The Impact of Benzodiazepine Management in the Randomized, Double-Blind Evaluation of D-Cycloserine or Alprazolam Combined With Virtual Reality Exposure Therapy

To the Editor: The study by Rothbaum et al. (1) in the June 2014 issue addressing the treatment of posttraumatic stress disorder (PTSD) in Iraq and Afghanistan war veterans may have been affected in three major ways relating to the alprazolam treatment and benzodiazepine management in general. First, the dose of alprazolam at 0.25 mg is subtherapeutic. A dose of 2 mg–3 mg is likely to have been more effective. Second, having participants discontinue their short-acting benzodiazepines 2 weeks before screening and discontinue their long-acting benzodiazepines 1 month before screening followed by a subtherapeutic dose of alprazolam is likely to have contributed to the lack of treatment effects in the alprazolam group. Third, the number of the prescreened benzodiazepine-treated individuals was not reported, nor was there a breakdown of these individuals into each study group, which could have also affected the observed treatment outcomes.

If each of these factors had been addressed, it is possible that the alprazolam group would have shown significant improvement in the D-cycloserine group.

Benzodiazepines can be a very safe and effective treatment for PTSD and all anxiety disorders and may offer substantial relief from suffering such that they should not necessarily be avoided due to excessive concerns about abuse potential. Ninety-eight percent of people taking benzodiazepines use them appropriately; 2% abuse them. This 2% also abuse alcohol and/or street drugs at the same time (2).

References

1. Rothbaum BO, Price M, Jovanovic T, Norrholm SD, Gerardi M, Dunlop B, Davis M, Bradley B, Duncan EJ, Rizzo A, Ressler KJ: A randomized, double-blind evaluation of D-cycloserine or alprazolam combined with virtual reality exposure therapy for posttraumatic stress disorder in Iraq and Afghanistan War veterans. Am J Psychiatry 2014; 171:640–648
2. American Psychiatric Association: The APA Task Force Report on Benzodiazepine Dependence, Toxicity, and Abuse. Am J Psychiatry 1991; 148:151–152

ABBOT LEE GRANOFF, M.D.

Dr. Granoff is in private practice in Norfolk, Va.

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Response to Granoff

To the Editor: Dr. Granoff comments on the benzodiazepine arm of our study in which Afghanistan and Iraq veterans with posttraumatic stress disorder (PTSD) received six sessions total, with five sessions of virtual reality exposure therapy combined with 0.25 mg of alprazolam or 50 mg of D-cycloserine or pill placebo administered 30 minutes prior to the virtual reality sessions. We agree with Dr. Granoff's first comment that the dose of alprazolam at 0.25 mg is generally subtherapeutic. However, we would point out that this can be an effective dose for some people with anxiety, so it is not entirely a subclinical dose. With that said, we did purposefully choose a low dose of alprazolam in an attempt to not break the blind. D-Cycloserine is virtually undetectable when administered as used in our study (i.e., 50 mg once/week), and it was felt that even 0.50 mg of alprazolam may be noticeable by the subject and thus break the blind. Dr. Granoff's second point, that "having participants discontinue their short-acting benzodiazepines 2 weeks before screening and discontinue their long-acting benzodiazepines 1 month before screening followed by a subtherapeutic dose of alprazolam is likely to have contributed to the lack of treatment effects in the alprazolam group," likely had less of an impact. This is because very few subjects in the study discontinued chronic benzodiazepine use, so we do not believe that this possibility explains our data. This also addresses Dr. Granoff's third point, that the number of patients who discontinued benzodiazepines was not reported. The fact that such a low dose of alprazolam was associated with lower efficacy of virtual reality exposure therapy we feel makes an even stronger case that benzodiazepines should be used with caution in general with patients with PTSD and certainly when patients are receiving exposure therapy. In conclusion, we agree that benzodiazepines in general can be quite useful for treatment of anxiety disorders. However, there is also the possibility, specifically with regard to extinction-based prolonged exposure therapy, that benzodiazepines may in some cases interfere with the consolidation of emotional memory during this process, as suggested in our study, and that this possibility warrants further investigation.

BARBARA OLASOV ROTHBAUM, PH.D., A.B.P.P.
KERRY RESSLER, M.D., PH.D.

From the Trauma and Anxiety Recovery Program, Emory University School of Medicine, Atlanta; and the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine.

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Possible Negative Effects of Extinction Learning on Outcomes for Patients Receiving Exposure Therapy

To the Editor: I am writing to comment on the article by Rothbaum et al. (1), "A Randomized, Double-Blind Evaluation of D-Cycloserine or Alprazolam Combined With Virtual Reality Exposure Therapy for Posttraumatic Stress Disorder in Iraq and Afghanistan War Veterans," in the June 2014 issue of the *Journal*. This article reports findings from an important double-blind study of virtual reality exposure therapy augmented by D-cycloserine (an N-methyl-d-aspartic acid receptor partial agonist/putative "extinction learning enhancer"), alprazolam, or placebo. However, I am worried that one important aspect of the findings may have been relatively overlooked. Uncommented upon, as far as I can tell in either the primary article or in the accompanying editorial by Dr. Neylan, is the fact that based on the 95% confidence interval, D-cycloserine