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Higher Pretreatment Blood Pressure is Associated with
Greater PTSD Symptom Reduction in Soldiers Treated with Prazosin

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Short title: Blood Pressure Predicts PTSD Response to Prazosin

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Abstract

Background: In a previously reported positive randomized controlled trial (RCT) of the alpha-1 adrenoreceptor (AR) antagonist prazosin for combat posttraumatic stress disorder (PTSD) in 67 active duty soldiers, baseline symptoms did not predict therapeutic response. If increased brain alpha-1 AR activation in PTSD is the target of prazosin treatment action, higher brain alpha-1 AR activation should predict greater prazosin efficacy. Although brain alpha-1 AR activation is not measurable, coregulated peripheral alpha-1 AR activation could provide an estimate of brain alpha-1 AR activation. Standing blood pressure (BP) is an accessible biologic parameter regulated by norepinephrine activation of alpha-1 AR on peripheral arterioles.

Methods: Effects of baseline standing systolic and other BP parameters on PTSD outcome measures from the previously reported RCT were analyzed using linear mixed effects models. Prazosin participants (n=32) and placebo participants (n=35) were analyzed separately.

Results: In prazosin participants each 10 mmHg higher baseline standing systolic BP increment resulted in an additional 14 point reduction (improvement) of Clinician Administered PTSD Scale total score at end point ($p=0.002$). All other combinations of baseline BP parameters and PTSD outcome measures were similarly significant or demonstrated trends in the predicted direction. In placebo participants there was no signal for a baseline BP effect on PTSD outcome measures.

Conclusion: These findings suggest that higher standing BP is a biomarker that helps identify those persons with combat PTSD likely to benefit from prazosin. These results also are consistent with alpha-1 AR activation contributing to PTSD pathophysiology in a subgroup of patients.

Augmentation Trial of Prazosin for Post-Traumatic Stress Disorder (PTSD)
<https://www.clinicaltrials.gov/ct2/show/NCT00990106>
NCT00990106

Introduction

The alpha-1 adrenoreceptor prazosin has been demonstrated effective for posttraumatic stress disorder (PTSD) symptoms in six randomized controlled trials (RCTs) (1-6). In a recent RCT for PTSD in active duty soldiers, prazosin was superior to placebo for PTSD symptoms and overall function with large effect sizes (5). As is common in positive RCTs for psychiatric disorders, there was substantial inter-subject variability of treatment response within the active medication group that was independent of symptom magnitude at baseline. Although 64 percent of soldiers treated with prazosin had a clinically meaningful therapeutic response (moderately or markedly improved on the Clinical Global Impression of Change [CGIC] (7) compared to 27% in the placebo group ($p < 0.001$), 36% of prazosin-treated soldiers were nonresponders. Finding a pretreatment biologic parameter that helps predict a given PTSD patient's therapeutic response to prazosin would be clinically valuable and might also clarify mechanisms of PTSD pathophysiology (8). If such a biomarker were easily measurable and the results readily available, it would be particularly useful clinically.

Although the pathophysiology of PTSD is multifactorial, elevated central nervous system (CNS) noradrenergic activity likely contributes to symptom expression in a substantial subgroup of persons who meet clinical criteria for PTSD (9-11). Prazosin, the most lipid soluble alpha-1 AR antagonist (12), has been demonstrated to reduce norepinephrine (NE) effects at CNS postsynaptic alpha-1 AR when administered peripherally (13). Stimulation of CNS alpha-1 AR results in behaviors resembling PTSD symptoms, including sleep disruption (14), heightened arousal (15), and "fight or flight"-relevant cognitive processes (16). Therefore, the therapeutic effect of prazosin and other CNS penetrant drugs with alpha-1 AR antagonist activity in PTSD

plausibly results from antagonism of CNS alpha-1 AR. If this model is correct, those PTSD patients with high CNS alpha-1 AR activation at baseline are most likely to benefit from prazosin treatment. Demonstration of high CNS alpha-1 AR activation pretreatment would be a rational candidate biomarker for predicting therapeutic response to prazosin.

Unfortunately, CNS alpha-1 AR activity *in vivo* cannot yet be measured directly. However, the co-regulation of CNS and peripheral noradrenergic systems (17) raises the possibility that measurement of an accessible peripheral biologic parameter regulated by alpha-1 AR could provide a pretreatment biomarker for predicting therapeutic response to prazosin in PTSD. Blood pressure (BP) is one such a potential peripheral biologic parameter. NE stimulation of alpha-1 AR on peripheral arterioles increases BP, particularly in the standing position (18). In addition, our clinical experience with prazosin treatment for PTSD in combat veterans suggests that those with elevated BP are most likely to benefit from prazosin (unpublished observations). We hypothesized that higher standing systolic BP and a smaller systolic BP decrease from supine to standing position (smaller orthostatic BP drop) at pretreatment baseline would predict greater PTSD symptom reduction and functional improvement in soldiers randomized to prazosin but not in soldiers randomized to placebo.

Methods

This study was approved by the Human Subjects Committees of the VA Puget Sound Health Care System and Madigan Army Medical Center. All participants provided written informed consent prior to any study procedures. A secondary analysis of a previously described prazosin RCT for PTSD (5) was performed to determine the effects of baseline BP measures on PTSD

treatment outcome measures. In this RCT, 67 active duty soldiers (mean age $\pm$ SD = 30 ± 6 years) were randomized to prazosin (n=32) or placebo (n=35) for 15 weeks. All participants had returned from combat deployments to Iraq and/or Afghanistan, met DSMIV criteria based on a SCID interview for PTSD attributable to combat-related events, and had frequent trauma content nightmares. Primary outcome measures included the recurrent distressing dreams “nightmare” item (B2) of the Clinician Administered PTSD Scale (CAPS) (19), the Pittsburgh Sleep Quality Index (PSQI) (20), and the CGIC (7) anchored to function; the 17-item total CAPS score was a secondary outcome. As previously reported (1), participants in the prazosin arm exhibited significantly greater reductions, both statistically and clinically, in all four outcome measures as compared to participants in the placebo arm; difference between groups in change from baseline and 95% confidence interval (CI): CAPS nightmare item 1.9 [1.0, 2.8], PSQI 2.8 [0.9, 4.7], CGIC 0.9 [0.3, 1.5], and total CAPS 11.3 [2.0, 20.7]. Prazosin or placebo was given twice daily (bedtime and midmorning) and titrated over six weeks to mean $\pm$ SD achieved bedtime doses of 15.6 ± 6.0 mg prazosin or 18.8 ± 3.3 mg placebo (maximum 20 mg), and midmorning doses of 4.0 ± 1.4 mg prazosin or 4.8 ± 0.8 mg placebo (maximum 5 mg) in men (n=57). Per protocol, maximum doses were lower for the ten women soldiers (10 mg bedtime and 2 mg midmorning) with achieved doses approximately 50% of those in men.

Behavioral ratings and BP were obtained at baseline and at weeks 7, 11, and 15. BP was obtained using a manual sphygmomanometer after five minutes supine and then after two minutes standing. The six BP parameters included supine systolic, standing systolic, systolic orthostatic change (supine minus standing), supine diastolic, standing diastolic, and diastolic orthostatic change.

The effects of baseline BP parameters on PTSD outcome measures were analyzed using linear mixed effects models, which include all participants and allow for missing values (21). The models included terms for week (treated as continuous), baseline BP, and (except for CGIC) a week by baseline BP interaction term, as well as the covariates gender and current use of any antidepressant drug. A significant week by baseline BP interaction term indicates an effect of baseline BP on the rate of change from baseline. We performed separate analyses for participants who were randomized to prazosin and those randomized to placebo.

Because CGIC inherently measures change from baseline, the linear mixed effects models for this outcome did not include a time by baseline BP interaction term. Instead, a significant baseline BP term would indicate an effect of baseline BP on CGIC. Participants who dropped out prior to the week 7 visit did not have any CGIC measures and were not included in the CGIC analyses.

We also used simple regression models to investigate whether there was any relationship between baseline BP and baseline PTSD measures, or between baseline BP and final dose achieved. Finally, we used linear mixed effects models to investigate change in BP as a function of baseline BP separately for each treatment group. These models included terms for week, baseline BP, and a week by baseline BP interaction term, as well as the covariates gender and current use of any antidepressant drug. All analyses were performed with R version 3.1.1 (22). Linear mixed effects models were fit using the `lme` function in the R package *nlme* (23).

Results

Table 1 shows demographic and baseline clinical characteristics by treatment group. Six placebo participants (17%) and 5 prazosin participants (16%) withdrew consent prior to the first behavioral outcome rating at week 7. Of the 56 participants with at least one post-randomization behavioral rating (29 placebo, 27 prazosin), 46 completed the full 15 weeks (23 placebo, 23 prazosin), 6 completed 11 weeks (5 placebo, 1 prazosin) and 4 completed 7 weeks (1 placebo, 3 prazosin). There was no association between baseline BP and value at baseline for the four outcome measures, or between baseline BP and final prazosin dose achieved (data not shown). As previously reported (5), BP did not significantly differ over time or between treatment groups. However, for the prazosin treatment group, there was a significant effect of baseline BP on change in BP for supine systolic, supine diastolic, and standing diastolic measures: additional 15-week change [95% CI] for every 10 mmHg increase in baseline BP: -5.4 [-9.1, -1.6], -4.6 [-7.9, -1.4], and -4.4 [-7.8, -1.0], respectively (for standing systolic BP the result was not significant but in the expected direction: -3.1 [-7.8, 1.7]). No such effects were observed in the placebo group.

Table 2 shows the results for all of the linear mixed effects model fits for participants in the prazosin arm, and Figure 1 illustrates the results of the linear mixed effects model fits for the four outcomes measures as a function of baseline standing systolic BP, where the fits for two different values (110 mmHg and 130 mmHg) are shown. Consistent with our hypotheses, there were substantially and significantly greater reductions (improvements) in total CAPS score with prazosin treatment for subjects with higher baseline standing systolic BP: 15-week decrease in CAPS of 21 (95% CI [14, 28]) for subjects with 120mm Hg at baseline, with an additional 15-

week decrease of 14 (95% CI [5, 23]) for every 10 mm Hg increase in BP ($p=0.002$) (e.g., 15-week decrease in CAPS of 7 for subjects with 110 mm Hg at baseline; 15-week decrease in CAPS of 35 for subjects with 130 mm Hg at baseline). There was a similar significant result for baseline supine systolic BP (additional 15-week decrease in total CAPS score of 9, 95% CI [0.5, 18], $p=0.04$), and a trend for greater reductions in total CAPS score with smaller baseline orthostatic systolic drop ($p=0.11$). All other combinations of baseline BP parameters and PTSD outcome measure responses to prazosin were similarly significant or demonstrated trends in the predicted direction (Table 2). In contrast, the same analyses in participants treated with placebo detected no signal for a baseline BP effect on treatment response (Table 3).

Discussion

The present findings suggest that higher standing systolic BP is a biomarker that helps identify those military PTSD patients likely to benefit from treatment with a CNS-penetrant alpha-1 AR antagonist drug such as prazosin. The specificity of this finding is strengthened by the absence of a signal for a baseline BP effect on treatment response in the placebo group. Two decades ago, Southwick and colleagues presented evidence for neurobiologic subgroups of PTSD in combat veterans based on differential responses to pharmacologic provocation of PTSD symptoms (24). One group of veterans developed acute PTSD symptoms in response to pharmacologic enhancement of CNS noradrenergic activity with the alpha-2 AR antagonist yohimbine, whereas another group developed acute PTSD symptoms in response to enhancement of CNS serotonergic activity with meta-chlorophenylpiperazine. Higher BP in the current study sample may be identifying those persons more likely to be in this “noradrenergic” PTSD subtype.

If higher standing BP in soldiers whose PTSD symptoms are responsive to prazosin does reflect increased CNS alpha-1 AR activation, it supports a noradrenergic mechanistic contribution to their PTSD pathophysiology. Arnsten and colleagues (16, 25) have demonstrated a central role for CNS noradrenergic activity in a neurobiologic model of PTSD such that the level of NE in prefrontal cortex (PFC) regulates top down inhibition of amygdala-mediated primitive “PTSD-like” cognitions, emotions and behaviors. During low stress conditions, moderate NE concentrations in PFC favor stimulation of high affinity postsynaptic alpha-2 ARs that enhance PFC rational cognitions and increase PFC inhibition of the amygdala. In contrast, during intense stress and perhaps chronically in PTSD, high NE concentrations in PFC stimulate low affinity alpha-1 AR that reduce PFC rational cognitions and weaken PFC inhibition of amygdala “fight or flight” responses.

Prazosin antagonism of CNS alpha-1 AR may also contribute to trauma content nightmare reduction. In preclinical studies, stimulation of CNS alpha-1 adrenergic receptors by the alpha-1 AR agonist methoxamine increases light sleep and decreases and disrupts REM sleep (14). Addition of prazosin reverses these effects (26-28). In their manuscript demonstrating increased wake after sleep onset in Veterans who experienced trauma related nightmares, Woodward et al. cite studies suggesting that trauma nightmares can arise during Stage 2 light sleep and during disruption in REM sleep (29). We previously have demonstrated normalization and increased duration of REM sleep coincident with nightmare reduction during prazosin treatment in civilian trauma PTSD (3). Such normalization of REM sleep may explain military veterans’ reporting return of long absent normal dreaming when trauma nightmares are reduced or eliminated by

prazosin (2). Normal dreaming appears important for removing excessive emotional tone from memories (30).

To our knowledge, the only treatment outcome prediction biomarker studies in PTSD have examined the ability of biologic parameters to identify those PTSD patients more likely to respond to trauma-focused psychotherapy. Candidate biomarkers that emerged from these studies include higher 5 α -reductase activity and methylation of a glucocorticoid receptor gene promoter (31), and cortisol level at awakening following dexamethasone suppression (32). The clinical utility of these candidate biomarkers, even if replicated in larger placebo controlled studies, may be limited by availability of specialized genotyping or neuroendocrine laboratory facilities and the timeliness of data availability. The current study is the first to address the ability of a biologic parameter to predict response to a pharmacotherapy for PTSD. If replicated in prospective studies, standing BP would be an easily performed and immediately available biomarker for helping determine the role of prazosin in a pharmacologic treatment regimen for combat trauma PTSD.

This study has limitations. These findings did not directly demonstrate that increased alpha-1 AR activation contributes to PTSD pathophysiology. That standing BP in our participants reflects peripheral arteriolar alpha-1 AR activation which in turn reflects brain alpha-1 AR activation status remains a reasonable but empirically untested assumption. Studies in which the BP response to an exogenously administered alpha-1 AR agonist is measured would more clearly define peripheral arteriolar alpha-1 AR status in PTSD. Even more challenging is direct evaluation of brain alpha-1 AR status in PTSD, given the absence of a sensitive and specific

alpha-1 AR positron emission tomography ligand suitable for human use. In addition, the RCT sample was comprised of young and healthy active duty combat soldiers with PTSD. Older veterans with PTSD, such as those who served in Vietnam, have a high prevalence of hypertension and treatment with antihypertensive medications (33). Antihypertensive medications and aging associated changes in BP regulatory factors other than alpha-1 AR status, such as fluid volume status, renin/angiotensin system activity and arterial wall stiffening, could obscure the alpha-1 AR activation state contribution to BP level and thus the relationship of standing BP to prazosin treatment outcome. Prospective studies in larger samples of military and civilian trauma PTSD patients across the age spectrum are necessary to confirm standing BP as a prazosin treatment outcome biomarker to determine its usefulness in clinical practice.

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The investigators have adhered to the policies for protection of human participants as prescribed in 45 CFR 46.

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Figure 1. Results of Linear Mixed-Effects Models for Outcome Measures in the Prazosin Treatment Arm as a Function of Baseline Standing Systolic Blood Pressure^a.

^a The linear mixed effects models included terms for week (treated as continuous), baseline BP, and, except for CGIC, a time by baseline BP interaction term, as well as the covariates gender and current use of any antidepressant drug. Symbols indicate adjusted means (covariates were set to their average value), and vertical lines indicate 95% confidence limits. In Figures A)-C), for each time point, results for 110 and 130 mmHg BP are slightly offset to the left and right, respectively. CAPS=Clinician-Administered PTSD Scale; CGIC=Clinical Global Impression of Change. CGIC score of 1 = “markedly improved”; CGIC score of 4 = “unchanged”. See Table 2 for information on how change from baseline in outcome measures varies by every 10 mmHg increase in baseline BP.

Table 1

Table 1. Demographic and Baseline Clinical Characteristics of Active-Duty Soldiers With Combat Trauma-Related PTSD With Nightmares

Characteristics	Treatment Condition			
	Prazosin n=32		Placebo n=35	
Age (yrs) (mean $\pm$ SD; [min, max])	30.0 $\pm$ 6.6 [20, 44]		30.8 $\pm$ 6.5 [20, 47]	
Supine Systolic BP (mmHg) (mean $\pm$ SD; [min, max])	126 $\pm$ 10 [110, 160]		126 $\pm$ 10 [110, 148]	
Standing Systolic BP (mmHg) (mean $\pm$ SD; [min, max])	121 $\pm$ 8 [104, 138]		125 $\pm$ 11 [98, 152]	
Supine – Standing Systolic BP (mmHg) (mean $\pm$ SD; [min, max])	3.2 $\pm$ 5.3 [-10, 14]		1.0 $\pm$ 7.0 [-16, 14]	
Supine Diastolic BP (mmHg) (mean $\pm$ SD; [min, max])	79 $\pm$ 9 [62, 98]		83 $\pm$ 10 [68, 104]	
Standing Diastolic BP (mmHg) (mean $\pm$ SD; [min, max])	81 $\pm$ 9 [60, 98]		85 $\pm$ 10 [60, 104]	
Supine – Standing Diastolic BP (mmHg) (mean $\pm$ SD; [min, max])	-2.5 $\pm$ 7.2 [-14, -16]		-2.9 $\pm$ 5.1 [-12, -10]	
Men (n [%])	26	(81%)	31	(89%)
Number of deployments (mean $\pm$ SD; ; [min, max])	2.6 $\pm$ 4.0 [1, 24]		1.9 $\pm$ 1.2 [1, 5]	
Maintained on any antihypertensive(s)	2	(6%)	3	(9%)

Table 2. Results of Linear Mixed-Effects Models for PTSD Measures in the Prazosin Treatment Arm^a.

Outcome	BP Type	Position	Change Over 15 Weeks ^b	Additional Change per 10 mmHg increase in BP ^c	P-value ^d
CAPS “nightmare item”¹	Systolic	Supine	-2.8 [-3.8, -1.9]	-0.5 [-1.4, 0.4]	0.28
		Standing	-2.9 [-3.7, -2.1]	-0.8 [-1.8, 0.1]	0.086
		Supine-Standing	-3.4 [-4.3, -2.5]	0.7 [-0.8, 2.3]	0.37
	Diastolic	Supine	-3.2 [-4.0, -2.5]	-0.7 [-1.5, 0.1]	0.102
		Standing	-3.0 [-3.8, -2.3]	-0.5 [-1.4, 0.4]	0.25
		Supine-Standing	-3.3 [-4.1, -2.4]	-0.5 [-1.6, 0.7]	0.42
PSQI²	Systolic	Supine	-5.2 [-6.8, -3.5]	-0.9 [-2.5, 0.9]	0.32
		Standing	-5.1 [-6.5, -3.7]	-1.8 [-3.5, -0.1]	0.043
		Supine-Standing	-6.5 [-8.1, -4.9]	3.1 [0.2, 6.1]	0.039
	Diastolic	Supine	-5.7 [-7.1, -4.4]	-1.7 [-3.2, -0.2]	0.031
		Standing	-5.3 [-6.7, -3.9]	-1.2 [-2.9, 0.5]	0.15
		Supine-Standing	-6.1 [-7.6, -4.6]	-1.4 [-3.5, 0.7]	0.19
Total CAPS³	Systolic	Supine	-19 [-28, -11]	-9 [-18, -0.5]	0.039
		Standing	-21 [-28, -14]	-14 [-23, -5]	0.002
		Supine-Standing	-29 [-38, -21]	12 [-3, 26]	0.11
	Diastolic	Supine	-26 [-33, -19]	-6 [-13, 2]	0.13
		Standing	-23 [-30, -16]	-9 [-17, -1]	0.031
		Supine-Standing	-24 [-32, -16]	3 [-8, 14]	0.62
CGIC⁴	Systolic	Supine	2.3 [1.8, 2.9]	-0.2 [-0.8, 0.4]	0.42
		Standing	2.4 [1.9, 2.8]	-0.6 [-1.2, -0.01]	0.046
		Supine-Standing	2.0 [1.4, 2.5]	0.8 [-0.1, 1.7]	0.094
	Diastolic	Supine	2.2 [1.7, 2.6]	-0.5 [-1.1, 0.0]	0.054
		Standing	2.3 [1.8, 2.7]	-0.3 [-0.8, 0.2]	0.24
		Supine-Standing	2.1 [1.6, 2.6]	-0.3 [-1.1, 0.4]	0.37

^a The linear mixed effects models included terms for week (treated as continuous), baseline BP, and, except for CGIC, a time by baseline BP interaction term, as well as the covariates gender and current use of any antidepressant drug.

^b For CAPS B2, PSQI and Total CAPS, this column shows the fitted change over 15 weeks assuming a baseline systolic BP of 120 mmHg or a baseline diastolic BP of 80 mmHg. For CGIC, this column shows the fitted CGIC at Week 15 assuming a baseline systolic BP of 120 mmHg or a baseline diastolic BP of 80 mmHg. 95% confidence intervals are in brackets.

^c For CAPS B2, PSQI and Total CAPS, this column shows the *additional* change over 15 weeks for every 10 mmHg increase in baseline BP. For CGIC, this column shows the *change* in CGIC at 15 weeks for every 10 mmHg increase in baseline BP. 95% confidence intervals are in brackets.

^d For CAPS B2, PSQI and Total CAPS, this column shows the p-value associated with the test for significance of the Week by BP interaction term (i.e., the significance of the term shown in the previous column). For CGIC, this column shows the p-value associated with the test for significance of the term BP.

1. Clinician Administered PTSD Scale item B2, recurrent distressing dreams related to traumatic event.
2. Pittsburgh Sleep Quality Index.
3. Clinician Administered PTSD Scale 17 item total score.
4. Clinical Global Improvement of Change.

Table 3. Results of Linear Mixed-Effects Models for PTSD Measures in the Placebo Treatment Arm^a.

Outcome	BP Type	Position	Change Over 15 Weeks ^b	Additional Change per 10 mmHg increase in BP ^c	P-value ^d
CAPS “nightmare item”¹	Systolic	Supine	-1.3 [-2.0, -0.7]	0.1 [-0.4, 0.7]	0.65
		Standing	-1.2 [-1.9, -0.6]	0.03 [-0.5, 0.5]	0.90
		Supine-Standing	-1.3 [-1.8, -0.7]	0.2 [-0.6, 1.1]	0.62
	Diastolic	Supine	-1.2 [-1.8, -0.6]	-0.02 [-0.6, 0.6]	0.95
		Standing	-1.2 [-1.8, -0.5]	-0.1 [-0.7, 0.4]	0.64
		Supine-Standing	-1.1 [-1.7, -0.4]	0.6 [-0.6, 1.8]	0.35
PSQI²	Systolic	Supine	-2.8 [-4.3, -1.3]	0.006 [-1.3, 1.3]	0.99
		Standing	-2.7 [-4.1, -1.4]	-0.1 [-1.3, 1.0]	0.84
		Supine-Standing	-2.9 [-4.2, -1.5]	0.4 [-1.6, 2.4]	0.69
	Diastolic	Supine	-3.1 [-4.4, -1.8]	0.9 [-0.4, 2.2]	0.17
		Standing	-3.0 [-4.5, -1.6]	0.4 [-0.8, 1.6]	0.52
		Supine-Standing	-2.4 [-3.8, -0.9]	1.7 [-1.0, 4.4]	0.22
Total CAPS³	Systolic	Supine	-14 [-21, -6]	-0.3 [-7, 6]	0.92
		Standing	-14 [-20, -7]	-0.2 [-6, 5]	0.94
		Supine-Standing	-14 [-20, -7]	0.0 [-10, 10]	1
	Diastolic	Supine	-15 [-21, -8]	4 [-3, 10]	0.25
		Standing	-15 [-22, -8]	1 [-4, 7]	0.62
		Supine-Standing	-12 [-19, -5]	7 [-6, 20]	0.30
CGIC⁴	Systolic	Supine	3.1 [2.7, 3.6]	0.2 [-0.3, 0.5]	0.50
		Standing	3.2 [2.7, 3.6]	0.1 [-0.2, 0.5]	0.50
		Supine-Standing	3.2 [2.8, 3.7]	-0.05 [-0.7, 0.6]	0.86
	Diastolic	Supine	3.1 [2.7, 3.6]	0.3 [-0.1, 0.6]	0.20
		Standing	3.1 [2.6, 3.6]	0.2 [-0.1, 0.6]	0.22
		Supine-Standing	3.2 [2.7, 3.7]	0.04 [-0.9, 1.0]	0.94

^a The linear mixed effects models included terms for week (treated as continuous), baseline BP, and, except for CGIC, a time by baseline BP interaction term, as well as the covariates gender and current use of any antidepressant drug.

^b For CAPS B2, PSQI and Total CAPS, this column shows the fitted change over 15 weeks assuming a baseline systolic BP of 120 mmHg or a baseline diastolic BP of 80 mmHg. For CGIC, this column shows the fitted CGIC at Week 15 assuming a baseline systolic BP of 120 mmHg or a baseline diastolic BP of 80 mmHg. 95% confidence intervals are in brackets.

^c For CAPS B2, PSQI and Total CAPS, this column shows the *additional* change over 15 weeks for every 10 mmHg increase in baseline BP. For CGIC, this column shows the *change* in CGIC at 15 weeks for every 10 mmHg increase in baseline BP. 95% confidence intervals are in brackets.

^d For CAPS B2, PSQI and Total CAPS, this column shows the p-value associated with the test for significance of the Week by BP interaction term (i.e., the significance of the term shown in the previous column). For CGIC, this column shows the p-value associated with the test for significance of the term BP.

1. Clinician Administered PTSD Scale item B2, recurrent distressing dreams related to traumatic event.
2. Pittsburgh Sleep Quality Index.
3. Clinician Administered PTSD Scale 17 item total score.
4. Clinical Global Improvement of Change.

Figure 1

A)

B)

C)

D)