## Early Career Psychiatrists

# It is illegal to post this copyrighted PDF on any website. Effect of Concomitant Benzodiazepines on the Antidepressant Effects of Ketamine: Findings From the RAPID Intravenous Ketamine Study

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### ABSTRACT

**Objective:** Ketamine is a novel and rapidly acting treatment for major depressive disorder (MDD). Benzodiazepines are commonly coprescribed with antidepressants in MDD. This study sought to examine data from a randomized clinical trial that compared a single infusion of intravenous (IV) ketamine to midazolam placebo in treatment-resistant depression (*DSM-IV-TR* MDD) and to assess whether the use of concomitant oral benzodiazepines differentially affected treatment response to ketamine versus midazolam.

**Methods:** This trial ran from December 2015 to December 2016. Subjects who were taking oral benzodiazepines (n = 44) were compared to those who were not (n = 55). A significant treatment-by-benzodiazepine effect could be interpreted as a possible moderator of differential treatment response to ketamine versus midazolam. Benzodiazepine use was examined as both a binary and a continuous predictor, to assess the impact of dosage.

**Results:** Benzodiazepine users did not differ from non-users on the original study's primary outcome measure, score on the 6-item Hamilton Depression Rating Scale (HDRS-6), at baseline, but the former had more severe anxiety. When oral benzodiazepine use was modeled as a binary predictor, benzodiazepine use did not impact differential treatment response. However, when benzodiazepine dosage was considered, there was a significant impact of benzodiazepine use on differential treatment response. Oral benzodiazepines significantly impacted HDRS-6 (P=.018) and Clinical Global Impressions–Severity of Illness scale (CGI-S; P=.008) scores at day 1 (24 hours post treatment); effects were nonsignificant for all day 3 outcomes. Among ketamine subjects, higher doses of benzodiazepines were associated with less improvement in depression scores at day 1.

**Conclusions:** Concomitant oral benzodiazepines at higher doses may attenuate the antidepressant effects of IV ketamine at day 1 but not day 3 post-infusion.

Trial Registration: ClinicalTrials.gov identifier: NCT01920555.

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etamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a novel and rapidly acting treatment for major depressive disorder (MDD). Intravenous (IV) ketamine, though not currently approved as an antidepressant by the US Food and Drug Administration (FDA), is increasingly being prescribed by clinicians, often as an adjunctive therapy to patients with treatment-resistant depression (TRD).<sup>1-3</sup> In clinical practice, patients with MDD are often prescribed benzodiazepines for associated anxiety symptoms and/or insomnia, as anxiety often coexists with depression<sup>4</sup> and studies have shown the benefit of the combination of benzodiazepines with antidepressants.<sup>5,6</sup> In a large US cohort study,<sup>7</sup> 10.6% of patients with depression who initiated an antidepressant medication did so concurrently with a benzodiazepine. A small number of studies have examined the impact of benzodiazepines on the antidepressant effects of ketamine and esketamine to date, with contradictory findings. Some studies<sup>8,9</sup> have found that benzodiazepines do not impact the antidepressant effects of ketamine and esketamine, while, conversely, other studies<sup>10-13</sup> have concluded that benzodiazepines may attenuate or slow the antidepressant effects of ketamine, particularly at higher benzodiazepine doses.

As benzodiazepines are often prescribed for anxiety associated with MDD, previous studies of the impact of anxious features on ketamine's effects may be informative. We previously studied the efficacy of a range of doses of a single infusion of IV ketamine compared to active placebo as an adjunct to standard antidepressant therapy in outpatients with TRD.<sup>14</sup> In that study, the 0.1-mg/ kg, 0.5-mg/kg, and 1.0-mg/kg doses of IV ketamine were superior to IV midazolam placebo on the primary outcome measure of depressive symptoms. A post hoc analysis



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## **Clinical Points**

- Patients with depression are often prescribed benzodiazepines for associated anxiety or insomnia symptoms; however, it is not clear whether benzodiazepines may impact the antidepressant effects of ketamine.
- This study examined the impact of concomitant benzodiazepines on response to ketamine versus midazolam placebo.
- At higher doses and early on, concomitant oral benzodiazepines may be associated with a reduction in ketamine's antidepressant effects.

of those data examined the effect of anxious depression at baseline on response to ketamine versus placebo at 1 and 3 days post-infusion; response to IV ketamine was observed to be similar in anxious and non-anxious TRD subjects.<sup>15</sup> An open-label study of the effect of a single infusion of IV ketamine in unmedicated patients with TRD<sup>16</sup> found that those with anxious depression at baseline had greater improvement in depressive symptoms and longer time to relapse compared to those with non-anxious depression. These observations further support the need to better understand how commonly used medications for anxiety, such as benzodiazepines, impact response to IV ketamine.

Benzodiazepines act as y-aminobutyric acid-A (GABA-A) receptor agonists and increase the inhibitory tone of GABA interneurons.<sup>17,18</sup> The mechanism of action of ketamine is not yet fully understood; it is proposed to involve NMDA receptor blockade of GABA interneurons, a glutamate surge, activation of α-amino-3-hydroxy-5methyl-4-isoxazolepropionic acid receptors, up-regulation of brain-derived neurotrophic factor, and activation of downstream signaling pathways.<sup>19,20</sup> GABAergic interneurons are therefore a shared target of both ketamine and benzodiazepines: by blocking NMDA receptors on these interneurons, ketamine decreases inhibition, enabling the glutamate surge, while on the other hand, benzodiazepines increase the inhibitory tone of these interneurons. These seemingly oppositional effects would suggest that benzodiazepines might interfere with or attenuate ketamine's antidepressant effects.<sup>21</sup>

Against this background, we sought to examine the data from a large randomized clinical trial to assess whether the concomitant use of oral benzodiazepines affected the antidepressant effect of IV ketamine observed in this trial. In particular, we sought to elucidate the extent to which benzodiazepine dosage is important in considering the impact of concomitant benzodiazepines on ketamine's effects.

#### **METHODS**

#### Study Overview and Design

A detailed description of the original trial design has already been published.<sup>14</sup> This multisite, randomized,

efficacy of IV ketamine compared to IV midazolam, added to ongoing antidepressant treatment in adults with TRD. The trial ran from December 2015 to December 2016. This work was a collaborative effort between the Massachusetts General Hospital (MGH) Clinical Trials Network and Institute (CTNI), multiple academic sites, and the National Institute of Mental Health (NIMH). All participants signed written informed consent forms approved by the respective Institutional Review Board and NIMH Data Safety and Monitoring Board. The study was registered at ClinicalTrials.gov (identifier: NCT01920555).

All participants had a Montgomery-Asberg Depression Rating Scale  $(MADRS)^{22}$  score > 20 at the screening and baseline visits. Ninety-nine participants were randomly assigned to 1 of 5 arms (1:1:1:1:1): a single infusion of ketamine 0.1 mg/kg (n = 18), 0.2 mg/kg (n = 20), 0.5 mg/ kg (n = 22), or 1.0 mg/kg (n = 20) or midazolam 0.045 mg/ kg (n = 19). Midazolam was used as the active placebo as it can mimic some of the psychotropic effects of ketamine and therefore minimize unblinding.

The study drug was given at the baseline visit (day 0); assessments were done at days 0, 1, 3, 5, 7, 14, and 30. The 6-item Hamilton Depression Rating Scale (HDRS-(6),<sup>23–25</sup> assessing the past 24 hours, was administered as the primary outcome measure at each visit by independent, remote MGH CTNI raters. The primary analysis of the original study examined the first 72 hours post-infusion. The Clinical Global Impressions-Severity of Illness scale (CGI-S)<sup>26</sup> was also administered at day 1; the HDRS-6, CGI-S, and MADRS were administered at day 3.

#### **Patient Selection**

Outpatients (aged 18 to 70 years) with a primary diagnosis of MDD (defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [DSM-IV-TR] criteria) of at least 8 weeks' duration were selected. Participants met criteria for TRD in this episode, defined as the failure to achieve a subjective satisfactory response (< 50% improvement of depression symptoms) to at least 2 adequate treatment courses during the current episode, with current treatment at a minimal dose approved for the treatment of MDD, lasting at least 8 weeks. Treatment resistance was assessed using the MGH Antidepressant Treatment Response Questionnaire (ATRQ).<sup>27</sup> Allowed psychotropic medications were kept constant in dose for 4 weeks prior to randomization and throughout the study. Chronic use of a benzodiazepine hypnotic at a stable dose was allowed. The use of benzodiazepines as anxiolytics was not initially allowed; however, to facilitate recruitment and optimize generalizability, the protocol was later revised to allow for the inclusion of subjects taking chronic benzodiazepines as anxiolytics. Benzodiazepines had to be stable in dose for at least 4 weeks prior to randomization and could not be taken within 2 hours of the study infusion. No maximum daily benzodiazepine dose was specified.

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Table 1. Characteristics of Subjects With and Without Benzodiazepine Use

	Subjects Ta Benzodia: n=44 (44. Study Su	king Oral zepines, 4% of All bjects)	Subjects Not Taking Oral Benzodiazepines, n = 55 (55.6% of All Study Subjects)		
Characteristic	Mean (SD)	n (%)	Mean (SD)	n (%)	Р
Demographics					
Age, y Female Hispanic Race White Asian Black Other	48.7 (12.1)	23 (52.3) 3 (6.8) 43 (97.7) 0 (0.0) 1 (2.3) 0 (0.0)	44.1 (12.8)	26 (47.3) 0 (0.0) 45 (81.8) 5 (9.1) 3 (5.5) 2 (3.6)	.465 .621 .111 .141
BMI, kg/m <sup>2</sup>	25.5 (4.3)	. (,	25.6 (4.1)	()	.891
Concomitant Medications					
Non-benzodiazepine hypnotic SSRI SNRI TCA Other antidepressants <sup>a</sup>		14 (31.8) 23 (52.3) 15 (34.1) 2 (4.5) 17 (38.6)		7 (12.7) 29 (52.7) 13 (23.6) 1 (1.8) 34 (61.8)	.021 .964 .251 .583 .022
Clinical Severity at Baseline, Scor	e				
HDRS-AS HDRS-6, total MADRS CGI-S	7.1 (2.4) 13.0 (2.3) 35.2 (7.2) 5.3 (0.7)		5.8 (2.5) 12.5 (1.8) 31.6 (5.1) 4.9 (0.7)		.009 .290 .005 .002

<sup>a</sup>Other antidepressants = bupropion, mirtazapine, and vortioxetine.

Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions–Severity of Illness scale, HDRS-6 = 6-item Hamilton Depression Rating Scale, HDRS-AS = Hamilton Depression Rating Scale Anxiety-Somatization factor, MADRS = Montgomery-Asberg Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective

serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

#### Statistical Analysis

Data analyses for this article were generated using SAS software, Version 9.4 of the SAS System for Windows 6.3 (SAS, 2013). To describe the sample with respect to the main variable of interest, ie, benzodiazepine use or not, we used  $\chi^2$  tests and Fisher exact tests to test for differences between participants who were and were not taking benzodiazepines. Demographics and clinical features at baseline were examined.

To test for an overall effect of concomitant benzodiazepine use on treatment response, we fit a fixed-effects model in which depression score was the outcome and the predictors were SITE (6 sites), depression score at baseline (scale corresponding with that being assessed as the dependent variable), randomized group (GROUP), benzodiazepine use (BENZO: yes/no), and the interaction effect between randomized group and benzodiazepine use (treatment-by-benzodiazepine effect). Site effect was modeled as a fixed effect, based on Feaster et al.<sup>28</sup> We fit separate models for day 1 and day 3 outcomes. A significant treatmentby-benzodiazepine effect could be interpreted as a possible moderating effect of benzodiazepines on the treatment effect of ketamine, in which the use of benzodiazepines could lead to differential ketamine treatment effects. Of main interest was the effect of concomitant benzodiazepine use on HDRS-6 scores at day 1, the primary outcome of the original study.<sup>14</sup> In separate exploratory analyses, we also examined the impact of benzodiazepine use on treatment effects as measured by CGI-S and MADRS scores. Because statistical power was limited due to the small sample size and corresponding statistical power in this post hoc analysis, we examined all ketamine doses combined versus midazolam.

In a more detailed analysis, we examined the impact of benzodiazepine dosage. As patients were taking various oral benzodiazepines, we used

an online calculator (https://clincalc.com/ Benzodiazepine/) to convert all benzodiazepines to an equivalent daily dosage of diazepam, in milligrams. The overall model structure was the same as described in the previous paragraph, except that benzodiazepine use was entered as a continuous rather than a binary predictor. A simple linear trend was modeled. Subjects who did not use benzodiazepines were assigned a 0, and benzodiazepine use ranged between 3.8and 60-mg diazepam equivalent. Lower dosages were more common; the median benzodiazepine dose was 8.0 mg. Three subjects were taking more than one oral benzodiazepine; equivalent diazepam doses were summed. For subjects taking benzodiazepines on an "as needed" (or "pro re nata") basis, it was assumed that they were taking the maximum daily dosage allowed. As this approach could have overestimated the amount of benzodiazepine subjects were receiving, we conducted a sensitivity analysis in which we excluded those taking "as needed" benzodiazepines. In this reduced sample, the range remained 3.8–60 mg, but the new median was 11.0 mg. To describe the directionality of the continuous dosage variable, we calculated means and examined for differences between those on no benzodiazepines, those on a low dose (below the median), and those on a high dose (above the median).

Finally, in an analysis focused only on subjects randomized to ketamine, we tested whether benzodiazepine dosage had an impact on change in depression scores at days 1 and 3. In this model, depression score was the dependent variable, and site, depression score at baseline, and benzodiazepine dosage were the predictor variables. For all analyses, significance was set at P < .05.

#### RESULTS

### Comparison of Subjects With and Without Benzodiazepine Use

In comparing subjects with and without benzodiazepine use (Table 1), there were no significant demographic differences. Some differences were noted regarding medication use and clinical severity at baseline. The use of non-benzodiazepine hypnotics was more common among benzodiazepine users (31.8% vs 12.7%, P=.021) and "other" antidepressant use (bupropion, mirtazapine, and vortioxetine) was less common among benzodiazepine users (38.6% vs 61.8%, P=.022). At baseline, severity of anxious depression (determined by the Hamilton Depression Rating Scale Table 2. The Differential Effect of Concomitant Oral Benzodiazepine Use on Response to Ketamine Versus Midazolam (ie, Significance of the Treatment-by-Benzodiazepine Effect) With Benzodiazepine Use as a Binary Predictor<sup>a</sup>

Outcome	Num df	Den <i>df</i>	F Value	Р
Day 1				
HDRS-6	1 1	84 85	1.29 1.03	.259
Day 3		05	1.05	.512
HDRS-6	1	82	0.57	.454
MADRS	1	83	0.10	.758
CGI-S	1	83	0.00	.988

<sup>a</sup>Analysis of all ketamine arms combined vs midazolam group; MADRS was not administered on day 1; the full model for each outcome was outcome = SITE + BASELINE + GROUP + BENZO + treatment-by-benzodiazepine.

Abbreviations: BASELINE = depression score at baseline,

BENZO = benzodiazepine use, CGI-S = Clinical Global Impressions–Severity of Illness scale, Den = denominator, GROUP = randomized group, HDRS-6 = 6-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, Num = numerator, SITE = 1 of 6 sites.

Table 3. The Differential Effect of Concomitant Oral Benzodiazepine Use on Response to Ketamine Versus Midazolam (ie, Significance of the Treatment-by-Benzodiazepine Effect) With Benzodiazepine Use as a Continuous Predictor<sup>a</sup>

Outcome	Num <i>df</i>	Den <i>df</i>	F Value	Р
Day 1				
HDRS-6	1	83	5.86	.018
CGI-S	1	83	7.45	.008
Day 3				
HDRS-6	1	81	1.74	.191
MADRS	1	81	2.64	.108
CGI-S	1	81	1.16	.285

<sup>a</sup>Analysis of all ketamine arms combined vs midazolam group; MADRS was not administered on day 1; the full model for each outcome was outcome = SITE + BASELINE + GROUP + BENZODOSE + treatment-bybenzodiazepine dose.

Abbreviations: BASELINE = depression score at baseline,

BENZODOSE = benzodiazepine dose, CGI-S = Clinical Global

Impressions-Severity of Illness scale, Den = denominator,

GROUP = randomized group, HDRS-6=6-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, Num = numerator. SITE = 1 of 6 sites.

Anxiety-Somatization factor [HDRS-AS]) was higher among benzodiazepine users than among non-users (mean score = 7.1 vs 5.8, P=.009), as was the mean MADRS score (35.2 vs 31.6, P=.005) and CGI-S score (5.3 vs 4.9, P=.002). Notably, the two groups did not differ significantly at baseline on the primary outcome measure, the HDRS-6. A more detailed version of Table 1, dividing benzodiazepine users and non-users into those randomized to ketamine versus midazolam, is included as Supplementary Table 1.

## Effect of Benzodiazepine Use on Differential Treatment Response to Ketamine

The fixed-effects model, which tested the treatment-bybenzodiazepine effect, ie, the effect of benzodiazepine use on differential treatment effect (taking benzodiazepines as a binary predictor), was nonsignificant for the HDRS-6, CGI-S, and MADRS as measured on days 1 and 3 (Table 2). Table 4. Mean Change in HDRS-6 and CGI-S Scores by Treatment Group at Day 1 Among Subjects Taking No Benzodiazepines and Subjects on Concomitant Oral Benzodiazepines (Doses Above and Below the Median)

	Ra to	Randomized to Ketamine		Randomized to Midazolam	
Variable		Mean (SD)	n	Mean (SD)	
Change in HDRS-6 Score, Day 1					
No oral benzodiazepines Benzodiazepine dose below median (≤ 8 mg diazepam) Benzodiazepine dose above median	40 19 17	-6.2 (4.2) -4.9 (4.0) -3.7 (4.1)	12 3 3	-2.2 (3.2) -2.7 (1.5) -3.3 (3.1)	
(> 8 mg diazepam equivalent) Change in CGI-S Score, Day 1					
No oral benzodiazepines Benzodiazepine dose below median (≤ 8 mg diazepam)	41 19	-1.4 (1.2) -1.8 (1.6)	12 3	-0.3 (0.8) 0.0 (0.0)	
Benzodiazepine dose above median (> 8 mg diazepam equivalent)	17	-1.1 (1.5)	3	-1.7 (0.6)	

Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness scale, HDRS-6 = 6-item Hamilton Depression Rating Scale.

## Relationship Between Benzodiazepine Dosage and Differential Treatment Response to Ketamine

When the fixed-effects model that tested the treatmentby-benzodiazepine effect was repeated with benzodiazepine use entered as a continuous rather than a binary predictor, there was a significant effect on day 1 HDRS-6 and CGI-S outcomes; effects were nonsignificant for all day 3 outcomes (Table 3).

To demonstrate the directionality of the significant effects seen in Table 3, we examined mean change in HDRS-6 and CGI-S scores at day 1, using the median benzodiazepine dosage to divide subjects into high- and low-dose users. The median prescribed equivalent dosage of diazepam was 8 mg total per day. There was a greater mean reduction in HDRS-6 score at day 1 among ketamine subjects prescribed a "low" dose of benzodiazepine ( $\leq 8$  mg diazepam equivalent, n = 19, mean [SD] change: -4.9 [4.0]) than among those prescribed a "high" dose (>8 mg diazepam equivalent, n = 17, mean [SD] change: -3.7 [4.1]). These analyses are exploratory, in the context of a secondary analysis with small numbers of subjects in all groups (Table 4).

## Relationship Between Benzodiazepine Dosage and Response to Ketamine in the Active Treatment Group

When the fixed-effects model that tested the main effect of benzodiazepine dosage on change in depression score was repeated with only patients randomized to ketamine, there was a significant effect for the HDRS-6 at day 1 (estimate [EST] = 0.12; 95% CI, 0.04-0.20; P=.005), but not for the CGI-S at day 1 or for any day 3 outcomes (Table 5). In other words, with higher doses of concomitant oral benzodiazepines, less improvement on the HDRS-6 was observed at day 1 among subjects randomized to ketamine.

## Repeated Analyses Excluding Subjects Taking "as Needed" Benzodiazepines

Ten (22.7%) of 44 subjects taking benzodiazepines were taking "as needed" benzodiazepines. Given that we may

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Table 5. The Effect of Concomitant Oral Benzodiazepine	
Dose on Treatment Response Among Patients Randomized	
to Ketamine, With Benzodiazepine Use as a Continuous	
Predictor <sup>a</sup>	

Outcome	EST	95% CI	t Value	Р
Day 1				
HDRS-6	0.12	0.04 to 0.20	2.94	.005
CGI-S	0.02	-0.002 to 0.05	1.85	.069
Day 3				
HDRS-6	0.08	-0.006 to 0.16	1.85	.070
MADRS	0.16	-0.05 to 0.38	1.52	.133
CGI-S	0.02	-0.01 to 0.05	1.41	.162

<sup>a</sup>MADRS was not administered on day 1; the full model for each outcome was outcome = SITE + BASELINE + BENZODOSE.

Abbreviations: BASELINE = depression score at baseline,

BENZODOSE = benzodiazepine dose, CGI-S = Clinical Global Impression-Severity scale, EST = estimate, HDRS-6 = 6-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SITE = 1 of 6 sites.

have overestimated the amount of oral benzodiazepine some subjects were receiving (as we used the maximum daily dose for subjects on "as needed" benzodiazepines), we conducted a sensitivity analysis repeating the analyses reported in Tables 2, 3, and 5, but excluding subjects who were taking "as needed" benzodiazepines. Results were not impacted in a meaningful way for analyses examining benzodiazepine use in a binary fashion (ie, analyses in Table 2). In examining benzodiazepine use as a continuous variable, all effects remained significant, and in examining ketamine subjects only (ie, analyses in Table 5) two additional effects became significant, in the expected direction: the effect of dose on day 1 change in CGI-S score increased (EST change from 0.02 to 0.03; 95% CI, 0.003–0.05; P = .032), as did the effect on the day 3 MADRS score (EST change from 0.16 to 0.23; 95% CI, 0.01–0.45; P=.04).

## DISCUSSION

This study examined whether the use of concomitant oral benzodiazepines differentially affected treatment response to ketamine versus midazolam by analyzing data from a randomized controlled trial and found that higher doses of concomitant oral benzodiazepines were associated with a reduction in ketamine's antidepressant effects at day 1, but not day 3 post-infusion. By examining benzodiazepine dosage, our study goes further than previous reports toward understanding the impact of coadministration of benzodiazepines and ketamine, an important clinical question.

While our initial analysis, taking benzodiazepine use as a binary predictor, indicated no significant differences between the ketamine and midazolam groups, when benzodiazepine dosage was considered, differences emerged. Notably, the groups differed in scores on the HDRS-6 and CGI-S at day 1, but these differences were not observed at day 3. This finding may suggest that the impact of oral benzodiazepines on the antidepressant effects of ketamine is detectable only early on and at higher benzodiazepine doses. Higher doses of oral benzodiazepines were associated with a smaller reduction in HDRS-6 scores among patients randomized to ketamine. Changes in HDRS-6 scores were similar across benzodiazepine doses (none/high/low) among subjects randomized to midazolam (though numbers were small in these groups). When only ketamine subjects were examined and dosage was taken as a continuous predictor, again there was a significant effect on treatment response as measured at day 1, with higher doses of benzodiazepines associated with less improvement in depression scores.

An alternative explanation for our findings may be that those on higher doses of benzodiazepines might have had more severe symptoms, leading to less response to ketamine, rather than benzodiazepines' reducing the effects of ketamine. One further explanation may be that as benzodiazepine users were asked to hold their prescribed oral benzodiazepine in the 2 hours before the infusion, the observed reduced efficacy of ketamine among benzodiazepine users at day 1 could have reflected the missed dose of benzodiazepine rather than benzodiazepine dosage. It should also be noted that in our previous analysis of these data,<sup>15</sup> ketamine was found to be equally efficacious in treating TRD subjects with and without anxious depression.

Our results are in line with the findings of previous studies which have suggested that higher doses of concomitant oral benzodiazepines may attenuate ketamine's therapeutic effects. Specifically, Andrashko et al<sup>11</sup> found that a cutoff of 8 mg/d of diazepam distinguished ketamine responders from non-responders, with higher benzodiazepine doses attenuating response to ketamine. Notably, the overall response rate in that study was low, 28% (13/47 participants). Much smaller studies (N = 1 to 13) have found that mean daily dose of benzodiazepine among ketamine responders was significantly lower than that among non-responders,<sup>12</sup> that a high-dose benzodiazepine substantially impacted observed clinical response (a case report of a patient on equivalent of 26 mg diazepam),<sup>13</sup> and that benzodiazepines slowed time to ketamine response and shortened time to loss of therapeutic effect.<sup>10</sup>

However, other studies have concluded that concomitant oral benzodiazepines do not impact response to ketamine/ esketamine. In a secondary analysis of the ASPIRE I and II esketamine global clinical trial data (451 inpatients with MDD and acute suicidal ideation/behavior),<sup>8</sup> the antidepressant effects of esketamine were not attenuated or augmented by oral benzodiazepine use. Doses of  $\leq 6 \text{ mg}$ lorazepam (ie,  $\leq 45$  mg diazepam equivalent) were allowed in that study, and benzodiazepine use was taken as a binary predictor in the analysis. We, similarly, did not observe an effect in our binary analysis. Shiroma et al<sup>9</sup> also did not observe a difference between subjects taking and not taking concomitant benzodiazepines on endpoint MADRS score (24 hours after last infusion) in a study that compared 6 ketamine infusions to 5 midazolam infusions plus 1 ketamine infusion (N = 54).

Our study contributes to our knowledge of the clinical effects of IV ketamine and how oral benzodiazepines may

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**It is illegal to post this copy** influence these effects. Strengths of our study include that the original study had a double-blind, randomized, controlled design with use of an active placebo; that remote rating was used to reduce unblinding; that oral benzodiazepines and antidepressants were kept constant in dose in the 4 weeks prior to randomization and during the follow-up period; that the number of subjects in this analysis was larger than in most previous reports on this topic; and that benzodiazepine use was examined as both a binary and a continuous predictor.

Limitations of this study include that this was a post hoc analysis and the original study was not designed to measure the impact of oral benzodiazepines on treatment response; higher order interactions (3-way interactions, or more) and nonlinear interactions may also exist; the placebo used in this study, midazolam, is itself a benzodiazepine and could have influenced the observed effects of oral benzodiazepines in the placebo group; and due to the design of the original study, the number of subjects in the placebo group was small (n = 19) and only 6 of these patients were taking oral benzodiazepines. However, the effects of benzodiazepines

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International, Bristol-Myers Squibb, Cowen, EMA Wellness, Engrail Therapeutics, Clexio, Denovo Biopharma, Gilgamesh, Hoffman–La Roche, Intra-Cellular Therapies, Janssen, Levo, Lundbeck, Merck, Navitor Pharmaceuticals, Neurocrine, Novartis, Noven Pharmaceuticals, Otsuka, Perception Neuroscience, Praxis Therapeutics, Sage Pharmaceuticals, Servier Pharmaceuticals, Seelos Pharmaceuticals, Taisho Pharmaceuticals, Teva, Valeant, Vistagen Therapeutics, and XW Laboratories, and he received research contracts from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Johnson & Johnson, Merck, Naurex, and Usona over the past 36 months. Dr Sanacora holds equity in BioHaven Pharmaceuticals and is a co-inventor on a US patent (#8,778,979) held by Yale University and a co-inventor on US Provisional Patent Application No. 047162-7177P1 (00754) filed on August 20, 2018, by Yale University Office of Cooperative Research, Yale University has a financial relationship with Janssen Pharmaceuticals and may in the future receive financial benefits from this relationship. The University has put multiple measures in place to mitigate this institutional conflict of interest. Questions about the details of these measures should be directed to Yale University's Conflict of Interest office. Dr Mathew is supported through the use of facilities and resources at the Michael E. Debakey VA Medical Center, Houston, Texas, and receives support from The Menninger Clinic. Dr Mathew has served as a consultant to Alkermes, Allergan, Axsome Therapeutics, BioXcel Therapeutics, Clexio Biosciences, Eleusis, EMA Wellness, Engrail Therapeutics, Greenwich Biosciences, Intra-Cellular Therapies, Janssen, Levo Therapeutics, Neurocrine, Perception Neuroscience, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, and Signant Health. He has received research support from Biohaven Pharmaceuticals, Merck, Sage Therapeutics, and VistaGen Therapeutics. Dr DeBattista: Grant support: Biolite, Compass, Sage, Relmada, and Janssen Consultant: Corcept Therapeutics, Sage, Alkermes, and AbbVie. Dr lonescu is a full-time employee of Janssen. Dr Cusin has served as consultant at Janssen, Takeda, Alkermes and Perception

**contect PDF on any website** observed when just subjects taking ketamine were considered are informative. In addition, this study ascertained treatment response after only a single infusion of ketamine; it is not clear if results would be consistent in protocols of repeated ketamine treatments. Finally, following a protocol change to facilitate recruitment and optimize generalizability, the inclusion of subjects on stable benzodiazepines for anxiety was allowed; this change could have influenced our findings. Because this change was approved on different dates at the 6 clinical sites and numbers at each site were small, a sensitivity analysis examining how this change influenced our results would likely be underpowered.

In conclusion, our study indicates that the use of concomitant oral benzodiazepines may be associated with a reduction in ketamine's antidepressant effect after a single IV infusion; this effect was seen only at higher benzodiazepine doses and only at day 1. Future research should examine the impact of benzodiazepine dosage on ketamine's effects among larger samples and in studies with this specific objective, rather than by retrospective analysis like the current literature.

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Effect of Benzodiazepines on Antidepressant Effects of Ketamine

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## REFERENCES

- Wilkinson ST, Sanacora G. Considerations on the off-label use of ketamine as a treatment for mood disorders. JAMA. 2017;318(9):793–794.
- Wilkinson ST, Toprak M, Turner MS, et al. A survey of the clinical, off-label use of ketamine as a treatment for psychiatric disorders. Am J Psychiatry. 2017;174(7):695–696.
- Skånland SS, Cieślar-Pobuda A. Off-label uses of drugs for depression. *Eur J Pharmacol.* 2019;865:172732.
- Cosci F, Fava GA. When anxiety and depression coexist: the role of differential diagnosis using clinimetric criteria. *Psychother Psychosom*. 2021;90(5):308–317.
- Smith WT, Londborg PD, Glaudin V, et al. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. *Am J Psychiatry*. 1998;155(10):1339–1345.
- 6. Papakostas GI, Clain A, Ameral VE, et al. Fluoxetine-clonazepam cotherapy for anxious depression: an exploratory, post-hoc analysis of a randomized, double blind study. *Int Clin*

- Psychopharmacol. 2010;25(1):17–21.
  Bushnell GA, Stürmer T, Gaynes BN, et al. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001–2014. JAMA Psychiatry. 2017;74(7):747–755.
- Diekamp B, Borentain S, Fu DJ, et al. Effect of concomitant benzodiazepine use on efficacy and safety of esketamine nasal spray in patients with major depressive disorder and acute suicidal ideation or behavior: pooled randomized, controlled trials. *Neuropsychiatr Dis Treat*. 2021;17:2347–2357.
- Shiroma PR, Thuras P, Wels J, et al. A randomized, double-blind, active placebocontrolled study of efficacy, safety, and durability of repeated vs single subanesthetic ketamine for treatment-resistant depression. *Transl Psychiatry*. 2020;10(1):206.
- Albott CS, Shiroma PR, Cullen KR, et al. The antidepressant effect of repeat dose intravenous ketamine is delayed by concurrent benzodiazepine use. J Clin Psychiatry. 2017;78(3):e308–e309.
- Andrashko V, Novak T, Brunovsky M, et al. The antidepressant effect of ketamine is dampened by concomitant benzodiazepine medication. Front Psychiatry. 2020;11:844.
- Frye MA, Blier P, Tye SJ. Concomitant benzodiazepine use attenuates ketamine response: implications for large scale study design and clinical development. J Clin Psychopharmacol. 2015;35(3):334–336.
- Ford N, Ludbrook G, Galletly C. Benzodiazepines may reduce the effectiveness of ketamine in the treatment of depression. *Aust N Z J Psychiatry*. 2015;49(12):1227.
- Fava M, Freeman MP, Flynn M, et al. Doubleblind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry*. 2020;25(7):1592–1603.
- Salloum NC, Fava M, Freeman MP, et al. Efficacy of intravenous ketamine treatment in anxious versus nonanxious unipolar treatment-resistant depression. *Depress Anxiety*. 2019;36(3):235–243.
- Ionescu DF, Luckenbaugh DA, Niciu MJ, et al. Effect of baseline anxious depression on initial and sustained antidepressant response to ketamine. J Clin Psychiatry. 2014;75(9):e932– e938.
- Castellano D, Shepard RD, Lu W. Looking for novelty in an "old" receptor: recent advances toward our understanding of GABA<sub>A</sub>Rs and their implications in receptor pharmacology. *Front Neurosci.* 2021;14:616298.
- Balon R, Starcevic V. Role of benzodiazepines in anxiety disorders. *Adv Exp Med Biol.* 2020;1191:367–388.
- Strasburger SE, Bhimani PM, Kaabe JH, et al. What is the mechanism of Ketamine's rapidonset antidepressant effect? a concise overview of the surprisingly large number of possibilities. J Clin Pharm Ther. 2017;42(2):147–154.
- Irwin MN, VandenBerg A. Retracing our steps to understand ketamine in depression: a focused review of hypothesized mechanisms of action. *Ment Health Clin*. 2021;11(3):200–210.
- Veraart JKE, Smith-Apeldoorn SY, Bakker IM, et al. Pharmacodynamic interactions between ketamine and psychiatric medications used in the treatment of depression: a systematic review. Int J Neuropsychopharmacol. 2021;24(10):808–831.
- 22. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.

Feeney et al 23. Hamilton M. A rating scale for depression. 24. Guy W. ECDEU Assessment Manual for PDF Modeling site effects in the design and analysis

- 1960;23(1):56–65.
  Bech P, Allerup P, Gram LF, et al. The Hamilton Depression Scale: evaluation of objectivity using logistic models. *Acta Psychiatr Scand*. 1981;63(3):290–299.
- Carrozzino D, Patierno C, Fava GA, et al. The Hamilton Rating Scales for depression: a critical review of clinimetric properties of different versions. *Psychother Psychosom*. 2020;89(3):133–150.

Psychopharmacology. Rockville: US Department of Health, Education, and Welfare; Public Health Service; Alcohol, Drug Abuse, and Mental Health Administration; 1976.

- Chandler GM, losifescu DV, Pollack MH, et al. RESEARCH: Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci Ther. 2010;16(5):322–325.
- 28. Feaster DJ, Mikulich-Gilbertson S, Brincks AM.

of multi-site trials. *Am J Drug Alcohol Abuse*. 2011;37(5):383–391.

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# Supplementary Material

- Article Title: Effect of Concomitant Benzodiazepines on the Antidepressant Effects of Ketamine: Findings From the RAPID Intravenous Ketamine Study
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## List of Supplementary Material for the article

1. <u>Table 1</u> Characteristics of subjects with and without benzodiazepine use

## **Disclaimer**

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## Supplementary Table 1. Characteristics of subjects with and without benzodiazepine use

			Subjects taking oral benzodiazepines		Subjects not taking oral benzodiazepines					
			N=44 (44.4% of all study subjects)				N=55 (55.6% of all study subjects)			
			Ketami	ine n=38	Midazo	lam n=6	Ketamine n=42		Midazolam n=13	
			Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)
Demographics	Age		48.7 (12.2)		48.6 (11.9)		44.1 (12.3)		44.2 (14.8)	
	Female			19 (50.0)		4 (66.7)		19 (45.2)		7 (53.8)
	Hispanic			3 (7.9)		0 (0.0)		0 (0.0)		0 (0.0)
	Race									
		White		37 (97.4)		6 (100.00)		33 (78.6)		12 (92.3)
		Asian		0 (0.0)		0 (0.0)		5 (11.9)		0 (0.0)
		Black		1 (2.6)		0 (0.0)		3 (7.1)		0 (0.0)
		Other		0 (0.0)		0 (0.0)		1 (2.4)		1 (7.7)
	ВМІ		25.4 (4.3)		26.0 (4.5)		25.3 (4.1)		26.4 (4.2)	
Concomitant	Non-benzodiazepine			13 (34.2)		1 (16.7)		4 (9.5)		3 (23.1)
medications	hypnotic									
	SSRI			19 (50.0)		4 (66.7)		23 (54.8)		6 (46.2)
	SNRI			15 (39.5)		0 (0.0)		8 (19.1)		5 (38.5)
	ТСА			2 (5.3)		0 (0.0)		1 (2.3)		0 (0.0)
	Other antidepressants			14 (36.8)		3 (50.0)		26 (61.9)		8 (61.5)

Clinical Severity at		6.8 (2.5)	8.2 (3.3)	5.7 (2.5)	6.0 (2.6)
Baseline	HAMD-AS				
	HAM-D-6 - total	12.9 (2.4)	14.2 (2.5)	12.5 (1.6)	12.5 (2.2)
	MADRS	34.3 (6.9)	38.0 (11.0)	31.5 (5.2)	32.0 (4.9)
	CGI-S	5.3 (0.7)	5.2 (0.8)	4.8 (0.7)	4.9 (0.8)

Abbreviations: SD= Standard Deviation, BMI= Body Mass Index, SSRI= Selective Serotonin Reuptake Inhibitor, SNRI= Serotonin Norepinephrine Reuptake Inhibitor, TCA= Tricyclic Antidepressant,

HAMD-AS= Hamilton Depression Rating Scale Anxiety-Somatization factor, HAM-D-6= 6-item Hamilton Depression Rating Scale, MADRS= Montgomery-Asberg Depression Rating Scale, CGI-S= Clinical

Global Impression-Severity scale

Note: Other antidepressants= bupropion, mirtazapine and vortioxetine