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

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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.

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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

augmentation of virtual reality exposure therapy appeared to be associated with worse outcomes for the subset of patients experiencing little response or worsening of subjective distress during the treatment. Figure 1B of the article appears to suggest that if patients experienced approximately a ≤4-point mean improvement in their within-session subjective distress during the treatment, D-cycloserine augmentation was reported as being associated with significantly *worse* changes in the Clinician-Administered PTSD Scale scores compared with placebo. Unfortunately, at least one potentially plausible mechanism suggests itself, albeit speculative: perhaps patients who, for whatever reason, experience their posttraumatic stress disorder (PTSD) symptoms as worsening, rather than improving, over the first few exposure sessions start to "learn" that their PTSD symptoms are worsening and are more debilitating. While only a relatively small subset of patients may fall into this group, the possibility for an adverse medication-related effect on the primary outcome itself for some patients should command additional attention in future research. Such research is of particular importance in part because it is even conceivable that such an effect might pose at least a somewhat limiting condition for the use of "extinction learning enhancers" in general.

Fortunately, at least one potential remedy suggests itself: perhaps future trials should investigate only adding the D-cycloserine or a similar agent after the first couple of sessions and only for that subset of patients that have already started to experience a positive response to the treatment. Ways of doing this, even in a double-blind setting, suggest themselves.

The study by Rothbaum et al. is a very valuable contribution to the literature on the treatment of PTSD. However, part of its value seems to be in alerting us to the fact that more attention needs to be paid in characterizing those who do not respond to exposure therapy, and to considering seriously the possibility that extinction learning enhancers might potentially worsen outcomes for some patients undergoing exposure therapy. The study also appears to challenge us to think about how this possibility can be anticipated and whether efforts should be made to minimize this possibility in future trial design.

Reference

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

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Response to Smith

TO THE EDITOR: Dr. Smith asks an important question, namely if "D-cycloserine augmentation of virtual reality exposure therapy appeared to be associated with worse outcomes for the subset of patients experiencing little response or worsening of subjective distress during the treatment." The figure and analysis to which Dr. Smith refers are implied from a mixed-effect model that included all participants (N=156). Different outcomes were discovered based on different measures in this study. The most robust beneficial effects of D-cycloserine were seen in the more objective measures of psychophysiological startle and salivary cortisol, consistent with the animal literature on the facilitation of extinction by D-cycloserine. Less consistent were the posttraumatic stress disorder (PTSD) clinical measures that were all based on patient self-report. Even though the Clinician Administered PTSD Scale is a clinical interview, it is based on patient self-report of PTSD symptoms. Even more subjective is the Subjective Units of Distress Scale, which the analysis of emotional learning within and between sessions (to which Dr. Smith refers) is based. Using raw change in Clinician Administered PTSD Scale scores as an indicator of treatment response, we identified two participants in the D-cycloserine condition who had worse symptoms at posttreatment relative to pretreatment. This was less than the six participants in the alprazolam condition and eight in the placebo condition who had worse symptoms at posttreatment relative to pretreatment. The two participants in the D-cycloserine condition with negative scores did not demonstrate negative emotional learning. The graphs in the figure correspond to model-implied trajectories, suggesting that it is theoretically possible that a participant with sufficient negative emotional learning could have poorer outcomes with D-cycloserine relative to a lack of D-cycloserine. This phenomena, however, was not observed in our current sample. Furthermore, the graphs we presented correspond to response in the D-cycloserine condition relative to change in the placebo or alprazolam conditions. That is, these graphs suggest that the negative outcomes obtained are relative to other conditions as opposed to overall functioning. Dr. Smith then suggests "adding the D-cycloserine or a similar agent after the first couple of sessions and only for that subset of patients that have already started to experience a positive response to the treatment." We think this is a very interesting and important idea, and it is similar to what has been attempted in several recent trials of D-cycloserine combined with exposure therapy (1–3). Most of these have found benefit only for those patients who demonstrated emotional learning within that session, as was found in our study administering D-cycloserine 30 minutes prior to exposure therapy. We absolutely agree with Dr. Smith's suggestions to determine who is most likely to respond well to exposure therapy and to exposure therapy combined with cognitive enhancers. In this study, those patients who displayed larger startle responses prior to treatment and had lower salivary cortisol in response to the virtual scenes embedded with acoustic startle probes fared better when the virtual reality exposure therapy was combined with D-cycloserine compared with alprazolam or placebo.