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**The Antidepressant Effect of Repeat Dose Intravenous Ketamine Is Delayed by Concurrent Benzodiazepine Use**

**To the Editor:** Standard pharmacologic treatment options for depressive symptoms are generally unable to achieve remission quickly. This delay may account for the substantial morbidity and mortality associated with unremitted depression.<sup>1</sup> The discovery of the rapid-acting antidepressant effects of ketamine has generated significant interest and led to ketamine being labeled “the most important [drug] discovery in half a century.”<sup>2(p68)</sup> A growing literature attests to ketamine’s rapid but transient antidepressant actions in patients with treatment-resistant depression (TRD).<sup>3,4</sup> To extend the clinical applicability of ketamine, several open-label trials<sup>4-6</sup> have used ketamine as an augmenting agent, allowing participants to continue prestudy medications. Results from these studies enable characterization of potential drug interactions and shed light on the underlying mechanism of ketamine response.

**Method.** We present a post hoc analysis of an original study<sup>5</sup> examining the effect of concurrent benzodiazepine treatment on antidepressant response to 6 ketamine infusions (0.5 mg/kg; 1 infusion every Monday, Wednesday, and Friday for 2 weeks) in individuals with TRD. The study was conducted at the Minneapolis Veterans Affairs Medical Center from October 2012 to August 2013 and approved by the institutional review board. All subjects provided written and informed consent prior to participation.

Inclusion criteria included men and women aged 18–70 years, with major depressive disorder (MDD) resistant to treatment (defined as failure to achieve remission from 2 adequately dosed antidepressants of different pharmacologic classes per the Antidepressant Treatment History Form<sup>7</sup>).

Exclusion criteria included any unstable medical condition, any nonpsychiatric central nervous system disorder, any Axis I

disorder other than MDD judged to be the primary diagnosis, active substance use disorder within 6 months of study entry, lifetime history of psychosis, positive urine toxicology, or positive urine pregnancy screen for women. The Montgomery-Asberg Depression Rating Scale (MADRS)<sup>8</sup> was administered by study clinicians immediately before and after each infusion, as well as 1 hour and 2 hours after cessation of each infusion.

Of the 13 individuals who completed all 6 infusions, 4 were taking benzodiazepines (mean daily dose = 2.75 mg lorazepam equivalents).

**Results.** There was no statistically significant difference between benzodiazepine users and benzodiazepine nonusers in baseline demographic or clinical characteristics, depression response (MADRS score ≤ 50% of baseline) rate or remission (MADRS score < 10) rate after 6 infusions or in depression relapse (MADRS score ≥ 50% of baseline) rate during the 28-day follow-up period (Table 1). However, benzodiazepine users showed a significantly longer time to antidepressant response ( $P = .029$ ), a significantly longer time to depression remission ( $P = .042$ ), and a significantly shorter time to depression relapse ( $P = .020$ ) (Table 1). In short, benzodiazepine users reached the same outcomes as benzodiazepine nonusers but took a longer time to reach those outcomes and also showed a significantly shorter time to loss of therapeutic effect.

The current findings add to a prior clinical report suggesting that benzodiazepines interfere with ketamine response.<sup>9</sup> Interestingly, ketamine has been noted to be particularly effective for individuals with anxious depression and thus would be expected to be more effective in individuals requiring anxiolytic medications (eg, benzodiazepines).<sup>10</sup> The paradoxical finding of decreased ketamine efficacy in benzodiazepine users supports the hypothesis that benzodiazepines themselves interfere with ketamine’s mechanism of action.

**Table 1. Demographics, Baseline Clinical Characteristics, and Depression Outcomes in Veterans With TRD Using Benzodiazepines vs Veterans With TRD Not Using Benzodiazepines<sup>a</sup>**

Characteristic	Total Sample	Benzodiazepines	No Benzodiazepines	P
Participants, n (%)	13 (100)	4 (31)	9 (69)	...
Age at enrollment, mean ± SD, y	51.8 ± 14.9	63.5 ± 7.8	46.7 ± 14.6	.076
Education, mean ± SD, y	15.8 ± 2.8	17.5 ± 4.4	15.0 ± 1.6	.144
Age at onset of MDD, mean ± SD, y	32.3 ± 13.1	35.3 ± 6.8	31.0 ± 15.3	.612
Length of current episode, mean ± SD, y	16.8 ± 10.4	17.3 ± 12.8	16.7 ± 10.0	.930
No. of lifetime MDD episodes, mean ± SD	4.0 ± 2.2	3.5 ± 1.0	4.2 ± 2.6	.613
First-degree relative with mood disorder, n (%)	11 (84.6)	4 (100.0)	7 (77.8)	.305
No. of failed antidepressants (current episode), mean ± SD	3.2 ± 0.4	3.25 ± 0.5	3.1 ± 0.3	.561
Lifetime history of ECT, n (%)	2 (15.4)	1 (25.0)	1 (11.1)	.522
Lifetime history of suicide attempt, n (%)	3 (23.1)	1 (25.0)	2 (22.2)	.913
Past substance use disorder, n (%)	2 (15.4)	0 (0.0)	2 (22.2)	.305
Current anxiety disorder, n (%)	5 (38.5)	2 (50.0)	3 (33.3)	.569
No. of comorbid psychiatric diagnoses, mean ± SD	1.8 ± 0.9	1.5 ± 1.0	1.9 ± 0.9	.509
Baseline MADRS score, mean ± SD	29.9 ± 6.2	30.3 ± 7.3	29.8 ± 6.2	.906
Baseline HDRS score, mean ± SD	21.0 ± 4.2	19 ± 2.9	21.9 ± 4.5	.268
<b>Antidepressant outcomes</b>				
Antidepressant response, n (%)	12 (92.3)	4 (100.0)	8 (88.9)	.488
Depression remission, n (%)	9 (69.2)	2 (50.0)	7 (77.8)	.317
Depression relapse, n (%)	9 (69.2)	4 (100.0)	5 (55.6)	.109
Days to depression response, mean ± SD	7.7 ± 3.8	11.0 ± 1.2	6.2 ± 3.6	<b>.029</b>
Days to depression remission, mean ± SD	9.7 ± 2.7	12.0 ± 0.0	8.7 ± 2.8	<b>.042</b>
Days to depression relapse, mean ± SD	16.2 ± 11.9	5.3 ± 3.5	21.0 ± 11.1	<b>.020</b>

<sup>a</sup>Bolded values represent statistical significance determined at an  $\alpha$  level of 0.05.

Abbreviations: ECT = electroconvulsive therapy, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, TRD = treatment-resistant depression.

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Ketamine is a noncompetitive *N*-methyl-D-aspartate receptor (NMDAR) antagonist. The precise mechanism of ketamine's therapeutic effects continues to be a source of debate.<sup>11</sup> One hypothesis suggests that ketamine modulates NMDARs on inhibitory  $\gamma$ -aminobutyric acid–ergic (GABAergic) interneurons that exert tonic suppression of excitatory glutamatergic networks.<sup>12</sup> By blocking NMDARs on these interneurons, ketamine decreases inhibition, resulting in a burst of glutamate, signaling through the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and up-regulation of neuroplasticity-related transcription factors. Consistent with this model, agonism of the GABA-A receptor (as occurs with benzodiazepines) would increase inhibitory tone of these interneurons, thereby decreasing excitatory glutamatergic signal transduction and blocking the therapeutic effects of ketamine.

The current post hoc analysis provides support for the hypothesis that ketamine's mechanism of action involves effects on GABAergic neurotransmission. This finding may bear on the variable response rates to ketamine, particularly in single-infusion studies, and suggests that coadministration of medications interfering with GABAergic neurotransmission may hamper optimal ketamine response. Though limited by small sample size, this report corroborates a previous report of attenuated response to multiple ketamine infusions via GABAergic mechanisms.<sup>9</sup> As the likelihood of widespread use of ketamine for TRD nears and clinical trials examining the antidepressant efficacy of intranasal esketamine continue,<sup>13</sup> consideration of concurrent benzodiazepine treatment is evidently necessary when designing clinical trials aimed at understanding the magnitude, timing, and durability of ketamine effects. Ultimately, however, the hypothesis that concomitant benzodiazepine exposure attenuates ketamine response would best be addressed in a randomized clinical trial.

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