Doxazosin XL Reduces Symptoms of Posttraumatic Stress Disorder in Veterans With PTSD: A Pilot Clinical Trial

Christopher Rodgman, MD[a,b]; Christopher D. Verrico, PhD[a,b]; Manuela Holst, PhD[a,b]; Daisy Thompson-Lake, MA[a,b]; Colin N. Haile, PhD[a,b]; Richard De La Garza, II, PhD[a,b,c]; Murray A. Raskind, MD[d]; and Thomas F. Newton, MD[a,b,*]

ABSTRACT

Background: Serotonin and norepinephrine reuptake inhibitors are effective first-line agents for the treatment of posttraumatic stress disorder (PTSD), but treatment is associated with a range of side effects that limit treatment adherence. Prazosin, an α_1-noradrenergic antagonist with a half-life of roughly 2–3 hours, has shown promise in the treatment of sleep disturbance and nightmares. Doxazosin extended release (XL) is also an α_1-noradrenergic antagonist but with a half-life of approximately 15–19 hours.

Methods: We conducted a double-blind, placebo-controlled, within-subjects trial to characterize the impact of doxazosin XL on PTSD symptoms. Participants (N = 8) were diagnosed using *DSM-IV* criteria. They completed the study twice, once during treatment with doxazosin XL and once during treatment with matched placebo, with a 2-week washout separating the 2 episodes. Doxazosin XL was titrated from 4 mg/d to 16 mg/d over 12 days. After 4 days of treatment at 16 mg/d or the equivalent number of placebo capsules, PTSD symptoms were assessed using the Clinician-Administered PTSD Scale ($CAPS_{17}$) and the PTSD Checklist–Military version (PCL-M). Repeated measures analysis of variance were used to evaluate effects of treatment, time, and treatment × time. This study was run from November 20, 2013, to June 31, 2014.

Results: Doxazosin XL treatment was associated with a nonsignificant treatment × time reduction in ratings on the CAPS hyperarousal subscale ($P < .10$) (but not on the CAPS Total score) and with significant treatment × time reductions in PCL-M ratings ($P = .002$).

Conclusions: Doxazosin XL may be an effective alternative to prazosin for the treatment of some PTSD symptoms.

Trial registration: ClinicalTrials.gov Identifier: NCT02308202

J Clin Psychiatry 2016;77(5):e561–e565
dx.doi.org/10.4088/JCP.14m09681

[a]Michael E. DeBakey VA Medical Center
[b]Menninger Department of Psychiatry, Baylor College of Medicine, Houston, Texas
[c]MD Anderson Cancer Center, University of Texas, Houston, Texas
[d]VISN 20 Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC), Seattle, and the Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine
**Corresponding author:* Thomas F. Newton, MD, Baylor College of Medicine, Department of Psychiatry, Michael E. DeBakey VA Medical Center, 2002 Holcombe, Houston, TX 77030 (tnewton@bcm.edu).

Posttraumatic stress disorder (PTSD) is common among combat veterans, with estimated prevalence rates among soldiers returning from Iraq and Afghanistan ranging from 9% to 33%.[1–4]

Psychotherapy is effective for many veterans with PTSD,[5,6] but some require adjunctive medication treatment to achieve optimal outcomes. Currently, only 2 antidepressant medications (sertraline and paroxetine) have been approved by the US Food and Drug Administration as treatments for PTSD. Often used as first-line treatments in the clinical setting, these serotonin reuptake inhibitors work well in patients with civilian PTSD[7–9]; however, their effectiveness decreases with military-related PTSD[10,11] and may be even lower with combat-related PTSD.[12] Further complicating treatment with serotonin and norepinephrine reuptake inhibitors are their side effects, which include gastrointestinal distress, weight gain, and sexual dysfunction.[13–16] Side effects have been shown to lead to reduced medication adherence when used for the treatment of either depression[17] or PTSD.[18,19] Prazosin, an α_1-noradrenergic receptor antagonist that lacks these side effects, has shown efficacy for the treatment of PTSD-associated nightmares and sleep disturbances, leading to better clinical outcomes.[20–22] Problematic with prazosin, however, is its short half-life (2–3 hours) that necessitates high doses, and consequently it must be titrated slowly over several weeks (up to 6) in order to minimize side effects.[23]

Doxazosin is an α_1-noradrenergic antagonist like prazosin, but doxazosin XL has a long half-life (about 15–19 hours according to the *Physicians' Desk Reference*. It was previously thought that doxazosin did not readily penetrate the brain,[24–26] and therefore it has not been widely tested for the treatment of PTSD. Previous studies by our group[27–29] have demonstrated doxazosin does have behavioral effects that indicate it acts centrally, and so it might be a potentially effective treatment for PTSD. In this pilot study, we evaluated the impact of extended-release (XL) doxazosin treatment on PTSD symptoms in veterans with PTSD.

METHODS

Participants were recruited using newspaper advertisements and flyers and screened over the phone. This study was run from November 20, 2013, to June 31, 2014, and is registered at ClinicalTrials.gov (NCT02308202). Potential participants were then further screened in person at the Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas. Inclusion criteria were being a male veteran, between the ages of 21 and 55 years, and having a diagnosis of PTSD specifically based on their military service. Exclusion criteria were active substance use or an alternative severe psychiatric diagnosis such as bipolar disorder

Clinical Points

- The pharmacologic treatment options for posttraumatic stress disorder are limited and have a myriad of noxious side effects, with only 2 medications (sertraline and paroxetine) being FDA approved for the treatment of this illness.
- In veterans with posttraumatic stress disorder, doxazosin extended release appears to be a promising new treatment worth further consideration.

or schizophrenia, taking other psychiatric medications, or having hypotension. Psychotherapy was not provided during the study, and no participants were receiving it at the time of the study. Diagnosis of PTSD (*DSM-IV*) was made using clinical history, the Mini-International Neuropsychiatric Interview,[30] and the Clinician-Administered PTSD Scale (CAPS).[31]

Participants completed study procedures twice, once during treatment with increasing doses of placebo and once during treatment with increasing doses of doxazosin XL, with at least a 2-week washout between study episodes. A medication treatment duration of 16 days was chosen in order to see whether we could use this design to relatively rapidly screen new medication treatments for PTSD. The study was conducted using a double-blind, placebo-controlled design. The order of treatment (doxazosin XL, placebo) was randomized by the pharmacy on study day 1; the study medication was overencapsulated by the research pharmacy, and matched placebo capsules were manufactured using lactose to maintain the blind. Equal numbers doxazosin XL and placebo capsules were administered during the 2 study phases. We selected doxazosin XL over immediate-release doxazosin due to ease of titration and reduced likelihood of orthostatic adverse events. Doxazosin XL treatment was initiated at 4 mg/d and increased by 4 mg every 4 days to 16 mg/d, with close monitoring of blood pressure. This dose is about equal to 8–10 mg/d of the immediate-release preparation. The primary outcomes were scores on the $CAPS_{17}$ and the Posttraumatic Stress Disorder Checklist–Military version (PCL-M),[32] a 17-point questionnaire of PTSD symptoms based on the *DSM-IV-TR* criteria. PCL-M ratings range from 0 to 68, with higher scores indicating greater symptom severity. Other symptoms were assessed using the Beck Anxiety Index (BAI),[33] Beck Depression Inventory II (BDI II),[33] and the Pittsburgh Sleep Quality Index (PSQI).[34] Participants then had at least 2 weeks of no medication treatment and then returned for treatment with the alternate study medication. Repeated measures analyses of variance (ANOVAs) of CAPS scores, and CAPS subscale scores and items (ie, sleep, dreams, reexperiencing, avoidance, and hyperarousal), were calculated to compare treatment effects at the beginning (day 0) and end (day 16) of each treatment phase. Repeated-measures ANOVA comparisons of PCL-M, PSQI, BAI, and BDI scores were calculated across days 0, 8, and 16. Following completion of all assessments, study medication was discontinued without titration.

Table 1. Demographics for Doxazosin XL–Treated Veterans With Posttraumatic Stress Disorder (PTSD)[a]

Characteristic	Value
Participants, N	8
Male, n	8
Ethnicity	
White	2
African American	3
Hispanic	2
Native American	1
Age, y	34.8 (8.3)
Education, y	13.5 (1.7)
Branch of military, n	
Army	5
Marines	1
Navy	2
Years of service	4.8 (0.8)
Age at PTSD onset, y	22.1 (1.0)
Employment status, n	
Employed	1
Unemployed	7
Weight, lb	216 (32)
Marital status, n	
Single	2
Married	2
Divorced	4

[a]Data are shown as mean (SEM) unless otherwise noted.

RESULTS

Eight participants were enrolled, and all completed study procedures, with the exception of 1 participant who became anxious while completing the study instruments on the final day of treatment with placebo and was unable to complete the assessments. His results are therefore not available. Participants' demographic information is shown in Table 1. In terms of comorbid diagnoses, 3 participants had back pain, 2 had ankle pain, 2 had neck pain, and 2 had shoulder pain. In addition, participants' medical histories included retinal detachment, tinnitus, scars, dermatomyositis, compartment syndrome with fully healed bilateral fasciotomy, migraines, history of head injury, kidney stones, gout, past history of alcohol and cocaine use disorder, gastroesophageal reflux disease, tooth loss, complex partial seizures, and treated leg fracture. These did not impact the conduct of the study. One participant reported taking oxcarbazepine and phenytoin, 1 took sertraline sporadically, and 1 took low-dose amitriptyline for headaches. During the study, no major adverse events were noted. One patient developed a small, maculopapular rash on his neck that was determined to be contact dermatitis and was thought to be unrelated to study medication. One participant developed rhinitis successfully treated with pseudoephedrine; this is a recognized side effect and was determined to be medication-related but not a severe or serious adverse event. Another participant experienced brief stomach gassiness/bloating that resolved within 24 hours and was thought to be unrelated to treatment.

The primary outcome of interest was change in $CAPS_{17}$ scores and change in PCL-M ratings from premedication baseline to end of treatment for each phase of the study, placebo and doxazosin XL. A repeated-measures ANOVA on $CAPS_{17}$ scores revealed no significant effects of treatment

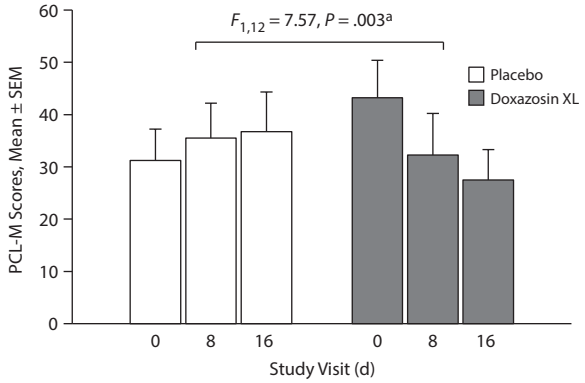
($F_{1,13}$ = 0.00, P = .992) or time ($F_{1,13}$ = 1.70, P = .215) and no significant treatment × time interaction ($F_{1,13}$ = 0.00, P = .978). A repeated-measures ANOVA on PCL-M scores revealed no significant effects of treatment ($F_{1,13}$ = 0.00, P = .963), although a significant effect of time ($F_{1,13}$ = 6.33, P = .026) and a significant treatment × time interaction ($F_{1,13}$ = 15.93, P = .002) were revealed.

As displayed in Figure 1, a repeated-measures ANOVA considering PCL-M ratings at the beginning, middle, and end of treatment revealed that while there was no main effect of treatment ($F_{1,12}$ = 0.10, P = .757) or time ($F_{1,12}$ = 3.08, P = .065), there was a significant treatment × time interaction ($F_{1,12}$ = 7.57, P = .003). Doxazosin XL treatment was associated with reductions in PCL-M scores over time, whereas placebo treatment was not.

Repeated-measures ANOVAs revealed that while there were significant effects of time (ie, day) on overall $CAPS_{17}$ scores (P = .016) and the sleep disturbances items (P = .042), there were no significant effects of treatment or treatment × time interactions on these or any of the other CAPS subscales (Table 2). The treatment × time interaction for the CAPS hyperarousal subscale approached significance (P = .09).

Repeated-measures ANOVAs revealed no main effects of treatment or time, and no significant treatment × time interactions for PSQI, BAI, or BDI scores (Table 2). The length of study is very likely too short to see significance in changes in mood on the BDI, and a longer study is needed to fully evaluate this result. Significant treatment order effects were observed. PCL-M ratings at the beginning of doxazosin XL treatment (before administration of the first dose of study medication in that study episode) were higher than PCL-M ratings at the beginning of the placebo condition (that is, 43.3 compared to 31.3, respectively, in Table 2). This difference is significant (t_7 = 3.053, P = .019). Those who received doxazosin XL during their first study episode (n = 3) had lower PCL-M scores when they subsequently entered the placebo phase of the study several weeks later (PCL-M = 22.5) compared to those who had placebo during their first study episode (n = 5) (PCL-M = 39.7, not shown in tables). This most likely contributed to the difference in change scores noted previously.

Figure 1. PCL-M Scores of Veterans Comparing Response to Doxazosin XL (n = 7) vs Placebo (n = 7) During the First, Third, and Final Study Visits



[a]Indicates a significant treatment × time interaction.
Abbreviation: PCL-M = Posttraumatic Stress Disorder Checklist–Military version.

DISCUSSION

To our knowledge, this controlled study is the first to test doxazosin XL in participants with PTSD. One open-label study[35] from the Netherlands published in 2010 as a letter suggested that doxazosin XL treatment produced statistically significant improvements in CAPS scores from 72 to 53 after 8 weeks of treatment, a statistically significant reduction. The CAPS "distressing recurrent dreams" scores also declined over time. Although the study included a 4-week no-treatment run-in to control for spontaneous improvements, placebo effects could not be ruled out. It should also be noted that participants were not titrated off medication, and no follow-up was arranged; however, no participants contacted study staff with any issues.

Table 2. Descriptive Statistics for Study on Doxazosin Efficacy in Veterans With Posttraumatic Stress Disorder

	Placebo		Doxazosin		Statistics[a]							
					N		Treatment		Day		Treatment × Day	
Measure	Day 0 (Pre), Mean ± SEM	Day 16 (Post), Mean ± SEM	Day 0 (Pre), Mean ± SEM	Day 16 (Post), Mean ± SEM	Placebo	Doxazosin	*F*	*P*	*F*	*P*	*F*	*P*
CAPS												
Total	96.1 ± 20.2	82.9 ± 21.3	85.6 ± 17.3	78.6 ± 17.3	7	8	0.08	.781	**2.21**	**.016**	0.21	.653
Sleep	6.43 ± 0.69	5.71 ± 1.17	6.50 ± 0.80	4.63 ± 1.24	7	8	0.15	.704	**5.06**	**.042**	1.02	.332
Dream	3.86 ± 0.96	3.14 ± 1.37	3.75 ± 1.15	3.25 ± 1.05	7	8	…	…	0.86	.371	0.03	.873
17	67.4 ± 12.6	61.4 ± 15.5	67.5 ± 12.9	61.8 ± 12.9	7	8	…	.992	1.70	.215	…	.978
Reexperience	16.3 ± 4.56	15.0 ± 5.36	19.0 ± 4.20	17.5 ± 4.26	7	8	0.17	.685	0.74	.405	…	.948
Avoidance	27.0 ± 4.46	21.0 ± 6.41	25.8 ± 5.50	24.9 ± 5.10	7	8	0.03	.859	1.81	.202	1.00	.335
Hyperarousal	24.1 ± 4.19	25.4 ± 4.18	24.0 ± 3.71	19.4 ± 3.98	7	8	0.32	.579	1.06	.322	3.32	.092
PCL-M	31.3 ± 6.53	36.7 ± 7.60	43.3 ± 7.17	27.5 ± 5.82	7	8	…	.963	**6.33**	**.026**	**15.9**	**.002**
PSQI	14.0 ± 3.58	17.0 ± 2.12	15.2 ± 16.8	13.2 ± 2.41	4	6	0.17	.689	0.13	.725	3.33	.105
BAI	18.9 ± 7.03	13.6 ± 4.80	22.0 ± 5.73	18.1 ± 6.07	7	8	0.22	.644	4.04	.066	0.10	.762
BDI	20.1 ± 6.58	20.9 ± 8.18	18.5 ± 4.94	23.0 ± 6.83	7	8	…	.978	0.66	.430	0.35	.565

[a]Degrees of freedom = 1,13 except for the PSQI, which = 1,8. Boldface values represent statistical significance.
Abbreviations: BAI = Beck Anxiety Index, BDI = Beck Depression Inventory, CAPS = Clinician-Administered PTSD Scale, PCL-M = Posttraumatic Stress Disorder Checklist–Military version, Pre = pretreatment, Post = day 16 of treatment, PSQI = Pittsburgh Sleep Quality Index.
Symbol: … = F < 0.01 and P > .999.

Our study demonstrated that 16 days of treatment with doxazosin XL statistically significantly lowered PCL-M scores, but had no effect on $CAPS_{17}$ or depression scores in veterans with PTSD. Doxazosin XL treatment was also associated with nonsignificant reductions on the CAPS hyperarousal subscale. It is possible that a longer duration of treatment is needed to impact depression scores and scores on the overall CAPS scale. At the end of the 16-day medication treatment period, participants remained symptomatic, and clearly a longer duration of treatment would be needed to produce symptom remission.

The rapidity of effect of doxazosin XL in lowering PCL-M (about 2 weeks) scores is encouraging. In most studies, such as those done with prazosin where CAPS is the primary outcome measure, the length of study is generally longer, typically 8 to 15 weeks.[21,23]

The CAPS, being clinician-administered, gives the clinician some degree of control over how different symptoms are elicited and investigated. Because of this, the scale is also more complicated and time-consuming than the PCL. It can trigger additional memories should a participant answer the first question in a series, thereby increasing the score. In a previous comparison[36] of the 2 instruments, treatment was associated with greater reductions in PCL-M compared to CAPS (CAPS scores were reduced by 0.75 to 0.82 standard deviations for every 1 standard deviation change on the PCL). It is possible the PCL is a more sensitive detector of treatment differences in PTSD.

We observed a treatment order effect in that participants who received doxazosin XL first had lower PCL-M ratings when they entered the placebo treatment arm several weeks later. The explanation for this apparent carryover effect following doxazosin XL treatment is unclear, as doxazosin XL has an elimination half-life of 15–19 hours, whereas at least 2 weeks separated the 2 study episodes. It may be that symptoms once suppressed tend not to return, or return slowly, as happens following effective psychotherapy.[5,6] The order effect suggests that doxazosin XL treatment may facilitate extinction of PTSD symptoms, or, alternatively, PTSD symptoms may have recurred later if we had waited.

Doxazosin, like prazosin, blocks noradrenergic α_1 receptors, and the 2 medications are approximately of equal potency even though doxazosin has a much longer half-life and duration of action.[37] Excessive stimulation of noradrenergic α_1 receptors causes increases in perseverative responding and impairments in working memory,[38–40] both of which are cognitive impairments observed in patients with PTSD.[41,42] In rodents, treatment with noradrenergic α_1 receptor antagonists reverses cognitive impairments produced by excessive norepinephrine signaling,[40] and indeed noradrenergic α_1 receptor blockade by prazosin improved cognitive functioning in patients with PTSD.[43]

This study has several limitations. Most importantly, the sample was small, and replication with a larger sample is needed. Treatment duration was short, limiting any potential clinical benefits, and a longer duration of treatment may be needed. Our sample was limited to Persian Gulf veterans. Participants, especially older ones, from other conflicts (eg, Vietnam) would increase confidence in the generalizability of the results. Along similar lines, no women veterans were enrolled for the study, so further research including women is important.

In summary, doxazosin XL treatment reduced some symptoms of PTSD when administered for 2 weeks. Treatment was well tolerated, and there were minimal side effects. Doxazosin XL may be an effective and safe alternative to prazosin for the treatment of some symptoms of PTSD.

Submitted: November 25, 2014; accepted June 22, 2015.

Drug names: doxazosin (Cardura and others), doxazosin extended release (Cardura XL), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), phenytoin (Dilantin, Phenytek, and others), prazosin (Minipress and others), sertraline (Zoloft and others).

Potential conflicts of interest: At the time this research was conducted, **Dr Rodgman** was a MIRECC fellow. **Drs Newton** and **Raskind** were also employed by the Department of Veterans Affairs. **Drs Rodgman, Verrico, Holst, Haile, Raskind, De La Garza,** and **Newton**, and **Miss Thompson-Lake** hereby attest that neither they nor their spouse/partner have had any relevant financial interests or personal affiliations during at least the past 12 months, and thereby have no conflicts of interest.

Funding/support: This study was conducted at and funded by a grant from the Michael E. DeBakey VA Medical Center. NIH grant R25DA028976 also provided financial support.

Role of the sponsor: The funding sources had no role in the design of the study.

Disclaimer: The views expressed herein are those of the authors and do not necessarily represent the views of the US Department of Veterans Affairs.

REFERENCES

1. McNally RJ. Are we winning the war against posttraumatic stress disorder? *Science*. 2012;336(6083):872–874.
2. Schneiderman AI, Braver ER, Kang HK. Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during the conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *Am J Epidemiol*. 2008;167(12):1446–1452.
3. Seal KH, Bertenthal D, Miner CR, et al. Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs facilities. *Arch Intern Med*. 2007;167(5):476–482.
4. Department of Defense. *An Achievable Vision: Report of the Department of Defense Task Force on Mental Health*. Falls Church, VA: Defense Health Board; 2007.
5. Monson CM, Schnurr PP, Resick PA, et al. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. *J Consult Clin Psychol*. 2006;74(5):898–907.
6. Goodson JT, Lefkowitz CM, Helstrom AW, et al. Outcomes of prolonged exposure therapy for veterans with posttraumatic stress disorder. *J Trauma Stress*. 2013;26(4):419–425.
7. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837–1844.
8. Davidson J, Pearlstein T, Londborg P, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1974–1981.
9. Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2006;(1):CD002795.
10. Friedman MJ, Marmar CR, Baker DG, et al. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry*. 2007;68(5):711–720.
11. Zohar J, Amital D, Miodownik C, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002;22(2):190–195.
12. van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. *J Clin Psychiatry*. 1994;55(12):517–522.
13. Cassano P, Fava M. Tolerability issues during long-term treatment with antidepressants. *Ann*

Clin Psychiatry. 2004;16(1):15–25.
14. Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc Patient Saf*. 2010;2:141–150.
15. Nurnberg HG, Hensley PL, Gelenberg AJ, et al. Treatment of antidepressant-associated sexual dysfunction with sildenafil: a randomized controlled trial. *JAMA*. 2003;289(1):56–64.
16. Clayton AH, Pradko JF, Croft HA, et al. Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry*. 2002;63(4):357–366.
17. Liu X, Chen Y, Faries DE. Adherence and persistence with branded antidepressants and generic SSRIs among managed care patients with major depressive disorder. *Clinicoecon Outcomes Res*. 2011;3:63–72.
18. Kronish IM, Edmondson D, Li Y, et al. Post-traumatic stress disorder and medication adherence: results from the Mind Your Heart Study. *J Psychiatr Res*. 2012;46(12):1595–1599.
19. Lockwood A, Steinke DT, Botts SR. Medication adherence and its effect on relapse among patients discharged from a Veterans Affairs posttraumatic stress disorder treatment program. *Ann Pharmacother*. 2009;43(7):1227–1232.
20. Raskind MA, Thompson C, Petrie EC, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2002;63(7):565–568.
21. Raskind MA, Peskind ER, Hoff DJ, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry*. 2007;61(8):928–934.
22. Raskind MA, Peskind ER, Kanter ED, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry*. 2003;160(2):371–373.
23. Raskind MA, Peterson K, Williams T, et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry*. 2013;170(9):1003–1010.
24. Guo TZ, Tinklenberg J, Oliker R, et al. Central α_1-adrenoceptor stimulation functionally antagonizes the hypnotic response to dexmedetomidine, an α_2-adrenoceptor agonist. *Anesthesiology*. 1991;75(2):252–256.
25. Kaye B, Cussans NJ, Faulkner JK, et al. The metabolism and kinetics of doxazosin in man, mouse, rat and dog. *Br J Clin Pharmacol*. 1986;21(suppl 1):19S–25S.
26. Cubeddu LX. New alpha$_1$-adrenergic receptor antagonists for the treatment of hypertension: role of vascular alpha receptors in the control of peripheral resistance. *Am Heart J*. 1988;116(1 pt 1):133–162.
27. Haile CN, Hao Y, O'Malley PW, et al. The α1 antagonist doxazosin alters the behavioral effects of cocaine in rats. *Brain Sci*. 2012;2(4):619–633.
28. Newton TF, De La Garza R 2nd, Brown G, et al. Noradrenergic α_1 receptor antagonist treatment attenuates positive subjective effects of cocaine in humans: a randomized trial. *PLoS ONE*. 2012;7(2):e30854.
29. Shorter D, Lindsay JA, Kosten TR. The alpha-1 adrenergic antagonist doxazosin for treatment of cocaine dependence: a pilot study. *Drug Alcohol Depend*. 2013;131(1–2):66–70.
30. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for *DSM-IV* and *ICD-10*. *J Clin Psychiatry*. 1998;59(suppl 20):22–33, quiz 34–57.
31. Blake DD, Weathers FW, Nagy LM, et al. The development of a Clinician-Administered PTSD Scale. *J Trauma Stress*. 1995;8(1):75–90.
32. Weathers FW, Litz BT, Keane TM, et al. The PTSD Checklist for *DSM-IV* and *DSM-5*. National Center for PTSD Web site. www.ptsd.va.gov. Accessed 2013.
33. Beck AT, Steer RA, Ball R, et al. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. 1996;67(3):588–597.
34. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
35. De Jong J, Wauben P, Huijbrechts I, et al. Doxazosin treatment for posttraumatic stress disorder. *J Clin Psychopharmacol*. 2010;30(1):84–85.
36. Monson CM, Gradus JL, Young-Xu Y, et al. Change in posttraumatic stress disorder symptoms: do clinicians and patients agree? *Psychol Assess*. 2008;20(2):131–138.
37. Elliott HL, Meredith PA, Sumner DJ, et al. A pharmacodynamic and pharmacokinetic assessment of a new α-adrenoceptor antagonist, doxazosin (UK33274) in normotensive subjects. *Br J Clin Pharmacol*. 1982;13(5):699–703.
38. Arnsten AF. Catecholamine influences on dorsolateral prefrontal cortical networks. *Biol Psychiatry*. 2011;69(12):e89–e99.
39. Arnsten AF, Mathew R, Ubriani R, et al. α-1 Noradrenergic receptor stimulation impairs prefrontal cortical cognitive function. *Biol Psychiatry*. 1999;45(1):26–31.
40. Birnbaum S, Gobeske KT, Auerbach J, et al. A role for norepinephrine in stress-induced cognitive deficits: α-1-adrenoceptor mediation in the prefrontal cortex. *Biol Psychiatry*. 1999;46(9):1266–1274.
41. Vasterling JJ, Duke LM, Brailey K, et al. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*. 2002;16(1):5–14.
42. Sanchez S, Barnhart S, Stellman S, et al. PTSD and cognitive impairment among rescue and recovery workers exposed to the 9/11 World Trade Centre Disaster. *Occup Environ Med*. 2014;71(suppl 1):A68–A69 [abstract 0073].
43. Ruff RL, Riechers RG II, Wang XF, et al. For veterans with mild traumatic brain injury, improved posttraumatic stress disorder severity and sleep correlated with symptomatic improvement. *J Rehabil Res Dev*. 2012;49(9):1305–1320.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Erika F. H. Saunders, MD, at esaunders@psychiatrist.com.