Correspondence

Is Pretreatment Blood Pressure a Marker of Prazosin Response in Posttraumatic Stress Disorder With Comorbid Alcohol Use Disorder?

To the Editor:

Posttraumatic stress disorder (PTSD) is a disabling psychiatric disorder, and central nervous system adrenergic system hyperactivity is thought to play a key role in its pathophysiology (1–3). Several studies have suggested that prazosin, an α_1-adrenoreceptor blocker, is effective in improving PTSD-related sleep symptoms, hyperarousal, global clinical status, and overall PTSD symptom burden (3–9). However, there is a wide variation in the effect(s) of prazosin across various patient populations (3). This includes two negative trials among individuals with PTSD and comorbid alcohol dependence (AD) (10,11).

A recent secondary analysis of clinical trial data found that higher standing systolic blood pressure (BP) before prazosin therapy initiation, a marker of adrenergic system hyperactivity, was associated with greater improvement in PTSD symptoms with prazosin therapy (12). Specifically, every 10-mm-Hg higher baseline standing BP was associated with a 14-point reduction in symptoms based on the Clinician-Administered PTSD Scale (CAPS). Based on these results, the authors suggested that BP may be a biomarker for efficacy of prazosin that may help identify which patients may respond to prazosin. Although baseline BP is a simple and attractive biomarker, this finding should be confirmed and replicated in multiple PTSD populations to establish clear clinical utility.

In this study, we tested the validity of pretreatment BP as a biomarker of benefit from prazosin therapy using data from a clinical trial conducted among individuals who met current DSM-IV criteria for PTSD and comorbid AD (10). Enrolled subjects (N = 96) were randomly assigned to prazosin (16 mg twice a day) or placebo in a double-blind fashion for 12 weeks. A research nurse collected BP measures at baseline using a manual sphygmomanometer, sitting BP after 5 minutes rest, and standing BP after 2 minutes. PTSD symptom severity was assessed every 4 weeks using the CAPS for the DSM-IV (13). Sleep was measured weekly using the Pittsburgh Sleep Quality Index (14) and two sleep-related questions from the CAPS. The results showed that subjects as a group had significant improvement in symptoms of PTSD and measures of sleep, but there was no significant advantage of prazosin. Further details regarding the methods and the results have been described (10). Using the basic analysis plan reported by Raskind *et al.* (12), we used linear mixed-effect models (that allow for missing values) to estimate the effects of baseline BP parameters (sitting systolic, standing systolic, sitting diastolic, and standing diastolic) on PTSD outcome measures (15). The first models included terms for week (treated as categorical and including baseline, weeks 1, 4, 8, and 12), baseline BP (treated as continuous), medication (prazosin vs. placebo), and all two- and three-way interactions. Additional analyses were conducted separately within the groups of participants who were randomly assigned to prazosin (n = 50) and to placebo (n = 46). Findings were adjusted for multiple comparisons within each outcome category (four types of BP results leading to adjusted p = .01).

There were no significant differences in baseline demographic and clinical characteristics (10) and baseline BP parameters (systolic sitting 125 vs. 125 mm Hg; systolic standing 124 vs. 123 mm Hg; diastolic sitting 75 vs. 76 mm Hg; and diastolic standing 78 vs. 79 mm Hg). There were no significant three-way interactions (week of follow-up by baseline BP by medication type) for any of the BP parameters and PTSD symptoms, sleep, or dreams within either medication group (Table 1). In the subsequent analysis, the two-way interactions (week of follow-up by baseline BP) were also not significant within the prazosin or placebo groups. Within the placebo group, those with lower sitting systolic BP had a significantly greater decrease in total CAPS score (p = .011).

The results of this study do not confirm the previous report because none of the baseline BP measurements were a predictor of improvement in PTSD symptoms or sleep parameters among those taking prazosin. There are several differences that might explain the discrepant results. The previous report mostly enrolled younger active military personnel (average age 30.0 years) who had recently returned from deployment (8), whereas the present study enrolled older veterans (average age 44.5 years) with longer histories of PTSD after termination of military service (10). Antidepressant use was also much lower (35.8%) among the individuals enrolled in the previous study compared to the current study (75.0%). These factors suggest that participants in the study by Raskind *et al.* (8,12) were less likely to have chronic or refractory PTSD. The other important factor is the presence of an active AD in the present study. AD and the level of symptom burden can modulate autonomic responses associated with PTSD in unpredictable ways (16,17). Also, several factors such as antihypertensive medications, aging, fluid volume status, renin/angiotensin activity, arterial wall stiffening, and comorbidities may also influence baseline BP and may undermine its utility as a biomarker for effectiveness of prazosin in PTSD, especially among those with comorbidities (12).

There were similarities between the studies as well; the dose of prazosin, baseline BP (e.g., standing systolic BP 121 vs. 124 mm Hg), and the severity of PTSD symptoms at baseline (CAPS scores 71.9 vs. 77.3) were comparable. The effect size for unadjusted CAPS total and CAPS nightmare item with prazosin treatment were large in our study (Cohen's d = 1.06 and 0.95, respectively), similar to that in Raskind *et al.* (Cohen's d = 1.04 and 1.71, respectively), indicating that a difference would be noted if there was one, even with adjustments. However, the effects were not significant after adjustments. A larger sample size is unlikely to produce different results.

The failure of a recent large clinical trial among veterans with chronic PTSD (18) to replicate the beneficial effect of prazosin seen in previous small trials (5,6,8,9) has led to a call for a "personalized medicine approach" targeting mechanistic

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Table 1. Results From the Mixed Model Analysis Comparing Prazosin and Placebo on Main Outcome Measures

Outcome and Blood Pressure Type	Overall Sample		Prazosin Group		Placebo Group	
	F^a	*p* Value	F^b	*p* Value	F^b	*p* Value
CAPS "Nightmare Item"						
SBP						
Sitting	0.608	.948	1.180	.302	1.519	.133
Standing	1.525	.052	1.702	.047	2.187	.081
DBP						
Sitting	1.042	.425	0.873	.704	1.095	.384
Standing	1.039	.431	1.318	.195	0.933	.607
PSQI						
SBP						
Sitting	0.533	.976	0.682	.921	1.244	.259
Standing	1.106	.346	1.311	.188	1.931	.037
DBP						
Sitting	1.143	.294	0.814	.767	1.640	.063
Standing	1.208	.234	0.749	.862	1.718	.038
Total CAPS						
SBP						
Sitting	0.814	.741	1.049	.500	2.082	.011
Standing	1.375	.124	1.274	.230	1.357	.163
DBP						
Sitting	0.754	.851	1.822	.043	1.065	.441
Standing	0.796	.780	0.882	.687	1.469	.115

CAPS, Clinician-Administered PTSD Scale; DBP, diastolic blood pressure; PSQI, Pittsburgh Sleep Quality Index; SBP, systolic blood pressure.

[a]Three-way interaction (week of follow-up by baseline blood pressure by medication type).

[b]Two-way interaction (week of follow-up by baseline blood pressure).

pathways involved in individual phenotypical variants of PTSD (19). The present study suggests caution regarding the use of BP as a marker, particularly in the presence of a comorbidity that might influence the marker. Nevertheless, previous findings that suggest BP as a biological marker warrants more study. This study underscores the importance of including diverse populations in evaluating the utility of BP as biomarker.

Ajay Manhapra
Elizabeth Ralevski
Ismene L. Petrakis

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Article Information

From the VA Hampton Medical Center (AM), Hampton, Virginia, and the Department of Psychiatry (AM, ER, ILP), Yale School of Medicine, New Haven, Connecticut.

Address correspondence to Ajay Manhapra, M.D., VA Hampton Medical Center, 100 Emancipation Dr., Hampton, VA 23667; E-mail: ajay.manhapra@yale.edu.

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