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Prazosin for Alcohol Use Disorder: A Clarification

To the Editor: In the March/April 2021 issue of JCP, Dr Andrade¹ discusses recent findings reported by my colleagues and I² on the use of prazosin in the treatment of alcohol use disorder and more broadly adrenergic agents such as prazosin to address symptoms of alcohol withdrawal in alcohol use disorder. This letter will point out inaccuracies in the summary of findings presented as well as clarify the premise and interpretation of our original study.²

First, it is incorrectly summarized that the study analyses were conducted by grouping patients according to high and low alcohol withdrawal symptoms. Alcohol withdrawal symptoms (AWS) were assessed as a *continuous* measure in all primary outcome analyses. That is, symptom counts were aggregated in a summary score, and that score was utilized in all primary outcomes analyses so as to avoid use of an arbitrary AWS cutoff score. While there are guidelines for cutoff scores for medical detoxification in the treatment of alcohol withdrawal syndrome, no such thresholds are established for any potential effects of alcohol withdrawal severity on alcohol drinking outcomes. It is only because we found significant AWS interactions with medication condition (prazosin versus placebo) on each primary drinking outcome that we conducted secondary analyses by dividing the sample into high and low AWS groups based on the median score of the distribution. Results of continuous measure of AWS and high and low AWS group analyses on drinking outcomes were highly consistent.

Second, the point that sedative effects may have unblinded the subjects is not based on the data reported. With the 2-week medication titration schedule used in this study, we did not find any differences in sedation rates between placebo and prazosin groups, and frequency of sedative effects in both groups was low, arguing against sedation unblinding the subjects in this double-blind randomized controlled study.

Finally, a point of clarification regarding the premise and interpretation of the findings. This was a proof-of-concept trial that was not targeting a reduction in alcohol withdrawal

symptoms as the potential pathway to reduce drinking outcomes. In fact, as pointed out in the column, AWS scores were lower than usually reported in the context of alcohol detoxification or medical concerns regarding alcohol withdrawal severity. Also, we did not find that prazosin reduced alcohol withdrawal symptoms over placebo. In fact, the study goal here was not to treat alcohol withdrawal symptoms. Rather, the focus was to assess whether alcohol withdrawal assessment may serve as a prognostic indicator of severity of alcohol abstinence pathology with the focus of treatment being improvement of alcohol drinking and relapse risk outcomes long term rather than targeting a reduction in acute alcohol withdrawal severity. This is important because of the wealth of evidence suggesting that alcohol abstinence symptoms, including abstinence related anxiety, depression, sleep, and craving and overall distress may maintain alcohol use and increase relapse risk. The premise was to assess whether an easy, clinically useful measure of AWS may serve as a prognostic indicator of treatment to improve drinking outcomes.

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Published online: September 21, 2021.

Potential conflicts of interest: None.

Funding/support: None.

J Clin Psychiatry 2021;82(6):21lr14076

To cite: Sinha R. Prazosin for alcohol use disorder: a clarification. *J Clin Psychiatry*. 2021;82(6):21lr14076.

To share: <https://doi.org/10.4088/JCP.21lr14076>

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Prazosin for Alcohol Use Disorder: Reply to Sinha

To the Editor: I do not contest the points that Dr Sinha makes.¹ However, I do wish to provide clarifications about the issues that she has raised. With regard to the first point, whereas statistical analyses are more appropriately performed on constructs that are operationalized as continuous variables, clinical decision-making often necessitates the examination of constructs as categorical variables.^{2,3} This means that, in an analysis of continuous data, if a study finds that prazosin is associated with better alcohol use disorder (AUD) treatment outcomes when alcohol withdrawal symptom (AWS) ratings are higher, clinicians who treat AUD would want to know beyond what point AWS scores indicate potential benefits with the drug. In fact, in her letter, Dr Sinha herself acknowledges that “the premise was to assess whether an easy, clinically useful measure of AWS may serve as a prognostic indicator of treatment to improve drinking outcomes.” Happily, the required information was available in the secondary analyses, and this information was presented to the reader in my commentary.⁴ It may be noted here that the purpose of my commentary was not to mechanically summarize the original study⁵ but to present to the reader theoretically and practically useful messages that emerged from the findings of the study.

With regard to the second point, a review of prazosin for the treatment of posttraumatic stress disorder nightmares identified sedation as an adverse effect of the drug.⁶ More specifically, previous RCTs of prazosin in patients with AUD,^{7,8} which uptitrated prazosin in the same way that Sinha et al⁵ did, found significantly more drowsiness with prazosin than with placebo. If the RCT by Sinha et al⁵ failed to identify drowsiness or sedation with prazosin, it may have been because adverse effects were assessed weekly, or because the sedating effect may have been therapeutic for AUD-related sleep disturbances such as insomnia, and so was not elicited as an adverse effect.

With regard to the final point, regardless of the premise of the original study,⁵ it is the prerogative of a commentator to interpret findings and to construct hypotheses in the light of the background literature, which is exactly what I did.

On a parting note, Dr Sinha writes, “we did not find that prazosin reduced alcohol withdrawal symptoms over placebo.” However, in Table S4 in the online supplement to the study,⁵ the prazosin vs placebo treatment effect was statistically significant for

the baseline Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar) by week interaction, indicating (as stated in a footnote to the table) “reduction in CIWA-Ar scores across weeks but only in those with higher AW (cont.) scores and no change by week in those with no/low levels of AW.” So, it appears reasonable to speculate that the benefits of prazosin in patients with AUD emerge through reduction of AWS in persons with high baseline AWS scores.

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Published online: September 21, 2021.

Potential conflicts of interest: Please see <https://www.psychiatrist.com/jcp/about-dr-andrade>.

Funding/support: None.

J Clin Psychiatry 2021;82(6):21r14076a

To cite: Andrade C. Prazosin for alcohol use disorder: reply to Sinha. *J Clin Psychiatry*. 2021;82(6):21r14076a.

To share: <https://doi.org/10.4088/JCP.21r14076a>

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