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.

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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.

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Correction

In the article "Adverse Consequences of Glucocorticoid Medication: Psychological, Cognitive, and Behavioral Effects," by Lewis L. Judd et al., published in the October 2014 issue (AJP 2014;171:1045–1051), the affiliation for Benno Roozendaal was listed incorrectly. He is affiliated with the Department of Cognitive Neuroscience, Radboud University Medical Center, Nijmegen, the Netherlands.