

Prazosin Outcomes in Older Veterans With Posttraumatic Stress Disorder

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Even at relatively high dosages, prazosin was well tolerated and significantly improved posttraumatic stress disorder severity and related nightmares in an older patient population.

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Posttraumatic stress disorder (PTSD) is a common psychiatric condition in the veteran population and is associated with significant sleep disturbances and trauma-related nightmares.¹ PTSD can present with intrusive symptoms, such as recurrent memories or dreams, which are associated with traumatic events.² Clinical studies have described an increase in central nervous system (CNS) noradrenergic activity in PTSD; specifically, noradrenergic outflow and/or postsynaptic adrenoreceptor responsiveness is increased.^{3,4} Targeting a reduction in noradrenergic activity via antagonism of noradrenergic receptors has been a therapeutic treatment strategy in PTSD.

Prazosin crosses the blood-brain barrier and works to antagonize α -1 adrenoreceptors to decrease noradrenergic outflow.⁵ It has been shown in multiple trials to effectively reduce nightmares and improve sleep quality in the veteran population.⁶⁻¹² However, a recent negative trial contributed to a downgraded recommendation for prazosin in the treatment of PTSD-related nightmares in the joint PTSD guideline from the US Department of Veterans Affairs (VA) and US Department of Defense (DoD).^{13,14}

The diagnosis of PTSD in veterans aged ≥ 65 years has been increasing due to improved recognition.¹⁵ As a result, prazosin may be considered more frequently as a treatment option for those patients who report PTSD-related nightmares. It is important to recognize that the normal physiologic process of aging is associated with increased noradrenergic outflow, which may change the pharmacodynamics of prazosin in geriatric patients.^{12,16} This may necessitate increased doses to adequately antagonize the α -1 adenoreceptor.¹⁷ High doses of prazosin may increase the risk

of hypotension in older patients.¹² This increased risk is especially concerning for patients who already receive multiple medications or have comorbid conditions that impact blood pressure (BP).

The existing literature has few studies that have reported on outcomes with prazosin use in older veterans.^{11,12} The few existing reports provide clinically valuable descriptions of tolerability and efficacy with prazosin. For example, Peskind and colleagues showed prazosin to be an effective agent in the treatment of PTSD-related nightmares.¹² However, in older veterans prazosin dosing > 4 mg has not been described or reported in the literature.

There appears to be a lack of clinical guidance with regards to dosing of prazosin in older patients. The goal of the current study was to assess the outcomes of older veterans with PTSD under pharmacist management of prazosin at our outpatient Prazosin Titration Clinic (PTC) in order to contribute to the minimal, yet valuable, existing clinical literature.

METHODS

This study was approved by the University of Iowa Institutional Review Board and Iowa City Veterans Affairs Health Care System (ICVAHCS) research and development committee. The study was a retrospective chart review of older patients with consultations referred to the ICVAHCS PTC. To be eligible for inclusion, veterans with a PTSD diagnosis must have been evaluated at an initial consult appointment with a mental health clinical pharmacy specialist (MH CPS) from February 1, 2016 to August 31, 2018, and had at least 1 follow-up appointment. Follow-up visits were conducted either by telephone or in a face-to-face clinic visit.

Prazosin Titration Clinics

VA health care systems use pharmacists to manage veterans prescribed prazosin through PTC consultations. PTCs provide a process for close follow-up and assessment of PTSD-related outcomes. Due to the frequency of follow-up, this service may be beneficial for older veterans with more complex comorbidities and medication regimens. Any veteran with PTSD-related nightmares may be referred to the PTC for a consultation by any health care provider. Once referred to the clinic, MH CPSs assume responsibility for the prazosin prescription, including dose adjustments. For example, if a veteran reported no issues with tolerability but continued to have frequent and distressing nightmares, the dose may be increased, typically by 1-mg to 2-mg increments. Once the veteran reaches a stable and tolerable dose of prazosin, they are discharged from the PTC, and the referring health care provider resumes responsibility for the prazosin prescription.

Clinically Measured Outcomes

Nightmare frequency and intensity were measured using the Recurrent Distressing Dreams item B2 of the Clinician Administered PTSD Scale (CAPS) (Table 1). The PTSD Checklist (PCL-5), Insomnia Severity Index (ISI), and total sleep hours were used to determine the effect of prazosin on symptom severity (Table 2). The PCL-5 is a 20-item self-report used to monitor and quantify symptom level and change over time. It evaluates the frequency over the past month that a patient was bothered by any of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* PTSD criterion.² Scores range from 0 (not at all) to 4 (extreme), with a maximum score of 80. The ISI is a 7-item self-report of sleep symptoms, with a total score of 28, where increasing scores indicate increasing severity of insomnia (Table 3).

Clinically measured outcome scales were performed and assessed by MH CPSs. CAPS frequency and intensity were measured at each clinic visit. PCL-5 and ISI scores were assessed at baseline and at the endpoint of study or discharge from clinic (Table 4). Patients who continued in the PTC after the end of the study date or who were lost to follow-up did not complete these measures at time of discharge.

TABLE 1 Clinician Administered Posttraumatic Stress (CAPS) Disorder Scale Nightmare Measures

Nightmare Measures	Description
Frequency	
0	Never
1	Once/twice
2	1 to 2 times/wk
3	Several times/wk
4	Daily/almost daily
Intensity	
0	None
1	Mild/minimal distress, may not have awoken
2	Moderate, may have awoken in distress but can readily return to sleep
3	Severe, considerable distress, difficulty returning to sleep
4	Extreme, incapacitating distress, did not return to sleep

TABLE 2 Posttraumatic Stress Disorder Checklist Scale (PCL-5)

Scale	Symptoms Reported
0-10	None/minimal
11-20	Mild
21-40	Moderate
41-60	Severe
61-80	Very severe

TABLE 3 Insomnia Severity Index (ISI)

Scale	Levels of Clinical Insomnia
0-7	Not clinically significant
8-14	Subthreshold
15-21	Moderate
22-28	Severe

Data Analysis

The primary outcome was change in CAPS nightmare frequency and intensity from time of initial clinic visit to time of discharge or end of study. The secondary outcomes included change in PCL-5, ISI, and sleep hours. Other secondary outcomes included measures of tolerability: BP changes, adverse effects (AEs) reported, and outcome of prazosin therapy when AEs were reported. Change in PTSD symptoms, PCL-5, and ISI were assessed using the Wilcoxon signed rank

TABLE 4 Clinically Measured Outcomes

Baseline	Follow-up	Discharge or End of Study
1. PCL-5	1. Total sleep hours	1. PCL-5
2. ISI	2. CAPS frequency and intensity	2. ISI
	3. Adverse effects	3. All included measures completed during follow-up, excluding dose adjustments
	4. Dose adjustments	

Abbreviations: CAPS, Clinician Administered Posttraumatic Stress Disorder Scale; ISI, Insomnia Severity Index; PCL-5, Posttraumatic Stress Disorder Checklist.

TABLE 5 Baseline Characteristics (N = 32)

Variables	Results
Posttraumatic stress disorder diagnosis, %	100
Age, mean (SD), y	69.7 (3.3)
Male gender, %	100
Race, %	
White	93.8
African American	3.1
Unknown/declined to answer	3.1
Military service era, ^a %	
Vietnam War	93.8
Post-Korean War	6.3
Persian Gulf wars	3.1
Combat history, %	
Yes	87.5
No	12.5
Referring provider, %	
Psychiatry resident	53.1
Mental health physician assistant or nurse practitioner	28.1
Psychiatrist	15.6
Primary care physician	3.1

^aSome veterans served in more than 1 era.

tests. Findings were considered to be statistically significant at $P \leq .05$. Other variables were reported descriptively.

RESULTS

Thirty-two veterans, aged ≥ 65 years, with clinical diagnosis of PTSD at the time of referral to the PTC were reviewed (Table 5). All patients were male and 93.8% were white. Thirty were Vietnam era veterans, 1 served in the Persian Gulf era, and 2 served in the post-Korean War era. Twenty-eight veterans had a combat history. Severe PTSD symptoms were reported as indicated by baseline PCL-5 scores, and moderate severity insomnia symptoms as indicated by baseline ISI scores.

All veterans had at least 1 comorbid med-

ical condition, and the majority had multiple medical comorbidities. All were taking multiple medical and psychiatric medications. More than 80% of veterans were taking antihypertensive agents at baseline (Table 6). Twenty-two of the 32 veterans were prescribed a VA/DoD PTSD guideline-recommended antidepressant.

Primary Outcomes

The baseline, final, and changes in the primary outcomes are included in the Figure. Treatment with prazosin was associated with significant improvement in median scores from baseline to endpoint for CAPS nightmare frequency ($-2, P = .0001$), CAPS nightmare intensity ($-2, P = .001$), and total CAPS item score ($-4, P < .001$).

Secondary Outcomes

Of the 32 patients included in the study, PCL-5 was obtained from 20 veterans and ISI from 17 veterans at discharge from clinic. Thirty veterans reported final sleep hours, 2 veterans were unable to quantify average sleep hours per night at their final visit. PTSD symptom severity showed significant median change from baseline to endpoint of management in PTC for PCL-5 ($-20.5, P = .0002$) and ISI ($-6.5, P = .002$). Total sleep hours also showed significant improvement from baseline to endpoint ($1.5, P = .003$) (Table 7).

Prazosin Dosing

Maximum prazosin total daily doses were evaluated from the study baseline to the endpoint (Table 8). The mean (SD) maximum total daily dose of prazosin reached was 5.6 (5.1) mg (median, 3.5 mg; range, 1-17 mg). The mean (SD) total daily dose of prazosin at endpoint of study was 5.1 (5.3) mg (median, 2.5 mg; range, 0-17 mg). The average (SD) change of prazosin dose from baseline to endpoint was 3.5 (4.6) mg (median, 2 mg; range, -2 to 15 mg).

Tolerability

The average (SD) baseline systolic BP (SBP) was 135.8 (20.5) mm Hg and diastolic BP (DBP) was 77.2 (11.0) mm Hg. The average SBP and DBP at study endpoint were 131.8 (16.6) mm Hg and 75.9 (13.7) mm Hg, respectively. Endpoint BP values were missing for 6 patients.

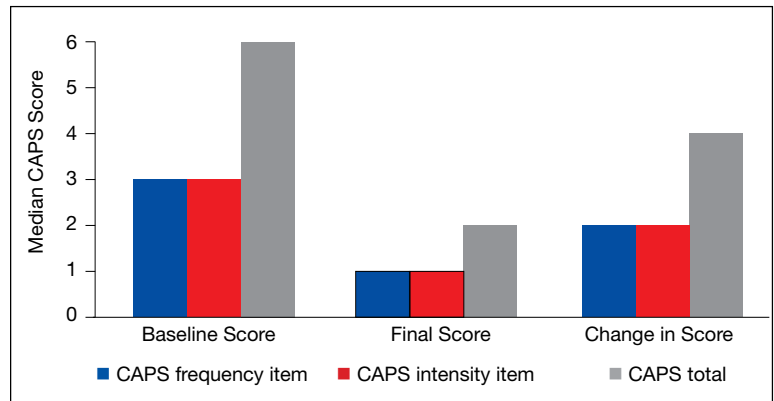
Nine of 32 veterans reported AEs during PTC management of prazosin. Dizziness was the most common AE reported. Other AEs noted included orthostatic hypotension, headache, and falls. Of 12 reported AEs, 8 were related to dizziness, 5 of which were transient or tolerable. One veteran had a dose reduction of prazosin due to dizziness, and 3 veterans discontinued prazosin due to orthostasis. Several veterans had changes made to their antihypertensive medication regimen during prazosin titration, including dose reductions and/or decreased number of medications. If indicated, the MH CPS collaborated with the antihypertensive prescriber to make dosing adjustments. Two veterans reported a fall during prazosin titration; 1 veteran had other mobility-related factors thought to precipitate to their fall, and neither veterans were injured because of the falls.

Twenty-eight veterans (87.5%) treated in the PTC continued prazosin therapy after discharge. Six months postdischarge, 70% of veterans had maintained prazosin therapy. Two veterans required a dose increase postdischarge from PTC, and 1 veteran required a dose reduction. About one-third of veterans included in this study continued in the PTC beyond the end of the study period. Common reasons for clinic discharge were symptom resolution (37.5%), adverse reactions (12.5%), lost to follow-up (6.3%), or nonadherence (3.1%).

DISCUSSION

The existing literature reports few outcomes for older veterans prescribed prazosin for PTSD. One report included a 75-year-old otherwise-healthy veteran, who received 2-mg prazosin at bedtime. At this dose, he reported good tolerability and response, as indicated by a reduction in his CAPS nightmare severity score.¹¹ An open-label trial assessed prazosin in 9 geriatric men with chronic PTSD and found low-dose prazosin (average [SD] maximum prazosin dose reported was

FIGURE CAPS Score Primary Outcomes (N = 32)



Abbreviation: CAPS, Clinician Administered Posttraumatic Stress Disorder Scale.

2.3 [0.7] mg, range 2-4 mg per day) greatly reduced nightmares and overall PTSD severity in 8 of 9 subjects.¹² Despite the veterans in that study having multiple medical comorbid conditions and taking concomitant medications, prazosin was reported to be well tolerated, and changes in BP were determined to be clinically insignificant.¹² A recent study of middle-aged veterans (average [SD] age 52 [14] years) reported prazosin did not significantly alleviate PTSD-related nightmares.¹³ However, we observed prazosin therapy significantly reduced nightmares and sleep disturbances, and significantly improved PTSD severity in our older veteran population.

To our knowledge, the current study is the largest retrospective study that evaluates prazosin therapy for the treatment of PTSD-related nightmares in older veterans. The findings of this study are similar to a previous study in older veterans as well as studies of prazosin in younger and middle-aged adult veterans, with the average age ranging from 30 to 56 years.⁶⁻¹² Like the previously reported studies, prazosin also was well tolerated in our sample of veterans with multiple comorbidities and concomitant medications. Changes in BP were not clinically significant.

Studies have demonstrated increased noradrenergic activity as a component of the normal aging process.^{16,17} This may require utilizing caution during prazosin dose titration and frequent patient assessment, due to the concern for risk of hypotension in older patients and in particular those who may require increased doses to achieve efficacy. In our study, favorable

TABLE 6 Baseline Comorbidities and Concomitant Medications

Comorbidities	Patients, %	Concomitant Medications ^b	Patients, %
Psychiatric conditions^a		Psychotropics	
Major depressive disorder	62.5	Patients prescribed an antidepressant	90.6
Anxiety disorder	15.6	Bupropion	25.0
Tobacco use disorder	12.5	SSRI (nonrecommended)	12.5
Alcohol use disorder	12.5	Mirtazapine	6.3
Substance use disorder	9.4	SNRI (nonrecommended)	3.1
Insomnia	9.4	Tricyclic antidepressant	3.1
Nonpsychiatric conditions^a		Sedative hypnotic	
Benign prostatic hyperplasia	15.6	Trazodone	21.9
Cardiovascular conditions		Melatonin	12.5
Hypertension	93.8	Benzodiazepine	9.4
Coronary artery disease	15.6	Tricyclic antidepressant	3.1
Stroke	12.5	Quetiapine	3.1
Edema	6.3	Topiramate 3.1	
Atrial fibrillation	6.3	Change to psychotropic medication made during titration 50.0	
Heart failure	6.3	Antihypertensives	
Tachycardia	3.1	Antihypertensive medications, No.	
		4	2.9
		3	11.8
		2	26.5
		1	44.1
		0	14.7
		Antihypertensive regimen change during prazosin titration 18.5	
		Others	
		Benign prostatic hyperplasia medications 12.5	

Abbreviations: SNRI, selective serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aBipolar disorder, schizophrenia, orthostasis, syncope, angina, history of palpitations, bradycardia, tachycardia, other arrhythmias, and history of myocardial infarction diagnoses were evaluated and were not medical conditions in the patient sample.

^bThere were no veterans in the patient sample prescribed the following medications: monoamine oxidase inhibitors or trazodone (at antidepressant doses), mood stabilizers, zolpidem, eszopiclone, ramelteon, mirtazapine (at low doses used for sleep), and hydroxyzine.

outcomes were achieved at an average (SD) total daily dose of 5.1 (5.3) mg (median, 2.5 mg; range 0-17 mg). A previous report showed efficacy of prazosin around an average (SD) maximum dose of 2.3 (0.7) mg, which is lower than the doses reported in the current study.¹² In addition, 13 veterans (40.6%) from our sample reached doses of ≥ 5 mg per day, and 8 veterans (25.0%) reached doses of ≥ 10 mg per day.

The doses reached in this study were reflective of a management approach using assessment of patient-reported symptoms at weekly to biweekly follow-up visits. The individualized management approach applied in the PTC by MH CPSs aids in uncovering the most efficacious and tolerated dose of prazosin for each veteran. Evaluation of symptom change during treatment in PTC was facilitated use of objective rating scales, which helped measure nightmare frequency and intensity, sleep satisfaction, and global PTSD severity. Given the variability in dosing

of prazosin reported in the literature, further studies may be warranted to provide more definitive clinical guidance as far as dosing prazosin in older patients.

The study by Peskind and colleagues rationalized that lower doses of prazosin may be used in older patients given pharmacokinetic effects of aging, age-associated changes in PTSD pathophysiology, and effects and interactions of concomitant medications.¹² However, our study found that prazosin could be well tolerated at higher doses. The rate of discontinuation due to intolerable AEs was low. AEs reported were consistent with the established AE profile of prazosin, with dizziness, orthostasis, and headache most commonly reported. Similar to the Peskind and colleagues study, BP had a tendency to decrease in this current study; however, the change was not clinically significant.¹² That study also reported transient dizziness with prazosin titration, which was shown to be tolerable in the

majority of our veterans reporting dizziness.¹² Other common AEs with prazosin, such as rash, priapism, sedation, syncope, other cardiac AEs, and sleep disturbance were not reported in our study population.

MH CPS-managed PTCs are one venue that may allow veterans to achieve favorable outcomes through frequent follow-up. As prazosin dosing is specific to each individual patient, frequent follow-up visits are helpful in determining optimal doses that maximize efficacy while minimizing intolerable AEs. The majority of veterans treated in our PTC continued use of prazosin 6 months postdischarge, while 3 veterans required a postdischarge dose change.

The 2017 VA/DoD PTSD guidelines recommend individual, trauma-focused psychotherapy over pharmacologic therapy for the primary treatment of PTSD.¹⁴ About half of the veterans in the current study participated in either group or individual psychotherapy during enrollment in the PTC. A systematic review of psychotherapy in older veterans reported mixed results, with 4 studies indicating positive effects of therapy, while the other 3 studies reported no benefit or mixed effects for PTSD symptoms. The review concluded that fewer older adults experience complete remission of symptoms with psychotherapy alone.¹⁸ A previous study of older veterans described improvement in PTSD-related symptoms with prazosin without concurrent psychotherapy.¹²

Limitations and Strengths

While this study is the largest study to evaluate outcomes of prazosin in older patients with PTSD, there are several important limitations. The study population was small and all were male. The results of this study may not be applicable to women. Another limitation was several missing values in our data set, as some secondary outcomes were not collected via telephone follow-up visits. This could potentially contribute a measurement bias in the reported secondary outcomes results, specifically for the PCL-5 and ISI. Additionally, some veterans in this study may have reported symptomatic improvement based on the additional supportive intervention that clinical pharmacists were able

TABLE 7 Secondary Treatment Outcomes

Measures	Baseline, median (range), [No.]	Final, median (range), [No.]	Change, median (range), [No.]
PCL-5	52.5 (26-80) [32]	32 (10-80) [20]	-20.5 (0-47) [20]
ISI	19 (11-28) [31]	13 (3-24) [17]	-6 (0-22) [17]
Sleep satisfaction score	3 (1-4) [31]	2 (0-3) [24]	-1 (-3-0) [24]
Sleep hours	6 (3-10.5) [32]	7.5 (3-9.5) [30]	1.5 (0-5) [32]

Abbreviations: PCL-5, Posttraumatic Stress Disorder Checklist; ISI, Insomnia Severity Index.

TABLE 8 Prazosin Dosing During Treatment

Prazosin Dosing	Mean (SD), mg	Median (range), mg
Baseline morning dose	0.09 (0.4)	0 (0-2)
Baseline bedtime dose	1.6 (2.1)	1 (0-10)
Baseline total dose	1.4 (2.2)	0 (0-10)
Maximum morning dose	0.4 (1.0)	0 (0-4)
Maximum bedtime dose	5.0 (4.8)	3 (0-16)
Maximum total dose	5.6 (5.1)	3.5 (1-17)
Final total dose	5.1 (5.3)	2.5 (0-17)
Prazosin dose change	3.5 (4.6)	2 (-2-15)
Daily Level	Veterans, %	
Prazosin dose \geq 5 mg/d, %	40.6	
Prazosin dose \geq 10 mg/d, %	25.0	

to offer, as well as concomitant participation in psychotherapy. This may be reflected in the study results. This study did not have a true placebo group, as we may find a reduction in symptoms with placebo.

Strengths of this study include multiple data points for assessment of prazosin tolerability and a pre- and poststudy design, which allowed for the veterans to serve as their own control. Another strength of this study is that data were complete for primary outcome measures, including the CAPS Recurrent and Distressing Dreams Item, where prazosin showed significant benefit in reduction of PTSD-related nightmares. While the results of this study are reassuring, further randomized, double-blind, placebo-controlled trials are likely needed in order to establish efficacy and tolerability of prazosin in older veterans for PTSD related nightmares.

CONCLUSION

These results demonstrate prazosin therapy in older veterans can significantly improve PTSD-related nightmares and PTSD severity. Prazosin was well tolerated in this population at doses higher than previously reported in other studies. This study shows that prazosin therapy can be effectively managed and tolerated in older veterans with complex medical and psychiatric comorbidities to provide favorable patient outcomes.

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