Clinical Predictors of Ketamine Response in Treatment-Resistant Major Depression

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ABSTRACT

Objective: The *N*-methyl-D-aspartate receptor antagonist ketamine has rapid antidepressant effects in treatment-resistant major depressive disorder (MDD) and bipolar depression. Clinical predictors may identify those more likely to benefit from ketamine within clinically heterogeneous populations.

Method: Data were analyzed from 4 studies of treatment-resistant inpatients with *DSM-IV-TR*–diagnosed MDD or bipolar I or II depression. Patients who were currently experiencing a moderate-to-severe major depressive episode were enrolled between November 2004 and March 2013. All subjects received a single subanesthetic (0.5 mg/kg) ketamine infusion over 40 minutes. Patients were analyzed at the 230-minute postinfusion time point (n = 108), at day 1 (n = 82), and at day 7 (n = 71). Univariate Pearson correlations were performed for each variable with percent change from baseline in the 17-item Hamilton Depression Rating Scale (HDRS). Multivariate linear regression was then conducted for statistically significant predictors ($P \leq .05$, 2-tailed).

Results: Higher body mass index correlated with greater HDRS improvement at 230 minutes (standardized $\beta = -0.30$, $P = .004$) and at day 1 (standardized $\beta = -0.37$, $P = .001$), but not at day 7 (standardized $\beta = -0.18$, $P = .10$). Family history of an alcohol use disorder in a first-degree relative was associated with greater HDRS improvement at day 1 (standardized $\beta = -0.27$, $P = .014$) and day 7 (standardized $\beta = -0.41$, $P < .001$). No prior history of suicide attempt(s) was associated with greater improvement only at day 7 (standardized $\beta = 0.28$, $P = .01$). The overall statistical model explained 13%, 23%, and 36% of HDRS percent change variance at 230 minutes, day 1, and day 7, respectively.

Conclusions: Despite its post hoc nature, this study identified several clinical correlates of ketamine's rapid and durable antidepressant effects. Further investigation of these relationships is critical for individualized treatment of depression.

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Developing clinical tools to predict treatment response is essential both for developing improved treatments and for personalizing medicine.[1] In mood disorders, a number of demographic and treatment characteristics that predict response to standard antidepressant treatments have been identified. For example, the large, real-world Sequenced Treatment Alternatives to Relieve Depression (STAR*D) effectiveness trial found that race, gender, employment status, level of education, and income were associated with higher remission rates after treatment with citalopram.[2] Comorbid psychiatric and substance use disorders, general medical conditions, longer index episodes, and lower psychosocial function were associated with lower remission rates.[2] The clinical and sociodemographic variables identified in the STAR*D trial were subsequently used to create an online calculator to assess risk for future treatment resistance.[3]

Although a large number of antidepressants are available, no reliable selection criteria currently exist. As a result, many patients are exposed to numerous and lengthy antidepressant trials before obtaining significant improvement. In recent years, however, there has been a shift in the field to develop more rapid-acting antidepressants that may streamline this iterative process. For example, both the muscarinic cholinergic receptor antagonist scopolamine and the *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine have rapid-acting antidepressant effects,[4,5] and clinical indicators and biomarkers of rapid treatment response to both medications have been investigated.[6] Baseline scores on the Profile of Mood States depression subscale, as well as the restlessness, sad, and irritated items on the Visual Analog Scales, discriminated scopolamine responders from nonresponders in both major depressive disorder (MDD) and bipolar depression.[7] Increased functional magnetic resonance imaging baseline blood-oxygen-level dependent signal in the middle occipital cortex during the stimulus-processing component of an emotional memory task also predicted increased antidepressant response to scopolamine.[8]

For ketamine, a positive family history of alcohol dependence was associated with better antidepressant response in both MDD[9] and bipolar depression.[10] In addition, although change in peripheral brain-derived neurotrophic factor (BDNF) levels did not correlate with ketamine's antidepressant response,[11] changes in peripheral BDNF (a major inducer of synaptic plasticity) were directly proportional to slow-wave sleep (a surrogate marker of synaptic plasticity) change in ketamine responders.[12] Also, the BDNF Val66Met rs6265 single-nucleotide polymorphism predicted antidepressant response to ketamine; specifically, Val/Val homozygotes responded more often than Met carriers.[13] Finally, baseline peripheral B_{12} (but not folic acid or homocysteine) levels predicted antidepressant response to ketamine in a small sample of patients with bipolar depression.[14]

Noninvasive neuroimaging techniques have also revealed potential biomarkers of ketamine's antidepressant efficacy. For instance,

Clinical Points

- Clinical and demographic predictors of treatment response are critical in the search for more personalized treatments for depression. These predictors have only recently begun to be investigated for the rapid-acting antidepressant ketamine.
- Increased body mass index, a family history of an alcohol use disorder in a first-degree relative, and no personal history of suicide attempt(s) were significant clinical predictors of antidepressant response to ketamine in the largest sample of treatment-resistant inpatients with depression to date.

increased pretreatment rostral anterior cingulate cortex reactivity to fearful faces predicted augmented antidepressant response to ketamine.[15] Magnetoencephalography response during a spatial working memory task also correlated with antidepressant response to ketamine.[16] Baseline slow-wave sleep activity—particularly the delta sleep ratio, as defined by slow-wave sleep activity (SWA)1(nonrapid eye movement [NREM1])/SWA2(NREM2)—positively correlated with ketamine's antidepressant effects.[17] Finally, increased tactile stimulus–evoked somatosensory cortical response from baseline correlated with better antidepressant response.[18] Potential biomarkers of antidepressant response to ketamine have also been studied via proton magnetic resonance spectroscopy (1H-MRS) and positron emission tomography. Although change in 1H-MRS–detectable amino acids did not correlate with antidepressant response to ketamine in the occipital cortex,[19] in the dorsomedial/dorsoanterolateral and ventromedial prefrontal cortex, the differential ratio of amino acid neurotransmitters at baseline correlated with antidepressant response to ketamine.[20] Regional glucose metabolism after ketamine infusion decreased significantly in the right habenula, insula, and ventrolateral and dorsolateral prefrontal cortices, although whole-brain metabolism did not change significantly.[21] Conversely, metabolism increased in the bilateral occipital, right sensorimotor, left parahippocampal, and left inferior parietal cortices. Improvement in depression ratings correlated directly with change in right superior and middle temporal gyri glucose metabolism and inversely correlated with metabolic changes in the right parahippocampal gyrus and temporoparietal cortex.

Despite these intriguing findings, a major weakness associated with these exploratory studies is their limited sample size and their inability to assess multiple variables in aggregate. To weigh the predictive power of multiple variables—particularly clinical and demographic characteristics—larger samples sizes are typically needed. Toward this end, we pooled subject-level data from our ketamine studies in order to better identify the clinical and treatment characteristics associated with acute and sustained antidepressant response to ketamine in individuals with MDD or bipolar depression. Several demographic variables analyzed in previous studies were also included so that their associations in a multivariate context could be explored in this larger sample.

METHOD

We combined subject-level data from 4 independent studies[4,22–24] investigating the use of ketamine in treatment-resistant MDD and bipolar I or II depression without psychotic features. Complete details regarding these patients have been previously published.[4,22–24] The studies are registered on ClinicalTrials.gov (identifier: NCT00088699). Briefly, patients between the ages of 18 and 65 years were admitted to the National Institute of Mental Health Mood and Anxiety Disorders research unit in Bethesda, Maryland, between November 2004 and March 2013. Participants gave written informed consent as approved by the National Institutes of Health Combined Central Nervous System Institutional Review Board. Patients were required to be experiencing a nonpsychotic major depressive episode of at least moderate severity (≥ 18 points[4] on the 21-item Hamilton Depression Rating Scale [HDRS], or ≥ 20 points[22,24] or ≥ 22 points[23] on the Montgomery-Asberg Depression Rating Scale) at screening and at the start of each infusion. All subjects met *DSM-IV-TR* criteria for either MDD or bipolar depression as assessed by the Structured Clinical Interview for Axis I *DSM-IV* Disorders, patient version, had no active substance use diagnosis (except caffeine or nicotine) for at least 3 months, and had no unstable medical illness as detected by clinical history, physical examination, and/or laboratory assessments.

All patients received a single subanesthetic (0.5 mg/kg) intravenous infusion of ketamine hydrocholoride over 40 minutes. Patients enrolled in the MDD ketamine crossover[4] and ketamine-riluzole[23] studies were free of all psychotropic medications for at least 2 weeks (5 weeks for fluoxetine) prior to the (first) infusion. Zarate and colleagues[4] had a double-blind, placebo-controlled, cross-over design. Ibrahim and colleagues' study[23] consisted of open-label ketamine followed 6 hours' postinfusion by randomization to either riluzole (100–200 mg/d) or placebo for 28 days. During this period, no concomitant psychotropic medications were permitted. The 2 bipolar depression studies[22,24] were identically designed: randomized, double-blind, placebo-controlled, crossover studies; all subjects were maintained on therapeutic levels of either lithium or valproate for at least 2 weeks prior to the first infusion.[22,24] The remaining patients included in this report participated in a variety of neurophysiological studies. As in the MDD studies, these patients were free of psychotropic medications for at least 2 weeks prior to ketamine infusion.

As in the Zarate et al study,[4] the primary measure in this combined post hoc analysis was the 17-item HDRS. Baseline and postinfusion scores were used to calculate percent change in HDRS score. Baseline ratings occurred 60 minutes before infusion. Data were examined at 230 minutes, day 1, and day 7 after ketamine infusion. The Beck Depression Inventory (BDI), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS) were obtained at baseline and throughout the study period, including the aforementioned time points.

A variety of baseline sociodemographic and clinical variables were studied because of either prior evidence of an association with antidepressant response or their relationship with outcome measures in longitudinal studies of MDD or bipolar depression. Some clinical variables previously studied include gender,[2,25,26] age,[25,26] and neuropsychiatric comorbidities.[2] Additional patient and family history data were analyzed alongside illness trajectory variables. Family history of an alcohol use disorder was defined as having at least 1 first-degree relative who met criteria for an alcohol use disorder.

Statistics

Pearson correlations were used to examine the associations between baseline variables and percent change in the 17-item HDRS. Scatterplots with predictors and HDRS percent change were used to visualize data and inspect for outliers. Separate correlations were run for each variable with changes in depression scores at 230 minutes, day 1, and day 7 after ketamine infusion. Statistically significant predictors in the univariate analysis advanced to a multivariate linear regression for each time point. Variables significant at any individual time point were analyzed at all time points for model consistency. Significance was evaluated at the $P \leq .05$ level, 2-tailed, with no multiplicity correction.

For linear regression analyses, variables that were not significant at all time points were excluded from the model. Tolerance was examined to assess potential multicollinearity problems. Standardized β coefficients are reported for all remaining variables at each time point to facilitate the contribution of each factor to the overall model. Overall r^2 values illustrate the amount of variance explained by this set of predictors.

RESULTS

All 108 patients received a single subanesthetic (0.5 mg/kg) ketamine infusion over 40 minutes, and data were available for all patients at the 230-minute time point. Patients who received a ketamine infusion and were later randomized to receive riluzole were excluded from analyses at days 1 and 7. Due to withdrawal, not all 108 patients had available data at subsequent time points; 82 patients were analyzed at day 1, and 71 patients were analyzed at day 7.

Demographic characteristics are summarized in Table 1. The sample had moderate-to-severe depression (HDRS score, mean = 21.2 [SD = 4.4]), with the current episode lasting a mean of 55.7 months (SD = 97.2). The mean age at onset was 20.2 years (SD = 11.3), and the mean length of illness was 27.0 years (SD = 12.9). The patient sample was predominantly white (85%, n = 92), with most completing college (57%, n = 59). Half of the sample was male (50%, n = 54), and the majority had MDD (68%, n = 74).

In the univariate analysis, a higher body mass index (BMI) and a family history of alcohol use disorder in a first-degree relative correlated with greater HDRS improvement from baseline to 230 minutes (Figure 1). The same relationships were significant at days 1 and 7 after infusion. One day after infusion, patients with more positive symptoms on the BPRS at baseline and a history of psychiatric hospitalization displayed greater change from baseline. These factors were not related to change in depression severity at day 7. One week after ketamine infusion, participants with no prior suicide attempt had more substantial change in depressive symptoms.

Clinical predictors that were significant at the $P \leq .05$ level at 1 time point in the univariate analysis advanced to the multivariate linear regressions: BMI, positive family history of alcohol use disorder, history of suicide attempt(s), history of psychiatric hospitalization, diagnosis, and baseline BPRS positive symptoms. Given the small proportion of nonwhite patients in the sample, race/ethnicity was not included in the multivariate analysis because of reliability concerns. After running initial regression models, history of psychiatric hospitalization, diagnosis, and baseline BPRS positive symptoms were not significant independent predictors at any time point, so these were removed from the final model.

In the final model, higher BMI correlated with greater improvement in HDRS at 230 minutes and day 1, but not at day 7 after infusion (Table 2). Patients with a family history of an alcohol use disorder in a first-degree relative had greater improvement in HDRS on days 1 and 7, but not at 230 minutes. Having no prior history of suicide attempt was associated with greater improvement at day 7 only. Tolerances remained above 0.7 for all models, so multicollinearity was not an issue. The overall statistical models explained a total of 13%, 23%, and 36% of the variance in HDRS percent change at 230 minutes, day 1, and day 7, respectively.

DISCUSSION

This secondary data analysis of 108 treatment-resistant patients with MDD or bipolar depression currently experiencing a major depressive episode who received a single subanesthetic infusion of ketamine assessed numerous demographic and clinical factors as potential predictors of antidepressant response to ketamine. In the univariate analysis, the following variables emerged as significant predictors of improvement: increased BMI, positive family history of alcohol use disorder, no history of suicide attempt(s), prior psychiatric hospitalization, MDD diagnosis, and more BPRS positive symptoms at baseline. In the multivariate analysis, only increased BMI, positive family history of alcohol use disorder, and no history of suicide attempt(s) remained significant; BMI tended to be associated with *acute improvement*, while positive family history of alcohol use disorder and no history of suicide attempt were associated with antidepressant *durability*.

The association between BMI and acute antidepressant response may be related to clinically effective dose, as patients with the highest dose (in mg) had greater improvements in HDRS scores. Our group and others have postulated that ketamine's mechanism of action is mediated by increased presynaptic release of glutamate ("glutamate surge") and the subsequent activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropanoic acid (AMPA) receptors.[27–29]

Table 1. Univariate Analysis of Demographic and Clinical Correlates of Antidepressant Response to Ketamine in Treatment-Resistant Depression

			Time Following Ketamine Infusion					
			230 Min (n = 108)		Day 1 (n = 82)		Day 7 (n = 71)	
Variable	Mean	SD	*r*	*P*	*r*	*P*	*r*	*P*
Age, y	47.2	12.0	−0.10	.319	0.08	.454	0.01	.926
Body mass index	30.5	6.9	−0.32	.001*	−0.38	<.001*	−0.34	.004*
Age at onset, y	20.2	11.3	−0.11	.262	0.01	.953	<0.01	.986
Length of current episode, mo	55.7	97.2	0.03	.797	0.06	.641	−0.12	.360
Length of illness, y	27.0	12.9	0.02	.807	0.09	.425	0.03	.841
No. of previous episodes	26.2	37.6	−0.10	.334	−0.01	.927	0.02	.880
Clinical ratings								
HDRS (17 item)	21.2	4.4	<0.01	.982	−0.04	.693	−0.13	.287
BDI	27.1	8.3	0.05	.627	0.16	.149	−0.02	.856
YMRS	4.9	2.6	−0.03	.721	−0.04	.744	0.06	.607
BPRS positive symptoms	9.8	1.5	−0.05	.640	−0.26	.020*	−0.11	.346
Percent change in HDRS score								
230 min	−39.6	25.3						
Day 1	−35.9	30.7						
Day 7	−23.4	29.7						
	n	%						
Diagnosis (bipolar disorder)	34	31.5	−0.03	.729	0.07	.537	0.24	.042*
Male	54	50.0	−0.07	.499	−0.04	.746	0.06	.617
Race/ethnicity (white)	92	85.2	0.09	.372	0.16	.152	0.25	.035*
College graduate	59	56.7	0.02	.854	0.06	.576	−0.03	.806
Psychiatric hospitalization	69	71.1	−0.07	.482	−0.24	.045*	−0.02	.851
ECT	37	41.0	0.18	.096	−0.09	.502	0.11	.457
Suicide attempt(s)	44	43.6	0.08	.409	−0.01	.921	0.37	.003*
Smoking (current)	21	20.6	−0.05	.602	0.12	.291	0.03	.810
Abuse								
Physical	22	22.0	−0.04	.705	−0.11	.356	−0.22	.083
Sexual	22	22.0	−0.13	.199	−0.14	.218	0.16	.216
Family history								
Alcohol use disorder (first degree)	40	39.2	−0.21	.031*	−0.33	.004*	−0.47	<.001*
Mood disorder (first degree)	88	83.8	−0.10	.294	−0.13	.236	−0.07	.555
Suicide	29	34.9	−0.02	.882	−0.18	.168	−0.04	.794
Alcohol use disorder	12	28.6	0.02	.922	0.10	.565	−0.14	.437
Comorbid diagnosis								
Agoraphobia (current)	10	9.3	0.04	.705	0.06	.610	0.07	.578
Anxiety NOS (current)	10	9.6	−0.04	.692	−0.14	.225	−0.08	.544
GAD (current)	15	14.4	<0.01	.977	<0.01	.981	0.09	.467
OCD (current)	9	8.7	−0.05	.623	0.05	.652	<0.01	.985
Panic disorder (current)	8	7.4	0.12	.229	0.15	.200	0.07	.591
PTSD (current)	3	2.9	0.01	.911	0.06	.591	0.02	.843
Social phobia (current)	29	26.9	0.05	.642	0.11	.348	0.15	.235
Specific phobia (current)	12	11.5	−0.09	.381	−0.12	.276	0.11	.393
MDD subtype								
Atypical	27	27.0	−0.02	.858	0.10	.375	−0.10	.418
Melancholic	31	31.0	−0.04	.692	0.01	.909	0.04	.748
Neither	42	42.0	0.05	.594	−0.11	.366	0.05	.681

*$P \leq .05$, 2-tailed.

Abbreviations: BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, ECT = electroconvulsive therapy, GAD = generalized anxiety disorder, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, NOS = not otherwise specified, OCD = obsessive-compulsive disorder, PTSD = posttraumatic stress disorder, YMRS = Young Mania Rating Scale.

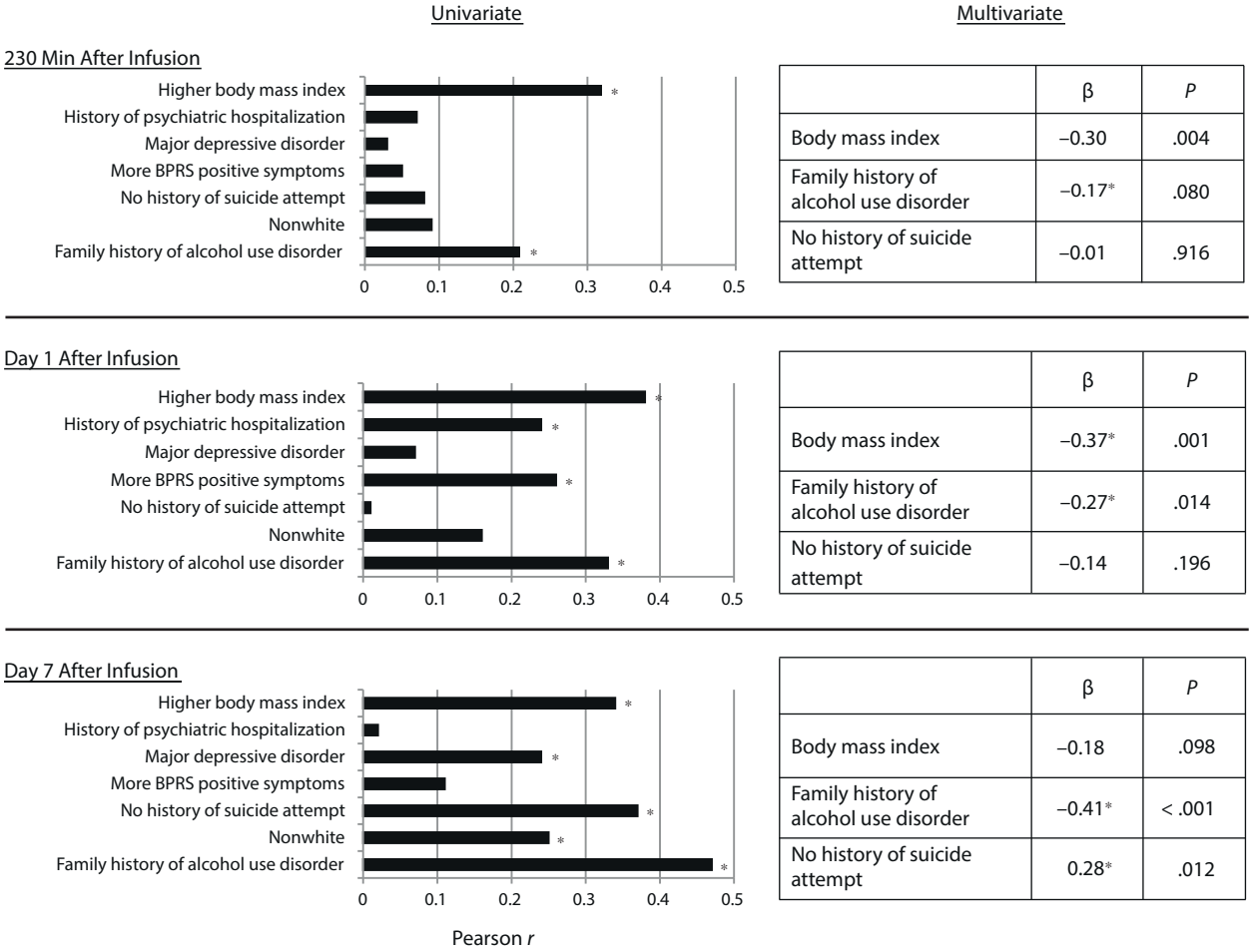
In this model, a higher dose of ketamine may result in greater NMDA receptor antagonism and parallel increases in both presynaptic glutamate release and postsynaptic AMPA receptor throughout. The extracellular glutamate levels resulting from ketamine have been reported to have "inverted U"–shaped pharmacodynamics, ie, a lower dose of ketamine increases extracellular glutamate levels until a peak, with subsequent decreases at higher doses.[30] The resultant biochemical and neurophysiological events involved in ketamine's antidepressant effects may reflect these pharmacodynamics.[31,32] Although a structured dose-finding study with ketamine in depression is currently underway (ClinicalTrials.gov identifier: NCT01558063), a previous study in healthy volunteers reported that a 0.1-mg/kg ketamine infusion was associated with fewer psychotomimetic and dissociative effects than 0.5 mg/kg[33]; this indicates that ketamine's adverse effects result from differences in NMDA receptor antagonism. It may be important, therefore, in dose-finding studies to take BMI into account, as an imbalance in weight among the different dose-level groups may lead to differences in antidepressant efficacy. It is also interesting to note that a prior study[34]

Table 2. Multivariate Linear Regression of Significant Predictors of Antidepressant Response to Ketamine in Treatment-Resistant Depression

	230 Min			Day 1			Day 7		
Predictor	Standardized β	*P*	r^2	Standardized β	*P*	r^2	Standardized β	*P*	r^2
Body mass index	−0.30	.004*		−0.37	.001*		−0.18	.098	
Family history of alcohol use disorder (first degree)	−0.17	.080		−0.27	.014*		−0.41	< .001*	
Suicide attempt(s)	−0.01	.916		−0.14	.196		0.28	.012*	
Total			0.130			0.229			0.360

*$P \leq .05$, 2-tailed.

Figure 1. Synopsis of Univariate and Multivariate Predictors of Ketamine's Antidepressant Response in Treatment-Resistant Depression



*$P \leq .05$, 2-tailed.
Abbreviation: BPRS = Brief Psychiatric Rating Scale.

found that increased BMI was associated with higher rates of tachyphylaxis following treatment with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Thus, while BMI may predict initial response to ketamine, our results are in agreement with prior studies suggesting that patients with higher BMIs may not sustain response.

Improvement in depressive symptoms at day 7 after ketamine infusion (indicating more sustained antidepressant effects) confirmed our previous findings of antidepressant durability in patients with a positive family history of alcohol use disorder; it should be noted, however, that the current dataset overlaps these prior reports.[9,10] Previous studies found that glutamatergic dysfunction is involved in the pathophysiology of mood disorders, both alone[35] and co-occurring with alcoholism.[36] One study[36] found that patients with bipolar disorder in long-term remission from alcoholism showed reduced dorsolateral prefrontal cortex glutamate levels compared to bipolar disorder patients who never developed alcoholism. At the genetic level, Schumann and colleagues[37] found a significant association between risky drinking behavior in adolescents and the genes encoding

metabotropic glutamate receptor type 5 (mGluR5) and the NR2A subunit of the NMDA receptor. Because ketamine has antagonist effects at NR2A and alcohol is also a weak NMDA receptor antagonist,[38] it is feasible that genetic polymorphisms in NMDA receptor subunits may render patients with a family history of an alcohol use disorder in a first-degree relative more responsive to its antidepressant effects. The antidepressant efficacy of ketamine may also be augmented in patients with comorbid depression and alcoholism, a hypothesis currently under investigation (ClinicalTrials.gov identifier: NCT01551329). Future genetic studies may unveil polymorphisms in NMDA receptor complex subunits that will further elucidate glutamatergic dysfunction in mood and alcohol use disorders and their relationship to ketamine's antidepressant efficacy.

In the STAR*D trial, race, gender, employment status, level of education, and income were associated with greater rates of remission with citalopram, while psychiatric comorbidities, general medical conditions, longer index episodes, and lower psychosocial function were associated with lower remission rates.[2] However, gender, education level, and neuropsychiatric and medical comorbidities were not associated with antidepressant response to ketamine in our sample. There are several potential explanations for these differences. First, the selected STAR*D population (n = 2,876)[2] was much larger than the 108 patients in this study. Second, STAR*D was an "all comers" outpatient study, while our ketamine protocols included only treatment-resistant inpatients. Third, there are differences in the antidepressant mechanism of action of conventional monoaminergic antidepressants and cognitive-behavioral therapy in STAR*D versus ketamine's glutamatergic properties. Finally, differences in the outcome measures used may have played a role; STAR*D examined remission, while the present study used response rates.

One of the major strengths of this study is our well-characterized group of treatment-resistant depressed inpatients. All patients were hospitalized at the same site for an average of 6 weeks before receiving ketamine, thus providing ample resources and time to precisely describe their clinical and treatment characteristics. This inpatient milieu allowed us to pay attentive detail to the timing of response and side effect profile in the period following infusion. Another significant strength was our relatively large sample studied under similar conditions, thus permitting the exploration of multiple variables and their variance alone and in aggregate. In addition, our group examined multiple time points and studied the potential variables longitudinally in a multivariate context. Potential limitations of the study include its post hoc design, the pooled patient group that included patients with treatment-refractory MDD as well as bipolar depression, and the combination of open-label and randomized, placebo-controlled, crossover designs.

Despite the fact that all predictors were studied post hoc, this study is an important first step in the search for potential correlates of ketamine's rapid and relatively sustained antidepressant properties. While ketamine remains a promising key for future research into rapidly acting antidepressants, further investigation into its mechanism, safety, and feasibility is needed to determine its ultimate clinical utility. Nonetheless, uncovering clinically relevant predictors of antidepressant response remains an important step toward improving the clinical care of depressed patients. Notably, obtaining BMI, identifying family history of alcohol use disorders in relatives, and asking about a past history of suicide attempt(s) are all part of the initial psychiatric interview. In the future, we seek to integrate such research findings to advance our predictive capacity for personalized antidepressant selection.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), ketamine (Ketalar and others), lithium (Lithobid and others), riluzole (Rilutek and others).

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Potential conflicts of interest: **Dr Zarate** is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. He 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 Niciu**, **Ionescu**, **Machado-Vieira**, and **Richards**; **Messrs Luckenbaugh** and **Nolan**; and **Mss Guevara** and **Brutsche** have no conflict of interest to disclose, financial or otherwise.

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