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RESEARCH ARTICLE

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# Efficacy of intravenous ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression

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**Objective:** To examine the effect of high baseline anxiety on response to ketamine versus midazolam (active placebo) in treatment-resistant depression (TRD).

**Methods:** In a multisite, double-blind, placebo-controlled trial, 99 subjects with TRD were randomized to one of five arms: a single dose of intravenous ketamine 0.1, 0.2, 0.5, 1.0 mg/kg, or midazolam 0.045 mg/kg. The primary outcome measure was change in the six-item Hamilton Rating Scale for Depression (HAMD6). A linear mixed effects model was used to examine the effect of anxious depression baseline status (defined by a Hamilton Depression Rating Scale Anxiety-Somatization score ≥7) on response to ketamine versus midazolam at 1 and 3 days postinfusion.

**Results:** $N = 45$ subjects had anxious TRD, compared to $N = 54$ subjects without high anxiety at baseline. No statistically significant interaction effect was found between treatment group assignment (combined ketamine treatment groups versus midazolam) and anxious/nonanxious status on HAMD6 score at either days 1 or 3 postinfusion (Day 1: $F(1, 84) = 0.02$, $P = 0.88$; Day 3: $F(1, 82) = 0.12$, $P = 0.73$).

**Conclusion:** In contrast with what is observed with traditional antidepressants, response to ketamine may be similar in both anxious and nonanxious TRD subjects. These pilot results suggest the potential utility of ketamine in the treatment of anxious TRD.

**KEYWORDS**
active placebo, anxious depression, ketamine, major depressive disorder, midazolam, treatment-resistant depression

## 1 | INTRODUCTION

Anxious depression, defined as major depressive disorder (MDD) with high levels of anxiety, is a commonly encountered clinical depression subtype, present in approximately 50% of patients with MDD (Fava et al., 2004; Fava et al., 2008). In addition, this subtype seems particularly prevalent among patients suffering from treatment-resistant depression (TRD) (Wu et al., 2013), and proven particularly difficult to treat, compared to general MDD, in terms of response and remission rates (Fava et al., 1997; Papakostas et al., 2008; Souery et al., 2007). In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, for instance, significantly lower remission rates were observed in citalopram-resistant patients with anxious depression versus without anxious depression (Fava et al., 2008). Anxious depression has also been associated with higher rates of suicidal ideation and attempts, as well as treatment side effects (Chan et al., 2012; Fava et al., 2008; Seo et al., 2011).

Ketamine, an *N*-methyl-D-aspartate receptor antagonist and glutamatergic modulator, commonly used as a dissociative anesthetic, has garnered considerable attention in the past decade for use in TRD (Sanacora et al., 2017). Several controlled trials have now established

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the rapid and robust antidepressant effect of ketamine in patients with TRD (Berman et al., 2000; Murrough et al., 2013; Singh et al., 2016; Zarate et al., 2006). However, evidence for its efficacy in anxious depression remains scarce. Two post hoc reports have been published thus far by the National Institute of Mental Health (NIMH) group (Ionescu et al., 2014; Ionescu, Luckenbaugh, Niciu, Richards, & Zarate, 2015), suggesting that ketamine is efficacious in both anxious and nonanxious depression, with one study interestingly showing relatively higher ketamine efficacy in the anxious depression group (Ionescu et al., 2014). These results warrant further investigation.

Our NIMH-funded network (Rapidly Acting Treatments for Treatment-Resistant Depression [RAPID]; https://www.nimh.nih.gov/research-priorities/research-initiatives/rapidly-acting-treatments-for-treatment-resistant-depression-rapid.shtml) recently conducted a multisite, randomized, double-blind, active placebo-controlled trial of intravenous ketamine in patients with unipolar TRD, where response to ketamine-combined treatment groups was found to be superior to midazolam (active placebo; Fava et al., 2018). In light of the urgent need for more effective treatments in anxious depression, we conducted secondary analyses to compare treatment response to ketamine versus midazolam in patients with anxious depression to those with low levels of anxiety at baseline. Based on previous data (Ionescu et al., 2014), we predicted that subjects with anxious depression would have a significantly greater response to ketamine compared to patients without anxious depression.

## 2 | METHODS

### 2.1 | Overview

For a full description of the original trial design and patient selection, please refer to the main publication of results (Fava et al., 2018). In brief, this was a multisite, randomized, double-blind, active placebo-controlled trial of the acute efficacy of intravenous ketamine or midazolam added to ongoing, stable, and adequate antidepressant therapy (ADT) in the treatment of adults with TRD. This work was conducted as part of a collaborative effort between the MGH Clinical Trials Network and Institute (CTNI), multiple academic sites, and the NIMH. All patients signed written informed consent approved by the respective Institutional Review Board and NIMH Data Safety and Monitoring Board.

### 2.2 | Patient selection

Eligible patients were men and women between the ages of 18 and 70 years, with a primary psychiatric diagnosis of MDD and experiencing a major depressive episode (MDE) of at least 8 weeks in duration prior to screening as defined by the Diagnosis and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR$^{TM}$) criteria (American Psychiatric Association, 2000). Additionally, eligible patients were also confirmed to be experiencing TRD during the current MDE, defined as a failure to achieve a satisfactory response (<50% response) to at least two, but not more than seven, adequate treatment courses of ADT with a minimal dose approved for the treatment of MDD and of at least 8 weeks duration. To note, patients were required to be on stable doses of antidepressants for at least 4 weeks prior to screening. Remote raters reviewed and confirmed the eligibility of every study participant.

### 2.3 | Study design

Patients were screened between 7 and 28 days, during which eligibility was determined, and prohibited medications were discontinued. Subsequently, eligible patients were stratified by body mass index (≤30 and >30), and randomized into one of the five study arms, through a block randomization model. A total of 99 subjects were randomly assigned to one of these five arms in a 1:1:1:1:1 fashion: a single dose of ketamine 0.1 mg/kg ($n$ = 18), a single dose of ketamine 0.2 mg/kg ($n$ = 20), a single dose of ketamine 0.5 mg/kg ($n$ = 22), a single dose of ketamine 1.0 mg/kg ($n$ = 20), or a single dose of midazolam 0.045 mg/kg ($n$ = 19). At the baseline visit (Day 0), randomized subjects received their assigned study drug by continuous intravenous infusion via an electronic syringe infusion pump, over a period of 40 min. Subjects were continuously monitored throughout the process, with blood pressure and heart rate measured at time 0 (right before starting the infusion), and at 15–20-min intervals for 120 min following the initiation of the infusion.

### 2.4 | Anxious depression definition

We defined anxious depression as MDD with a score of 7 or more on the Hamilton Depression Rating Scale Anxiety-Somatization factor (HAMD-AS). The HAMD-AS, derived from a factor analysis of the HDRS, includes six items from the original HAMD-17: psychic anxiety, somatic anxiety, somatic symptoms-gastrointestinal, somatic symptoms-general, hypochondriasis, and insight (Cleary & Guy, 1977). This scale has been used in multiple large clinical trials and proven useful in assessing anxious depression (Fava et al., 2008; Ionescu et al., 2014; Ionescu et al., 2015; McClintock et al., 2011; Wiethoff et al., 2010; Wu et al., 2013).

### 2.5 | Assessments

The six-item Hamilton Depression Rating Scale (HAMD6; Bech et al., 1981) was defined a priori as the primary outcome measure (O'Sullivan, Fava, Agustin, Baer, & Rosenbaum, 1997). Secondary measures included the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) and the Clinical Global Impression-Severity scale (CGI-S) (Guy, 1976). Dissociative symptoms during the infusion were measured using the Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., 1998) at 5, 40, 80, and 120 min in relation to the start of the infusion. For a full report of secondary efficacy and safety measures used in the study, please refer to the original report (Fava et al., 2018).

### 2.6 | Statistical analyses

In order to assess the effect of anxious depression status at baseline on the acute antidepressant response to ketamine versus midazolam treatment, our a priori planned analyses focused on Days 1 and 3 out-

**TABLE 1** Subjects characteristics—anxious versus nonanxious depression

| | Anxious depression ($n = 45$) | | Nonanxious depression ($n = 54$) | | |
|---|---|---|---|---|---|
| | mean/% | (*SD*) | mean/% | (*SD*) | *P*-value |
| Demographics | | | | | |
| Age | 44.6 | (13.4) | 47.4 | (11.9) | 0.46 |
| Gender (% female) | 64.4 | | 37.0 | | 0.01* |
| Hispanic (% yes) | 4.4 | | 1.9 | | 0.54 |
| Race | | | | | 0.59 |
| White | 91.1 | | 87.0 | | |
| Asian | 4.4 | | 5.6 | | |
| Black | 2.2 | | 5.6 | | |
| Other | 2.2 | | 1.9 | | |
| BMI | 24.9 | (4.6) | 26.1 | (3.8) | 0.15 |
| Concomitant medications (% used) | | | | | |
| Benzodiazepine | 60.0 | | 31.5 | | 0.00** |
| Nonbenzodiazepine hypnotic | 15.6 | | 25.9 | | 0.23 |
| SSRI | 57.8 | | 48.1 | | 0.42 |
| SNRI | 24.4 | | 31.5 | | 0.51 |
| TCA | 4.4 | | 1.9 | | 0.59 |
| Other antidepressants | 48.9 | | 53.7 | | 0.69 |
| Clinical severity at baseline | | | | | |
| HAMD-AS | 8.64 | (1.5) | 4.42 | (1.2) | <0.0001*** |
| HAMD6 | 13.6 | (1.9) | 11.9 | (1.8) | <0.0001*** |
| MADRS | 35.3 | (7.0) | 31.4 | (5.1) | 0.00** |
| CGI-S | 5.2 | (0.7) | 4.9 | (0.7) | 0.06 |

BMI: body mass index; benzodiazepines included Alprazolam, Clonazepam, Clorazepic acid, Diazepam, and Lorazepam; nonbenzodiazepine hypnotics included Zaleplon, Zolpidem, and Trazodone; SSRI: selective serotonin reuptake inhibitors (incl. Fluoxetine, Citalopram, Escitalopram, Paroxetine, Sertraline, and Vilazodone); SNRI: serotonin–norepinephrine reuptake inhibitors (incl. Desvenlafaxine, Duloxetine, Venlafaxine, and Venlafaxine hydrochloride); TCA: tricyclic antidepressants (incl. Clomipramine and Nortriptyline); other antidepressants included Bupropion, Mirtazapine, Vortioxetine; HAMD6: six-item Hamilton Rating Scale for Depression; MADRS: Montgomery–Asberg Depression Rating Scale; CGI-S: Clinical Global Impression of Severity Scale; $^{*}P < 0.05$, $^{**}P < 0.005$, $^{***}P < 0.0005$.

come measures. To note, results from previous analyses showed that the difference in efficacy between ketamine and midazolam is most demonstrable at Day 1, therefore largely accounting for the 72-hr hypothesized effect of ketamine (Fava et al., 2018).

In the case of HAMD6 on Day 1 as the outcome measure, we fit a linear mixed effects model in which HAMD6 score on Day 1 was the dependent variable, HAMD6 score at baseline was a covariate, and predictor variables were ANX (anxious depression, not anxious depression), GROUP (ketamine and midazolam), and their interaction terms. We included a random effect for SITE (six sites). To examine if there was a different effect based on ketamine dosage, we used the same model, but with a five-level GROUP variable (ketamine 0.1, 0.2, 0.5, 1.0 mg/kg, and midazolam) instead of the two-level GROUP variable.

We repeated the same type of analyses for the following outcome measures: HAMD6 on Day 3, MADRS on Day 3 (to note: in the trial design, MADRS was not performed on Day 1), and CGI-S on Days 1 and 3 postinfusion.

In order to assess the effect of anxious depression status at baseline on the level of dissociative symptoms experienced by subjects who received ketamine treatment, we conducted two independent-samples *t*-tests, first including all subjects who received ketamine treatment and second including only subjects who received ketamine 0.5 and 1.0 mg/kg (due to these doses correlating significantly with higher levels of dissociative symptoms compared to placebo, as reported in the main paper; Fava et al., 2018). CADSS scores at 40 min postinfusion start (time at which the most significant level of dissociative symptoms was observed in ketamine vs. placebo, as reported in the main paper; Fava et al., 2018) was used as the dependent outcome variable.

To note, although analyzing baseline anxious status as a moderator of response to ketamine was a priori planned in the study protocol, the study was only powered to detect the main outcome (Fava et al., 2018), and therefore not powered to address this exploratory aim.

All tests were performed with a significance level of 0.05 (two tailed) using SAS 9.4 statistical software.

## 3 | RESULTS

Of all 99 randomized subjects, 45 (45.5%) met the predefined criteria for anxious depression status at baseline. Thirty-five (43.8%)

**TABLE 2** Subjects characteristics—anxious depression subjects only ($n = 45$)

| | Ketamine 0.1 mg/kg ($n = 9$) | | Ketamine 0.2 mg/kg ($n = 10$) | | Ketamine 0.5 mg/kg ($n = 12$) | | Ketamine 1.0 mg/kg ($n = 4$) | | Midazolam 0.045 mg/kg ($n = 10$) | | All Ketamine Groups (n = 35) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | mean/% | *SD* | mean/% | *SD* | mean/% | *SD* | mean/% | *SD* | mean/% | *SD* | mean/% | *SD* |
| Demographics | | | | | | | | | | | | |
| Age | 45.2 | (14.6) | 42.7 | (12.3) | 46.9 | (13.0) | 41.9 | (15.3) | 44.3 | (15.5) | 44.7 | (13.0) |
| Gender (% female) | 66.7 | | 70.0 | | 66.7 | | 50.0 | | 60.0 | | 65.7 | |
| Hispanic (% yes) | 0.0 | | 0.0 | | 16.7 | | 0.0 | | 0.0 | | 5.7 | |
| Race | | | | | | | | | | | | |
| White | 77.8 | | 100.0 | | 91.7 | | 75.0 | | 100.0 | | 88.6 | |
| Asian | 11.1 | | 0.0 | | 0.0 | | 25.0 | | 0.0 | | 2.9 | |
| Black | 11.1 | | 0.0 | | 0.0 | | 0.0 | | 0.0 | | 5.7 | |
| Other | 0.0 | | 0.0 | | 8.3 | | 0.0 | | 0.0 | | 2.9 | |
| BMI | 24.5 | (3.0) | 23.4 | (4.0) | 25.0 | (6.7) | 26.1 | (3.1) | 26.1 | (4.0) | 24.6 | (4.7) |
| Clinical severity at baseline | | | | | | | | | | | | |
| HAMD-AS | 8.3 | (1.2) | 9.0 | (2.0) | 8.4 | (1.4) | 8.8 | (1.0) | 8.8 | (1.8) | 8.6 | (1.5) |
| HAMD6 | 12.3 | (0.9) | 14.2 | (2.3) | 13.1 | (1.4) | 14.8 | (2.5) | 14.5 | (1.6) | 13.4 | (1.9) |
| MADRS | 31.6 | (6.2) | 39.1 | (8.6) | 33.0 | (4.3) | 35.8 | (9.5) | 37.4 | (6.3) | 34.7 | (7.2) |
| CGI-S | 4.8 | (0.7) | 5.5 | (0.7) | 5.0 | (0.6) | 6.0 | (0.8) | 5.2 | (0.6) | 5.2 | (0.8) |

BMI: body mass index; HAMD6: six-item Hamilton Rating Scale for Depression; MADRS: Montgomery–Asberg Depression Rating Scale; CGI-S: Clinical Global Impression of Severity scale.

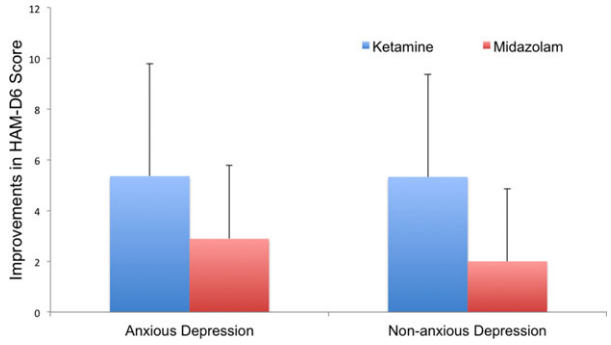


**FIGURE 1** HAMD6 score improvement on ketamine (combined treatment groups) versus midazolam between anxious and nonanxious depression on Day 1 postinfusion. GROUP*ANX interaction term: $F(1, 84) = 0.02$, $P = 0.88$. HAMD6: six-item Hamilton Rating Scale for Depression

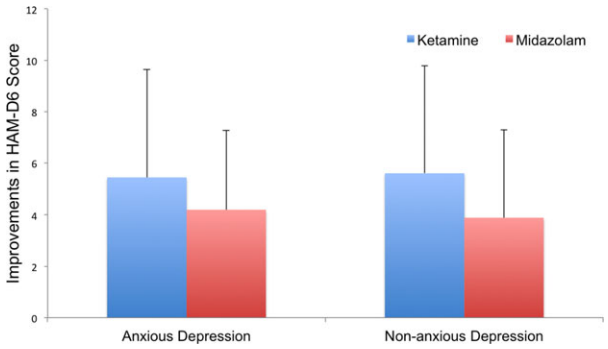


**FIGURE 2** HAMD6 score improvement on ketamine (combined treatment groups) versus midazolam between anxious and nonanxious depression on Day 3 postinfusion. GROUP*ANX interaction term: $F(1, 82) = 0.12$, $P = 0.73$. HAMD6: six-item Hamilton Rating Scale for Depression

of the 80 subjects randomized to ketamine fulfilled the criteria for anxious depression, whereas 10 (52.6%) of the 19 subjects randomized to midazolam did so. Demographic and clinical variables for anxious and nonanxious groups are depicted in Table 1. Table 2 shows baseline demographic and clinical variables across treatment arms for subjects with anxious depression.

When testing the two-group difference (ketamine dose groups combined vs. midazolam) with respect to HAMD6 scores on Day 1, the GROUP*ANX interaction term was not significant ($F(1, 84) = 0.02$, $P = 0.88$); HAMD6 change scores from baseline to Day 1 were not significantly different in subjects with anxious depression on ketamine (−5.36 ± 4.44) or midazolam (−2.89 ± 2.89) versus patients without anxious depression on ketamine (−5.33 ± 4.04) or midazolam (−2 ± 2.87; Figure 1). Nonsignificant results were also obtained with respect to HAMD6 on Day 3 ($F(1, 82) = 0.12$, $P = 0.73$); HAMD6 change scores from baseline to Day 3 were not significantly different in subjects with anxious depression on ketamine (−5.44 ± 4.2) or midazolam (−4.2 ± 3.07) versus patients without anxious depression on ketamine (−5.6 ± 4.18) or midazolam (−3.89 ± 3.41; Figure 2). Results were consistent with other depression outcome scales, including CGI-S on Day 1 ($F(1, 84) = 0.03$, $P = 0.85$), CGI-S on Day 3 ($F(1, 82) = 0.15$, $P = 0.70$), and MADRS on Day 3 ($F(1, 82) = 0.76$, $P = 0.39$) (Table 3). To note, MADRS was not captured on Day 1 postinfusion.

When modeling ketamine by its different dosages, using a five-level GROUP variable (ketamine 0.1, 0.2, 0.5, 1.0 mg/kg vs. midazolam), the GROUP*ANX interaction term was not significant with respect to HAMD6 on Day 1 ($F(4,78) = 1.62$, $P = 0.18$), and CGI-S on Day 1 ($F(4,78) = 0.20$, $P = 0.08$) or Day 3 ($F(4,76) = 2.16$, $P = 0.08$). However, the GROUP*ANX interaction term was statistically significant on Day 3 with respect to HAMD6 ($F(4,76) = 2.53$, $P = 0.05$) and

**TABLE 3** Effect of anxious depression status on response to ketamine (i.e., significance of the GROUP*ANX effect)

| | | Two-group comparison | | | | Five-group comparison | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Outcome | Num DF | Den DF | *F* Value | Pr > *F* | Num DF | Den DF | *F* Value | Pr > *F* |
| Day 1 | | | | | | | | | |
| | HAMD6 | 1 | 84 | 0.02 | 0.88 | 4 | 78 | 1.62 | 0.18 |
| | CGI-S | 1 | 84 | 0.03 | 0.85 | 4 | 78 | 2.20 | 0.08 |
| Day 3 | | | | | | | | | |
| | HAMD6 | 1 | 82 | 0.12 | 0.73 | 4 | 76 | 2.53 | 0.05* |
| | MADRS | 1 | 82 | 0.76 | 0.39 | 4 | 76 | 2.57 | 0.04* |
| | CGI-S | 1 | 82 | 0.15 | 0.70 | 4 | 76 | 2.16 | 0.08 |

Num DF: Numerator degrees of freedom; DenDF: Denominator degrees of freedom; Pr: Probability; HAMD6: six-item Hamilton Rating Scale for Depression; MADRS: Montgomery–Asberg Depression Rating Scale; CGI-S: Clinical Global Impression of Severity scale; MADRS was not assessed on Day 1; the full model for each outcome was: outcome = BASELINE + GROUP + ANX + GROUP*ANX; $^{*}P < 0.05$.

MADRS ($F(4,76) = 2.57$, $P = 0.04$). Post hoc analyses of individual doses show that for both measures, the significant GROUP*ANX interactions were only seen with ketamine 0.1 mg/kg (HAMD6: $P = 0.005$; MADRS: $P = 0.01$), where ketamine 0.1 mg/kg was more efficacious on Day 3 in nonanxious versus anxious depression, when compared to placebo. Results of these post hoc analyses are depicted in Supporting Information Table S1 and Supporting Information Figure S1.

Regarding the effect of anxious depression status at baseline on the level of dissociative symptoms experienced by subjects who received ketamine treatment, there was a significant difference in the CADSS scores at 40 min postinfusion start in subjects with anxious depression ($M = 8.26$, $SD = 9.52$) versus those without anxious depression ($M = 14.25$, $SD = 15.58$); $t(77) = 2.10$, $P = 0.04$. When using only ketamine 0.5 and 1.0 mg/kg subgroups, results trended toward significance in the same direction, where subjects with anxious depression had numerically lower CADSS scores ($M = 14.56$, $SD = 10.60$) than those without anxious depression ($M = 22$, $SD = 16.40$); $t(39) = 1.76$, $P = 0.09$.

## 4 | DISCUSSION

In this study, we found that ketamine is equally efficacious for treating TRD patients with or without anxious depression. Specifically, there was no significant interaction effect between treatment group assignment and baseline anxious/nonanxious status on the score change of multiple depression scales at Days 1 and 3 postinfusion, with ketamine analyzed as one pooled group. Results were consistent when analyzing ketamine as four separate groups at Day 1, but were found to be statistically significant with respect to both the HAMD6 and MADRS on Day 3, where the nonanxious group responded significantly better to ketamine 0.1 mg/kg compared to the anxious group. However, it is worth pointing out that these analyses were conducted with small sample sizes and without correcting *P*-values for multiple comparisons. No similar relationships were found for the other doses of ketamine. We also found that subjects with anxious depression experienced a lower level of dissociative symptoms at 40 min after infusion start compared to subjects without anxious depression. One possible explanation may be attributed to the significantly higher proportion of benzodiazepine use in subjects with high baseline anxiety state, therefore partially blunting dissociative symptoms in this subgroup (Krystal et al., 1998).

Only two other human studies have explored the interaction between baseline anxiety state and ketamine efficacy in depression: an open-label trial of a single infusion of ketamine in 26 patients with unmedicated TRD, in which post hoc analyses showed similar time to response, significantly lower depression scores, and longer time to relapse in those with versus without anxious depression (Ionescu et al., 2014). Another study conducted post hoc analyses on a pooled dataset of 36 inpatients with treatment-resistant bipolar depression from two randomized crossover trials. Results showed significant drug main effects favoring ketamine over midazolam (active placebo), but no significant drug by anxiety interactions, indicating that ketamine may be effective in both anxious and nonanxious depression groups (Ionescu et al., 2015). Taken together, our results as well as results of the two previous reports highlight the potential role of ketamine in the treatment of anxious depression.

In general, patients with anxious depression may represent a more difficult-to-treat subtype of MDD. Previous reports on the use of monoaminergic antidepressants show that patients with anxious depression do not maintain response or remission, and may have a higher side effect burden compared to subjects with nonanxious depression (Ionescu, Niciu, Richards, & Zarate, 2014). In the multisite STAR*D trial, remission rates were significantly lower in patients with versus without anxious depression, on citalopram monotherapy (level 1) or after augmentation or switch to another AD (level 2; Fava et al., 2008). Similarly, a large European-based open-label trial found strong association between anxious depression and failure to respond to at least two consecutive adequate AD treatments (Souery et al., 2007). Furthermore, Papakostas, Fan, and Tedeschini (2012) used a patient-level, clinical trial dataset composed of several RCTs comparing SSRIs versus placebo in MDD (total $N = 1{,}690$), and found that the number needed to treat (NNT) was 12 in the anxious group and 6 in the nonanxious group (nonsignificant difference). Interestingly, when subtyping subjects with severe MDD into anxious versus nonanxious groups, the NNT becomes 22 and 4 respectively ($P = 0.009$), representing the largest and smallest numbers needed to treat for remission following SSRI versus placebo monotherapy in subjects with MDD. Poorer

treatment outcomes to conventional antidepressants may be related to the fact that these patients tend to have lower socioeconomic status, more comorbid physical illnesses, and greater severity of depression (Fava et al., 2008; Wiethoff et al., 2010). In contrast to reports from monoaminergic antidepressants, our data suggest that patients with anxious depression respond equally as well to ketamine compared to those with nonanxious depression. The exact mechanism behind the differential response to ketamine versus other conventional antidepressants in anxious depression remains unclear.

Preclinical studies suggest that ketamine may have an anxiolytic effect (Fortress, Smith, & Pang, 2018; Parise et al., 2013). A recent study showed that the administration of a subanesthetic dose of ketamine to Wistar Kyoto rats, which have impaired long-term hippocampal potentiation and serve as an animal model of anxiety vulnerability, facilitated the extinction of perseverative avoidance behavior in a subset of rats, while also enhancing hippocampal synaptic plasticity in this same subset (Fortress et al., 2018). Additionally, male rats that received an intraperitoneal injection of ketamine 50 mg had increased entries into an elevated-plus maze, an experience that normally induces anxiety in rodents (Engin, Treit, & Dickson, 2009). On a cellular and molecular level, changes in glutamate-regulated synaptic plasticity, previously suggested as a mechanism of action underlying the antidepressant effect of ketamine, may also be related to its anxiolytic effect (Duman, Aghajanian, Sanacora, & Krystal, 2016). In particular, a series of events initiated by ketamine's actions lead to increased activation of postsynaptic AMPA receptors, inducing the release of neurotrophic factors (e.g., Brain-derived neurotrophic factor) and subsequently increasing local protein synthesis. The latter is responsible for synaptic formation and maturation (i.e., plasticity) in such areas as the prefrontal cortex or hippocampus.

A methodological strength of this study was the use of a randomized, active placebo-controlled design in the original trial. However, several limitations are worth noting. First, the study was not powered to assess baseline anxiety status as a moderator of response to ketamine versus midazolam. Second, when assessing ketamine as four separate groups (instead of one combined group), the sample size in each group becomes very small, making observed differences difficult to interpret. Third, the lack of postbaseline HAMD-17 measurements prevented us from assessing whether anxiety symptoms improved as rapidly and thoroughly as core depressive symptoms did (as measured by HAMD6).

In conclusion, results of the present study did not demonstrate differential efficacy of ketamine for the treatment of either anxious or nonanxious depression, pointing to the possibility that intravenous ketamine treatment may be equally efficacious in treating subjects with or without anxious TRD. These results are still exploratory and future larger and adequately powered studies designed to specifically test this aim are warranted.

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## CONFLICTS OF INTEREST

Naji C. Salloum: As part of his clinical translational fellowship at MGH, Dr. Salloum also works in the Pfizer digital medicine group. His work at Pfizer presents no financial or nonfinancial conflict of interest with the current manuscript.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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