Early Discontinuation and Suboptimal Dosing of Prazosin: A Potential Missed Opportunity for Veterans With Posttraumatic Stress Disorder

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ABSTRACT

Objective: Clinical Practice Guidelines issued by the US Department of Veterans Affairs (VA) and the Department of Defense recommend prazosin for sleep/nightmares for veterans with posttraumatic stress disorder (PTSD). As existing literature suggests this novel treatment option to be underutilized, we examined a cohort of veterans with PTSD initiating prazosin to characterize their typical duration of use and dosing patterns.

Method: Administrative data from fiscal year 2010 were used to identify veterans with PTSD according to *ICD-9* codes extracted from inpatient and outpatient encounters. The longitudinal course of prazosin use following initiation was examined using refill data, and estimated prazosin doses were calculated based upon total milligrams and the day's supply dispensed.

Results: A total of 12,844 veterans with PTSD initiated prazosin during 2010. Twenty percent of veterans never refilled the initial prescription, and 37.6% persisted on the drug for at least 1 year. Patients more likely to remain on prazosin for at least 1 year were older (ages 40–59 years [OR = 1.28; 95% CI, 1.15–1.45] and ages ≥ 60 years [OR = 1.25; 95% CI, 1.12–1.40]) relative to younger patients and taking more medications (4–6 [OR = 1.40; 95% CI, 1.27–1.55], 7–9 [OR = 1.73; 95% CI, 1.56–1.94], and ≥ 10 [OR = 2.04; 95% CI, 1.83–2.29]) relative to 0–3 medications. The mean maximum prazosin dose reached in the first year of treatment was 3.6 mg/d, and only 14.1% of patients reached the minimum guideline recommended dose of 6 mg/d.

Conclusions: Of patients with PTSD newly initiated on prazosin in 2010, < 40% were still taking the drug 1 year later, and < 20% received the minimum recommended dose according to current VA guidelines. Further investigation is required to determine the precise clinical factors underlying these prescribing patterns and overcome barriers to guideline-concordant treatment.

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Posttraumatic stress disorder (PTSD) has affected the lives of hundreds of thousands of US veterans and continues to afflict thousands of veterans returning from combat. The number of veterans receiving care for PTSD in the VA health care system increased nearly 3-fold from 170,685 in 1999 to 498,081 in 2009.[1] The safe and effective treatment of PTSD is a vital issue for the US Department of Veterans Affairs (VA), as they published the first clinical practice guidelines (CPG) for its treatment in 2004,[2] which were updated in 2010.[3] In addition to several evidenced-based psychotherapy options, the 2010 VA/US Department of Defense (DoD) and American Psychiatric Association CPG recommend selective serotonin reuptake inhibitors (SSRIs) as first-line pharmacologic monotherapy.[3,4] Despite US Food and Drug Administration approval of sertraline and paroxetine, studies testing SSRI efficacy in veterans has been mixed.[5–8] The 2010 VA/DoD CPG recommend as second-line pharmacologic options tricyclic antidepressants, monoamine oxidase inhibitors, mirtazapine, nefazodone, atypical antipsychotics as adjunct treatment, and prazosin for sleep/nightmares.

The updated 2010 VA/DoD CPG elevated the recommendation for prazosin for sleep/nightmares from a strength of evidence of C to B, which is defined as "a recommendation that clinicians provide (the service) to eligible patients."[2,3] However, in this update the recommendation of prazosin for global PTSD management remained at a level C. Interestingly, the American Academy of Sleep Medicine CPG utilizing similar evaluation criteria gave prazosin a level-A recommendation for treatment of PTSD-associated nightmares.[9]

Research interest in prazosin in the management of PTSD has increased significantly, as 172 articles have been published in the last 10 years.[10] Likewise, the proportion of veterans with a diagnosis of PTSD that received at least 1 prescription for prazosin between fiscal year 1999 and fiscal year 2009 increased from 1.4% to 9.1%.[11] However, a Veterans Health Administration (VHA) study reported in fiscal year 2006 that prazosin prescribing across VHA varied by 12-fold.[12]

The duration of exposure to prazosin in 5 controlled trials was 6, 7, 8, 8, and 10 weeks.[10,13] Although 1 retrospective prazosin study[14] reported on up to 6 years of exposure in 62 patients, the other uncontrolled trials were less than 13 weeks in duration and had fewer than 75 patients.[10]

The optimum dose for prazosin for PTSD-related sleep disturbances and global signs and symptoms has not been determined. However, a 2008 review[15] of the literature for PTSD-related sleep disturbance concluded there appeared to be a dose-related response. The maximum dose in 4 double-blind, placebo-controlled nightmare trials listed in a recent review[10] was 15 mg/d with mean doses of 3.1, 8.9, 9.5, and 13.3 mg, while in a 2013 trial[13] of active duty soldiers with PTSD that was the first study to utilize different gender dosing levels, the maximum dose was 12 mg/d and 25 mg/d for women and men, respectively. It

Clinical Points

- Prazosin, a treatment for trauma-related nightmares, is steadily being disseminated in the US Department of Veterans Affairs for patients with posttraumatic stress disorder.
- Approximately 40% of veterans receiving new prescriptions for prazosin continued the medication at least 1 year. Veterans taking concurrent selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants were more likely to continue prazosin.
- The majority of veterans who started prazosin never reached the minimum recommended target dose of 6 mg/d before discontinuation. Research is needed to identify what factors prohibit patients from reaching this threshold and what characteristics are associated with prazosin response.

has been suggested that more recent trauma may respond to lower doses than distant trauma.[15]

Therefore, little long-term information is available in veterans with a diagnosis of PTSD regarding prazosin duration of treatment and dosing. The objective of this study was to identify a cohort of veterans with PTSD initiating prazosin and then characterize the typical duration of use and dosing patterns over the first year following initiation.

METHOD

Data Source

National administrative VA data were obtained for fiscal years 2009 and 2010 from the VA Austin Information Technology Center (Austin, Texas). Outpatient care files and inpatient treatment files were used to identify patients with PTSD and determine their demographic characteristics. Outpatient medication exposure was determined using pharmacy dispensing information from the VA Decision Support System National Data Extract Pharmacy Dataset. This study was approved by the University of Iowa Institutional Review Board and the Iowa City Veterans Administration Research and Development Committee.

Patients

The goal of our selection criteria was to identify veterans with PTSD who were new starters of prazosin during 2010. Veterans with PTSD were selected by identifying all patients with at least 1 inpatient discharge or outpatient encounter during 2009 coded for PTSD (*ICD-9*: 309.81) as either a primary or secondary diagnosis.[1,11,12,16–20] False-positive cases resulting from administrative miscoding are infrequent using this methodology (< 4%),[21,22] and our prior analyses of VA prescribing practices have yielded similar findings across alternative case definitions for PTSD.[18] In addition, we required that patients were regular users of VA medication during 2009. *Regular medication use* was defined as a longitudinal course of outpatient medication fills where the day's supply periods spanned at least 240 of 365 days.[16,19,23,24] This criterion was applied to identify a population of stable and consistent VA health care users and was necessary to establish incident prazosin use during the subsequent year. *Incident prazosin use* was defined as a first filled prescription for prazosin during 2010 that was preceded by a 1-year period with no prazosin use.

Prazosin Exposure

The longitudinal course of prazosin use following initiation was characterized by examining the pattern of refill dates and day's supply values during the year following initiation. Day's supply values in VA are most often 30 or 90 days but can range from 1 to 90. For this analysis, the duration of prazosin treatment was defined as the time from initiation to discontinuation, where discontinuation was calculated by the date of the last observed fill during the 1-year observation period plus the day's supply dispensed on that date. Values in excess of 365 days were truncated at 1 year. An alternative criterion was applied to patients who had a prazosin fill following the 1-year observation period. If the time gap between this fill and the last refill during the 1-year period was less than twice the day's supply of the last fill during the observation period, then the duration of prazosin use was assigned a value of 1 year. This adjustment was made to allow for nonadherence but only for patients with evidence of ongoing prazosin use beyond the 1-year observation period. Estimated prazosin doses were calculated for each prazosin fill based on the total milligrams and the day's supply dispensed. Mean prazosin doses were characterized at initiation and over the course of treatment.

Analysis

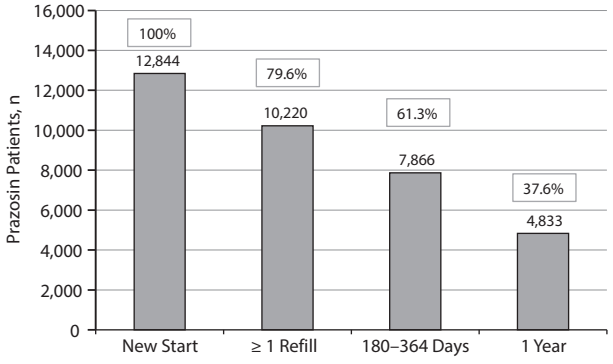
Multivariable regression was used to identify independent correlates of achieving 1-year duration of prazosin treatment (logistic regression) and separately for independent correlates of prazosin dose (linear regression). We also conducted a logistic regression analysis modeling maximal prazosin dose in excess of 6 mg/d as the independent variable, and the findings were consistent with the linear regression model of continuous dose. In addition to commonly reported patient characteristics, we included distance from the patient's primary site of PTSD care to the Puget Sound VA medical center. Distance to Puget Sound VA was included because of prior research[12] demonstrating an inverse correlation between the likelihood of receiving prazosin and distance from Puget Sound VA, the site where the majority of the initial prazosin PTSD clinical studies were conducted. The prevalence of prazosin use in 2006 was 33.3% for Puget Sound VA patients, 19.7% within 500 miles, and decreased progressively to only 2.8% beyond 2,500 miles.[12] Therefore, we hypothesized that patients close to Puget Sound would also be more likely to receive an adequate trial of prazosin, both in terms of dose and duration of therapy. Finally, we examined concurrent use of an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) at the time of prazosin initiation. All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc; Cary, North Carolina) and all tests were 2-tailed at the .05 significance level.

Table 1. Patient Characteristics

Characteristic	Value
Total no. of veterans	12,844
Age, mean (SD), y	52.9 (12.5)
Age, n (%), y	
≤ 39	2,266 (17.6)
40–59	5,693 (44.3)
≥ 60	4,885 (38.0)
Sex, n (%)	
Men	11,852 (92.3)
Women	992 (7.7)
VA service connection, n (%)	
None	2,558 (19.9)
10%–40%	2,471 (19.2)
≥ 50%	7,815 (60.9)
Residence, n (%)	
Urban	9,358 (72.9)
Rural	3,486 (27.1)
Total no. of medications, mean (SD)	6.3 (4.0)
Total no. of medications, n (%)	
0–3	3,552 (27.7)
4–6	3,903 (30.4)
7–9	2,840 (22.1)
≥ 10	2,549 (19.8)
Concurrent SSRI/SNRI use, n (%)	
Yes	7,463 (58.1)
No	5,381 (41.9)
Distance from Puget Sound, n (%)	
At Puget Sound	300 (2.3)
≤ 499 miles	752 (5.9)
500–999 miles	852 (6.6)
1,000–2,499 miles	5,928 (46.2)
≥ 2,500 miles	5,012 (39.0)

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

Figure 1. Duration of Prazosin Treatment in the Year Following Initiation



RESULTS

Patients

A total of 12,844 veterans with PTSD initiated new use of prazosin during fiscal year 2010 (Table 1). The mean age was 52.9 years, and 7.7% were women. Patients were taking a mean number of 6.3 medications at the time of prazosin initiation, and 19.8% were taking 10 or more medications.

Duration of Prazosin Use

The duration of prazosin use following initiation is characterized in Figure 1. Among the initial cohort of 12,844 prazosin starters, 2,624 patients (20.4%) never refilled their initial prazosin prescription and another 2,354 (18.3%) discontinued therapy within 180 days of initiation. The remaining 7,866 (61.3%) remained on prazosin for ≥ 180 days, and 4,833 (37.6%) persisted with prazosin treatment for at least 1 year. Several clinical characteristics were significantly associated with the likelihood of achieving a full 1-year duration of prazosin therapy following initiation (Table 2). Of note, patients with concurrent use of SSRI or SNRI antidepressants were more likely to maintain prazosin treatment for 1 year (41.3%) compared to nonusers (32.5%), which remained significant after adjustment in multivariable analysis. In addition, 1-year prazosin persistence increased with age and with the number of concurrent medications. Prazosin persistence was not associated with sex, rural residence, or distance from the Puget Sound VA.

Table 2. Correlates of Prazosin Treatment Duration of ≥ 1 Year Following Initiation

	1-Year Prazosin Duration	
Variable	Unadjusted Frequency, %	Multivariable Logistic Regression, OR (95% CI)
Age, y		
≤ 39	30.2	1 (reference)
40–59	39.4	1.28 (1.15–1.43)
≥ 60	39.0	1.25 (1.12–1.40)
Sex		
Men	37.8	1 (reference)
Women	35.9	0.98 (0.85–1.13)
VA service connection		
None	35.3	1 (reference)
10%–40%	39.2	1.23 (1.09–1.37)
≥ 50%	37.9	1.05 (0.96–1.16)
Residence		
Urban	37.4	0.99 (0.91–1.07)
Rural	38.4	1 (reference)
Total no. of medications		
0–3	27.9	1 (reference)
4–6	36.7	1.40 (1.27–1.55)
7–9	42.5	1.73 (1.56–1.94)
≥ 10	47.2	2.04 (1.83–2.29)
Concurrent SSRI/SNRI use		
Yes	41.3	1.28 (1.19–1.38)
No	32.5	1 (reference)
Distance from Puget Sound		
At Puget Sound	35.3	1 (reference)
≤ 499 miles	37.4	1.04 (0.78–1.38)
500–999 miles	34.0	0.91 (0.68–1.20)
1,000–2,499 miles	37.6	1.03 (0.81–1.32)
≥ 2,500 miles	38.5	1.05 (0.82–1.34)

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

Prazosin Dose

Estimated daily doses of prazosin at the time of initiation and over the course of the first year of treatment are characterized in Table 3. Prazosin doses generally increased over the course of treatment, reaching a mean maximum dose of 3.6 mg/d across all patients. Mean maximum doses were slightly higher at 1 year of treatment (3.8 mg/d) for the subgroup of patients who maintained therapy for the entire period (n = 4,833). However, only 1,813 (14.1%) reached the minimum guideline-recommended dose to determine an

Table 3. Prazosin Dosing at Initiation and Over the First 1-Year of Treatment

Variable	At Initiation (N = 12,844)	First Refill (n = 10,220)	Last Observed Refill, All Patients (n = 10,220)	Final Refill, 1-Year Persistent Patients (n = 4,833)	Maximum Dose (N = 12,844)
Daily dose, mean (SD), mg	2.4 (1.8)	2.7 (2.0)	3.5 (2.8)	3.8 (2.9)	3.6 (2.9)
Daily dose, n (%)					
≤ 2 mg	8,831 (68.8)	6,514 (63.7)	5,033 (49.3)	2,191 (45.3)	6,764 (52.7)
2.01–5.99 mg	3,352 (26.8)	3,067 (30.0)	3,778 (37.0)	1,850 (38.3)	4,267 (33.2)
6–10 mg	523 (4.1)	588 (5.8)	1,243 (12.2)	693 (14.3)	1,568 (12.2)
> 10 mg	53 (0.4)	51 (0.5)	166 (1.6)	99 (2.1)	245 (1.9)

Table 4. Correlates of Maximal Prazosin Dose Reached During the First Year Following Initiation

Variable	Unadjusted Dose, Mean (SD), mg	Multivariable Regression, Estimate (*P* value)
Age, y		
≤ 39	3.7 (3.0)	Reference
40–59	3.6 (2.8)	−0.19 (.011)
≥ 60	3.5 (2.9)	−0.38 (< .001)
Sex		
Men	3.6 (2.9)	Reference
Women	3.3 (2.5)	−0.41 (< .001)
VA service connection		
None	3.7 (3.0)	Reference
10%–40%	3.7 (2.9)	−0.04 (.649)
≥ 50%	3.5 (2.9)	−0.23 (< .001)
Residence		
Urban	3.6 (2.9)	−0.01 (.863)
Rural	3.6 (2.9)	Reference
Total no. of medications		
0–3	3.5 (2.8)	Reference
4–6	3.6 (2.9)	0.14 (.045)
7–9	3.7 (3.0)	0.27 (< .001)
≥ 10	3.8 (3.0)	0.38 (< .001)
Concurrent SSRI/SNRI use		
Yes	3.7 (2.9)	0.11 (.032)
No	3.5 (2.8)	Reference
Distance from Puget Sound		
At Puget Sound	4.2 (3.4)	Reference
≤ 499 miles	3.9 (3.1)	−0.32 (.101)
500–999 miles	3.6 (3.4)	−0.59 (.002)
1,000–2,499 miles	3.7 (3.0)	−0.52 (.003)
≥ 2,500 miles	3.3 (2.7)	−0.91 (< .001)

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

adequate prazosin trial of 6 mg/d at some point during the course of therapy, where 1,568 patients (12.2%) used 6–10 mg/d, and 245 (1.9%) exceeded 10 mg/d. Several clinical variables were significantly associated with maximum observed prazosin dose after adjustment in multivariable analysis, including age, sex, number of medications, and the distance from Puget Sound VA medical center (Table 4). Maximum observed doses were slightly lower for women, who received 0.40 mg/d less than men after adjustment. The most clinically meaningful difference was observed for distance from Puget Sound VA, where the mean prazosin dose for Puget Sound patients was 4.2 mg/d, and descended to 3.3 mg/d for patients more than 2,500 miles away.

DISCUSSION

Prazosin was discovered to reduce combat-related nightmares and generally improve sleep in Vietnam veterans with PTSD undergoing treatment for benign prostatic hypertrophy.[25] Sleep disturbances are common in PTSD and may be a core feature, rather than merely a secondary symptom.[26] It is estimated that 70%–87% of patients with PTSD experience difficulty in falling or staying asleep, periodic limb movement disorder, and sleep-disordered breathing.[27,28] In addition, recurrent combat-related trauma nightmares and overall sleep disturbance are among the most treatment-resistant symptoms experienced by patients with chronic PTSD.[10,26,29] Finally, the first-line pharmacologic treatment option for PTSD, the SSRIs, exacerbate sleep disturbances through decreases in sleep efficiency, total sleep time, sleep continuity, and slow-wave sleep.[30] Therefore, effective treatment for sleep-related symptoms is important in the overall management of PTSD for improving daily functioning and quality of life. The effectiveness of prazosin for reducing the severity and frequency of nightmares associated with PTSD is backed by more than 20 clinical studies.[10] Alternative pharmacologic approaches for PTSD-related sleep disturbances include antidepressants, antihistamines, antipsychotics, valproic acid, nonbenzodiazepine hypnotics, and benzodiazepines.[31] However, none of these alternatives have a favorable risk-benefit ratio, and all fall short of prazosin in terms of support in guideline recommendations.[3] The primary focus of prazosin has been on sleep disturbance, but 1 study in civilians and 3 studies in veterans and active duty Army personnel indicate that prazosin added to existing treatments improved global symptomatology.[13,29,32–34] Two of the studies administered prazosin only at bedtime, and two administered a dose at bedtime and once midday. Therefore, prazosin has a unique role in the overall management of veterans with PTSD, and it is absolutely essential to gain the most benefit from this medication through optimal dosing over a sufficient course of treatment.

Experience gained through clinical trials suggests that an initial treatment trial of 8 to 10 weeks is necessary to assess initial response to prazosin for sleep disturbances associated with PTSD.[10] Unfortunately, there are no empirical data to determine how long prazosin or other psychotropic drug treatment should be maintained after achieving a satisfactory response during the acute treatment phase, and expert consensus guidelines have not offered suggestions beyond the necessity for future research.[3] However, limited anecdotal evidence suggests that the benefit of prazosin in PTSD is maintained with extended treatment and that symptoms often return with discontinuation and resolve with reintroduction.[10] The recommendation from experts in the field is to maintain prazosin treatment for at least

1 year (Murray Raskind, MD, personal communication, January 16, 2014). We found that 20.4% of new prazosin starters never obtained a refill, suggesting that these were acute-phase treatment failures. A further 18.3% obtained at least 1 prazosin refill but discontinued within 180 days following initiation, and an additional 23.7% within 1 year. Ultimately, only 37.6% of new starters persisted with prazosin use beyond 1 year. Unfortunately, we were unable to ascertain the reasons for discontinuation. Possible explanations include lack of efficacy, adverse drug events, and patient noncompliance. We were able to identify some statistically significant, albeit clinically weak, predictors of 1-year treatment persistence, including age > 40 years, intermediate service-connected disability (10%–40%), and an increasing number of concurrent medications. Perhaps the most notable predictor was concurrent SSRI or SNRI antidepressant exposure, where users were more likely to persist with prazosin therapy than nonusers (41.3% vs 32.5%). This observation runs contrary to recent trial data suggesting that SSRIs may blunt prazosin efficacy.[13] Whether SSRI or SNRI antidepressants impede the therapeutic benefit of prazosin is an open and important clinical question since these drugs are first-line VA/DoD guideline treatment options for PTSD and the most commonly prescribed medications for veterans with PTSD.[11]

Another factor contributing to low 1-year persistence rates may be treatment failures resulting from prazosin doses falling short of the target dose of 6–10 mg/d recommended by the 2010 VA/DoD CPG.[3] This recommendation is consistent with the average dose of 8.5 mg/d across double-blind, placebo-controlled trials of prazosin for sleep disturbances in PTSD prior to 2012[10] and the average dose of 6.3 mg/d in 1 retrospective trial.[14] However, we found that the majority of veterans with PTSD starting prazosin (85.9%) never reached the minimum recommended target dose of 6 mg/d before discontinuation. Even among patients who persisted on prazosin for 1 year, the mean prazosin dose was just 3.8 mg/d, with only 16.4% receiving ≥ 6 mg/d. Unfortunately, we could not determine the clinical rationale for prazosin dosing in individual patients. For the 37.6% of patients remaining on prazosin for a full year, it is possible that they achieved an adequate response on lower than recommended doses. For the remaining patients, however, it is unclear whether discontinuation was due to insufficient response as a function of lower than recommended doses. It is also possible that prazosin dosing was limited by the occurrence of dose-dependent adverse events and thus leading to treatment failures. However, information from a recent review[10] of controlled trials and more recent trial data[13] involving active duty soldiers with PTSD reported prazosin was well tolerated even with doses of 25 mg/d. In keeping with prior research demonstrating greater implementation of prazosin treatment with proximity to the primary hub of prazosin PTSD research (Puget Sound VA medical center),[12] we observed a significant dosing gradient, with the highest dose at Puget Sound VA (4.2 mg/d) and descending to 3.3 mg/d at sites ≥ 2,500 miles away. We also found that women had a mean prazosin dose that was 0.4 mg/d lower than men. This difference could be clinically appropriate as women may respond to lower doses, as indicated by separate gender-based dosing in a recent prazosin clinical trial.[13] However, women veterans with PTSD are also less likely to receive prazosin than their male counterparts, so the potential for gender-based inequities must be considered.[17] Also, it is possible patients with PTSD who exhibit traumatic nightmares or other PTSD symptoms most indicative of adrenergic hyperarousal such as insomnia, hypervigilance, irritability, and general anxiety/agitation are most likely to respond to prazosin (Murray Raskind, MD, personal communication, January 16, 2014). Although this hypothesis has not been formally studied, if true, it might explain early discontinuation of prazosin in an unknown percentage of patients.

This analysis is subject to several limitations. First, the selection of veterans with PTSD was based exclusively on *ICD-9* codes extracted from administrative databases. While this approach has been used by prior authors, the accuracy of PTSD coding in the VA has not been well characterized.[12,20] A second limitation is that we could only observe care provided by the VA. It is possible that veterans received PTSD treatment and prazosin medication outside the VA system. While information concerning VA care outside the VA would provide a more complete picture of prazosin use, it would be unexpected to see a different pattern of use. Although we identified all patients diagnosed as having PTSD nationally, a limitation of this study is that we could not clearly differentiate between patients prescribed prazosin for PTSD and patients prescribed the drug for hypertension, benign prostatic hypertrophy, or other potential off-label uses. However, it seems unlikely that prazosin was prescribed for the latter reasons as it is not considered a first- or second-line treatment for these conditions compared to other α-blockers available on the VA formulary.[35,36] We also did not examine the directions for prazosin administration, so we are unaware of bedtime only versus twice daily dosing.

Managing PTSD-related sleep disturbances is a critical component in gaining functional recovery, and prazosin fills a unique niche in PTSD pharmacotherapy. Of veterans with PTSD who were new prazosin starters, < 40% were still taking the drug 1 year later and < 20% received the minimum recommended dose according to current VA guidelines. This low rate of prazosin persistence may not be surprising given the complexity of PTSD management in real-world practice. However, our findings justify the need for further investigation to identify the precise clinical factors underlying these prescribing patterns. If we understood the distribution of underlying causes for prazosin treatment failure, it is entirely feasible to design a health services intervention (eg, academic detailing) to overcome these barriers and improve the real-world effectiveness of prazosin. For example, if prazosin is being discontinued due to lack of efficacy, our findings suggest that insufficient dosing may be a primary factor. If prazosin use is limited by adverse events, then perhaps alternative dosing strategies involving variations in administration times or slower titration schedules can

overcome this barrier, as prazosin has been well-tolerated in clinical trials even in doses up to 25 mg/d. In addition, prazosin initiation for PTSD may be more challenging in patients with preexisting antihypertensive drug regimens or another α-blocker for benign prostatic hypertrophy and will require careful coordination of care when these conditions are managed by separate providers. While the development of new PTSD treatments is important, our findings demonstrate a vital opportunity for more optimal use of a treatment we already have.

Drug names: mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), prazosin (Minipress and others), sertraline (Zoloft and others), valproic acid (Depakene and others).

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REFERENCES

1. Lund BC, Bernardy NC, Alexander B, et al. Declining benzodiazepine use in veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2012;73(3):292–296.
2. Department of Veterans Affairs, Department of Defense. Clinical practice guideline for management of post-traumatic stress, version 1.0. http://www.healthquality.va.gov/ptsd/ptsd_full.pdf. Published January 2004. Accessed March 7, 2015.
3. Department of Veterans Affairs, Department of Defense. Clinical practice guideline for management of post-traumatic stress, version 2.0. http://www.healthquality.va.gov/guidelines/MH/ptsd/. Published October 2010. Accessed March 7, 2015.
4. Ursano RJ, Bell C, Eth S, et al; Work Group on ASD and PTSD; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. *Am J Psychiatry*. 2004;161(suppl):3–31.
5. van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. *J Clin Psychiatry*. 1994;55(12):517–522.
6. Hertzberg MA, Feldman ME, Beckham JC, et al. Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans. *Ann Clin Psychiatry*. 2000;12(2):101–105.
7. 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.
8. Martenyi F, Brown EB, Zhang H, et al. Fluoxetine v placebo in prevention of relapse in post-traumatic stress disorder. *Br J Psychiatry*. 2002;181(4):315–320.
9. Aurora RN, Zak RS, Auerbach SH, et al; Standards of Practice Committee; American Academy of Sleep Medicine. Best practice guide for the treatment of nightmare disorder in adults. *J Clin Sleep Med*. 2010;6(4):389–401.
10. Kung S, Espinel Z, Lapid MI. Treatment of nightmares with prazosin: a systematic review. *Mayo Clin Proc*. 2012;87(9):890–900.
11. Bernardy NC, Lund BC, Alexander B, et al. Prescribing trends in veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2012;73(3):297–303.
12. Harpaz-Rotem I, Rosenheck RA. Tracing the flow of knowledge: geographic variability in the diffusion of prazosin use for the treatment of posttraumatic stress disorder nationally in the Department of Veterans Affairs. *Arch Gen Psychiatry*. 2009;66(4):417–421.
13. 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.
14. Byers MG, Allison KM, Wendel CS, et al. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. *J Clin Psychopharmacol*. 2010;30(3):225–229.
15. Miller LJ. Prazosin for the treatment of posttraumatic stress disorder sleep disturbances. *Pharmacotherapy*. 2008;28(5):656–666.
16. Abrams TE, Lund BC, Bernardy NC, et al. Aligning clinical practice to PTSD treatment guidelines: medication prescribing by provider type. *Psychiatr Serv*. 2013;64(2):142–148.
17. Bernardy NC, Lund BC, Alexander B, et al. Gender differences in prescribing among veterans diagnosed with posttraumatic stress disorder. *J Gen Intern Med*. 2013;28(suppl 2):S542–S548.
18. Lund BC, Bernardy NC, Vaughan-Sarrazin M, et al. Patient and facility characteristics associated with benzodiazepine prescribing for veterans with PTSD. *Psychiatr Serv*. 2013;64(2):149–155.
19. Lund BC, Charlton ME, Steinman MA, et al. Regional differences in prescribing quality among elder veterans and the impact of rural residence. *J Rural Health*. 2013;29(2):172–179.
20. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the US Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. *J Clin Psychiatry*. 2008;69(6):959–965.
21. Gravely AA, Cutting A, Nugent S, et al. Validity of PTSD diagnoses in VA administrative data: comparison of VA administrative PTSD diagnoses to self-reported PTSD Checklist scores. *J Rehabil Res Dev*. 2011;48(1):21–30.
22. Lund BC, Abrams TE, Gravely AA. Rebuttal to Gravely et al: validity of PTSD diagnoses in VA administrative data: comparison of VA administrative PTSD diagnoses to self-reported PTSD Checklist scores. J Rehabil Res Dev. 2011; 48(1):21–30. available from: http://www.rehab.research.va.gov/jour/11/481/pdf/gravely.pdf. *J Rehabil Res Dev*. 2011;48(5):vii-ix.
23. Ernst ME, Lund BC. Renewed interest in chlorthalidone: evidence from the Veterans Health Administration. *J Clin Hypertens (Greenwich)*. 2010;12(12):927–934.
24. Lund BC, Ernst ME. The comparative effectiveness of hydrochlorothiazide and chlorthalidone in an observational cohort of veterans. *J Clin Hypertens (Greenwich)*. 2012;14(9):623–629.
25. Raskind MA, Dobie DJ, Kanter ED, et al. The alpha1-adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. *J Clin Psychiatry*. 2000;61(2):129–133.
26. Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev*. 2008;12(3):169–184.
27. Leskin GA, Woodward SH, Young HE, et al. Effects of comorbid diagnoses on sleep disturbance in PTSD. *J Psychiatr Res*. 2002;36(6):449–452.
28. Mellman TA, Kulick-Bell R, Ashlock LE, et al. Sleep events among veterans with combat-related posttraumatic stress disorder. *Am J Psychiatry*. 1995;152(1):110–115.
29. 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.
30. Oberndorfer S, Saletu-Zyhlarz G, Saletu B. Effects of selective serotonin reuptake inhibitors on objective and subjective sleep quality. *Neuropsychobiology*. 2000;42(2):69–81.
31. 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.
32. Germain A, Richardson R, Moul DE, et al. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. *J Psychosom Res*. 2012;72(2):89–96.
33. 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.
34. Taylor FB, Lowe K, Thompson C, et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. *Biol Psychiatry*. 2006;59(7):577–581.
35. Chapman N, Chen CY, Fujita T, et al. Time to re-appraise the role of alpha-1 adrenoceptor antagonists in the management of hypertension? *J Hypertens*. 2010;28(9):1796–1803.
36. Pool JL, Kirby RS. Clinical significance of alpha1-adrenoceptor selectivity in the management of benign prostatic hyperplasia. *Int UrolNephrol*. 2001;33(3):407–412.