses for at least 2 months following exposure,[38] suggesting that ketamine treatment results in an enduring resilient/stress-resistant phenotype. In addition, male rats that received an intraperitoneal injection of ketamine 50 mg had antidepressant and anxiolytic-like effects (as evidenced by increased entries into an elevated-plus maze, an anxiety-inducing experience for rodents).[39] On a cellular and molecular level, the release of local translation of brain-derived neurotrophic factor (BDNF),[40] increased mammalian target of rapamycin (mTOR) phosphorylation,[41,42] glycogen synthase kinase-3 (GSK-3) inhibition,[43] and increased α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) to NMDA receptor throughput[44–47] are necessary and/or sufficient for ketamine's antidepressant-like efficacy in rodent models of despair. Additionally, increased peripheral mTOR phosphorylation correlated with ketamine's antidepressant time course in a single patient with treatment-resistant major depression.[48] However, it is unknown if these molecular mechanisms are relevant to the augmented antidepressant response in treatment-resistant dimensional anxious depression versus nonanxious depression, which is a critical need for future investigation. Indeed, both preclinical and clinical evidence is building for the potential usefulness of treating depressed and anxious patients with novel glutamatergic therapies such as ketamine.

Several important limitations deserve attention. First, this was a post hoc examination of a relatively small dataset of 26 patients. Second, ketamine was administered open-label. All patients were randomized in a double-blind fashion to either placebo or riluzole as part of a larger treatment trial; here, we only report results of those randomized to placebo. As such, we cannot rule out the possibility of placebo effect on the results. Third, all patients were considered "treatment resistant" and were required to have failed at least 2 adequate trials of antidepressants, drawing into question the generalizability of these results to patients with MDD as a whole. Fourth, the HDRS anxiety somatization factor score is only one way of defining anxious depression dimensionally.[14] However, this score has been deemed useful for both clinical and research purposes, justifying its use as a way of subtyping depressed patients into anxious and nonanxious groups.[30] Fifth, the concept of nonanxious depression may be somewhat of a misnomer, as patients who do not meet threshold criteria for dimensional anxious depression can still, in fact, have symptoms of anxiety. Finally, despite previous reports that anxious and nonanxious depressed patients differ clinically,[1,4,17] our results did not show significant clinical differences between the 2 groups. This discrepancy may be due to low power (previous reports all had much larger sample sizes) or greater treatment refractoriness of patients in our study.

In conclusion, our results indicate that patients with anxious depression respond better to ketamine than those with nonanxious depression with regard to depressive symptoms. In addition, responders with anxious depression have more durable improvements with longer time to relapse compared to nonanxious responders. The rapid antidepressant onset of ketamine is intriguing, as treatment with standard antidepressants can take weeks to induce significant effects. In addition, patients with anxious depression generally take longer to respond, if at all, to traditional antidepressants, though we did not find this to be the case following ketamine administration. This decreased response time following ketamine may have large implications in restoring patients' functioning and decreasing disease burden. In light of these findings, the need for larger hypothesis-driven studies, replication projects, and a priori research examining treatment differences between anxious and nonanxious depressed patients must be underscored. Given the high prevalence of anxiety within depression, and calls for future explorations of the impact of anxiety within depression in ketamine use,[49] further studies are critical. In addition, future projects focused on non–treatment-resistant patients may provide valuable insights into the general usefulness of glutamatergic medications for the treatment of anxious depression. Nevertheless, patients with anxious depression demonstrated a rapid antidepressant effect following the administration of the novel antidepressant ketamine, providing treatment hope for this traditionally difficult-to-treat population.

Drug names: fluoxetine (Prozac and others), ketamine (Ketalar and others), riluzole (Rilutek and others).

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Potential conflicts of interest: **Dr Zarate** is listed as a coinventor on a patent application for the use of ketamine and its metabolites in major depression. Dr Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government. **Drs Ionescu**, **Niciu**, **Richards**, and **Vande Voort**; **Mr Luckenbaugh**; and **Mss Slonena** and **Brutsche** report no conflicts of interest related to the subject of this article.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Effect of Baseline Anxious Depression on Initial and Sustained Antidepressant Response to Ketamine

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List of Supplementary Material for the article

1. Supplementary Material

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Material

In order to examine the extent to which anxious status predicted response among all depressed patients (regardless of whether they were randomized to riluzole or placebo; *n*=52)*, further analyses were completed at day 1 (the day of randomization to riluzole or placebo) through day 28 following a single ketamine infusion. Testing revealed an overall drug x anxiety status interaction (*p*=.044). In the placebo group, patients with anxious depression had significantly lower mean MADRS scores compared to those with nonanxious depression (21.8 *vs* 29.7, respectively; p=.01), a result consistent with our original results. However, in the riluzole group, patients with anxious depression were not significantly different from those with nonanxious depression (25.8 *vs* 24.3, respectively; *p*=.66). Further, the interaction between drug, anxiety status, and time was not significant (p=.75). Therefore, the effect of riluzole following ketamine did not appear to be influenced by anxiety grouping.

*Note, since the initial analyses from the original article, 1 additional participant was recruited into the study, for a total sample size of 52. This additional patient was randomized to riluzole following a single infusion of ketamine, and therefore would not have been included in the analysis of the placebo group that was the focus of the main article."