Curr Treat Options Psych (2015) 2:192–203
DOI 10.1007/s40501-015-0040-y

Post-Traumatic Stress Disorders (T Garacioti and K Chard, Section Editors)

Prazosin for the Treatment of PTSD

Murray A. Raskind, MD

Address
VA Puget Sound Health Care System, 1660 S. Columbian Way S-116 MIRECC, Seattle, WA 98108, USA
Email: murray.raskind@va.gov

Published online: 7 April 2015

This article is part of the Topical Collection on *Post-Traumatic Stress Disorders*

Keywords PTSD · Prazosin · Trauma nightmares · Sleep · Alpha-1 adrenoreceptors · Arousal

Opinion statement

Prazosin is a generically available central nervous system (CNS) active alpha-1 adrenoreceptor antagonist that has been demonstrated effective in randomized controlled trials (RCTs) for posttraumatic stress disorder (PTSD) trauma nightmares, distressed awakenings, daytime hyperarousal symptoms, and global clinical function. The contribution of increased CNS noradrenergic activity to PTSD pathophysiology and the involvement of the postsynaptic alpha-1 adrenoreceptor in brain systems relevant to PTSD symptomatology provide neurobiologic rationale for prazosin as a PTSD pharmacotherapeutic. This article reviews the clinical observations that led to the development of prazosin therapy for PTSD in combat veterans and the subsequent RCTs that demonstrated prazosin efficacy.

Introduction

Posttraumatic stress disorder (PTSD) encompasses clusters of symptoms that follow exposure to one or more major traumatic events. The four PTSD symptom clusters include intrusion (or re-experiencing), avoidance, negative alterations in cognition and mood associated with the trauma(s), and hyperarousal. The phenomenologic features of several major PTSD hyperarousal symptoms including sleep disturbance (particularly distressed awakenings), hypervigilance, irritability/low anger threshold, and trauma nightmares, particularly when associated with sweating, tachycardia, and other manifestations of autonomic arousal, suggest that increased noradrenergic outflow and/or postsynaptic adrenoreceptor (AR) responsiveness to norepinephrine (NE) contribute to their pathophysiology [1]. Increased central nervous system (CNS) noradrenergic activity in PTSD is supported by multiple clinical studies [2–6]. Therefore, reducing CNS noradrenergic activity is a rational therapeutic strategy when distressing trauma nightmares and hyperarousal symptoms are major components of the patient's clinical presentation. This article focuses on the pharmacotherapeutic strategy of reducing CNS postsynaptic responsiveness in PTSD using the alpha-1 AR antagonist

prazosin. Among the clinically available alpha-1 ARs, prazosin is the most lipid soluble and therefore crosses the periphery into the CNS most easily [7].

Background

Prazosin was introduced as an antihypertensive drug more than 40 years ago. It is clinically available as an inexpensive generic drug. Prazosin has been used widely to treat both high blood pressure and benign prostatic hypertrophy urinary outflow obstruction [8, 9]. In these general medical disorders, prazosin acts by blocking NE stimulation of peripheral alpha-1 AR on arterial and urethral smooth muscle fibers. Understandably, most biomedical and pharmacologic interest in the alpha-1 AR has come from hypertension and urologic physiologists studying peripheral alpha-1 AR involvement in blood pressure regulation and urinary outflow. Less well known is that alpha-1 AR are widely expressed in the brain. When stimulated by NE released from the diffuse projections of the pontine locus ceruleus, these central alpha-1 AR increase attention (especially to novel stimuli), level of arousal, and wakefulness [10]. When noradrenergic stimulation of alpha-1 AR is excessive, the results are hypervigilance, anxiety, irritability, lowered threshold for "fight or flight" cognitions and behaviors, reduced sleep duration, and rapid eye movement (REM) sleep disruption [11–13].

Initial experience with prazosin for trauma nightmares with distressed awakenings in combat veterans

Recurrent trauma-related nightmares with distressed awakenings are prominent PTSD symptoms among military combat veterans [14]. Trauma content nightmares are a hallmark feature of PTSD [15]. These nighttime PTSD symptoms may be the most common reason combat veterans seek treatment for PTSD. They also are among the symptoms least responsive to treatment [16].

In 1996, while providing ongoing clinical care to The Black Veterans Support Group of Puget Sound, the author observed that terrifying trauma nightmares and severe sleep disruption were these Vietnam combat veterans' most troublesome and treatment refractory PTSD symptoms. Psychotropic medications including sedative hypnotics, SSRI antidepressants, and various types of psychotherapies, including prolonged exposure, rarely had been helpful for these veterans' nighttime PTSD symptoms.

Veterans' accounts of these nighttime PTSD symptoms revealed the following:

The most troublesome features of combat PTSD "sleep disturbance" were terrifying trauma nightmares and distressed awakenings accompanied by sweating and other manifestations of intense autonomic arousal. Because CNS and peripheral noradrenergic systems are coregulated [10], these autonomic arousal symptoms are consistent with inappropriately high nighttime CNS noradrenergic activity in combat PTSD, particularly at night [3]. Veterans' trauma nightmares were

accompanied by thrashing and other large excursion movements of the extremities that differentiated them from normal dreaming during REM sleep in which there is large muscle paralysis. Their distressed awakenings usually (but not always) were coincident with trauma content nightmares, but often occurred without recalled nightmares as well. Sleep initiation difficulty, when present, often was attributed to fear of entering a terrifying nightmare once sleep commenced.

A postsynaptic adrenoreceptor antagonist approach to PTSD treatment—failure of a beta AR antagonist but success with an alpha-1 antagonist

There are two major postsynaptic ARs in the human brain, the alpha-1 AR and the beta AR [7]. CNS active antagonists for both receptors were clinically available. Which postsynaptic AR antagonist should be evaluated for efficacy in PTSD? The decision to prescribe the CNS active beta AR antagonist propranolol initially was supported by its previous use in the treatment of other anxiety disorders [17], and a case series in which veterans and children reported PTSD symptom reduction following open label propranolol treatment [18, 19]. In contrast, no reports of alpha-1 AR antagonist beneficial for any behavioral disorders could be found in the clinical literature. Although the initial choice of a beta AR antagonist proved incorrect (see below), the unexpected stimulatory effect of propranolol on trauma nightmare intensity in the first veteran given the beta AR antagonist provided rationale for a trial of the alpha-1 AR antagonist prazosin.

The first Vietnam veteran prescribed prazosin for intractable PTSD trauma nightmares and sleep disruption was a Black infantryman who had fought through the bloody TET offensive in 1968 with the 1st Infantry Division. He suffered nightly severe combat trauma nightmares and sleep disruption accompanied by an "adrenaline storm" of sweating, tachycardia, hypervigilance, and inability to resume sleep once awakened. A particularly frequent and devastating nightmare graphically "replayed" a terrifying firefight with Viet Cong forces during which a round from the veteran's M16 assault rifle accidentally hit and killed his close friend. This recurrent nightmare intensified his remorse over this tragic event, and he developed suicidal ideation and alcohol dependence. The author first prescribed propranolol 20 mg twice daily (midmorning and at bedtime). Two weeks later, the veteran disappointingly stated "Doc, we are going the wrong direction. My nightmares are even worse." That propranolol appeared to increase this combat veteran's nightmare intensity was unexpected, but a review of the literature revealed that intensified dreaming and nightmares are indeed a reported adverse effect of propranolol and other beta AR antagonists [20]. This propranolol effect raised the possibility that the wrong postsynaptic AR had been targeted. In several CNS systems, the alpha-1 AR can have opposite effects to those of the beta AR [21]. If the CNS active beta AR antagonist propranolol worsened this veteran's trauma nightmares, would a CNS active alpha-1 AR antagonist reduce his trauma nightmares?

The veteran's propranolol was discontinued. Prazosin, an alpha-1 AR demonstrated active in the CNS when administered peripherally was initiated at 1 mg at bedtime (drug labeling recommends low-dose initiation and gradual titration of an alpha-1 AR antagonist to avoid "first dose" orthostatic hypotension) [22]. Prazosin was then titrated upward over 3 weeks to 8 mg at bedtime. At this dose, trauma nightmares ceased, reported sleep duration increased from 3 to 6 h, and the veteran reported resumption of "normal" dreaming that had been absent since his Vietnam combat traumas. This response to prazosin was consistent with two other veterans' subsequent reports of markedly reduced PTSD trauma nightmare intensity and improved sleep following initiation of prazosin for BPH urinary outflow hesitancy. In addition, the veteran's suicidal ideation disappeared and he became abstinent from alcohol. Although the veteran's nighttime PTSD symptoms improved substantially, irritability and hypervigilance re-emerged every afternoon. Addition of prazosin 5 mg midmorning and mid-afternoon greatly reduced these daytime hyperarousal symptoms. It is noteworthy that this veteran has maintained abstinence from alcohol from 1996 to the present (2015) on a continuous regimen of prazosin (unpublished observation).

The neurobiologic rationale for prazosin efficacy for PTSD

The apparent beneficial effects of open label prazosin effects on intractable PTSD symptoms in combat veterans under the author's care in the Black Veterans Support Group is consistent with alpha-1 AR regulation of neurobiologic systems relevant to PTSD pathophysiology. Alpha-1 AR stimulation by NE increases release of the anxiogenic neuropeptide corticotrophin releasing factor (CRF) [23], decreases prefrontal cortex inhibition of "fight or flight" cognitive set [24], and increases acoustic startle response [25]. Stimulation of CNS alpha-1 AR disrupts REM sleep stage continuity, shortens REM and slow wave sleep durations, and increases stages 1 and 2 light sleep [11, 12]. These effects of alpha-1 AR stimulation on sleep physiology favor emergence of trauma nightmares and reduction of restorative sleep [11, 12, 26–28].

Randomized controlled trials of prazosin for PTSD

Open label prazosin treatment observations in combat veterans together with the alpha-1 AR modulation of neurobiologic systems relevant to PTSD provided rationale for prazosin randomized controlled trials (RCTs) for nighttime PTSD symptoms. Five prazosin RCTs have been completed and published. Four were performed by our research group at VA Puget Sound and the University of Washington [29, 30••, 31, 32•]. The fifth was performed at the University of Pittsburgh and VA Pittsburgh [33•]. Taken together, these studies have demonstrated significant and substantial efficacy of prazosin for reducing nighttime PTSD symptoms, reducing daytime hyperarousal symptoms, and improving global clinical status. An additional effectiveness study supporting the usefulness of prazosin for military PTSD nighttime symptoms and its

superiority to quetiapine, an atypical antipsychotic commonly prescribed for PTSD sleep disturbances, was performed at the Phoenix VA Medical Center [34].

The first RCT was a double-blind placebo-controlled crossover study performed in ten Vietnam combat veterans [29], all of whom had chronic PTSD with frequent and distressing trauma nightmares. Prazosin or placebo in random order were begun at an initial dose of 1 mg at bedtime and titrated upward for 3 weeks to a dose that eliminated trauma nightmares or to a maximum dose of 10 mg HS. The achieved maintenance dose was maintained for 6 weeks. Because prazosin duration of action is approximately 6 to 10 h, the single evening dose regimen in this study was not optimally designed to test prazosin effects on daytime PTSD hyperarousal symptoms. Following a 1 week washout period, participants were crossed over to the other treatment condition, again for 3 weeks titration and 6 weeks maintenance. At a mean achieved maintenance prazosin dose of 9.6 mg, prazosin was significantly and substantially superior to placebo for reducing nightmares (Clinician Administered PTSD Scale (CAPS) "recurrent distressing dreams of the event" item) [35] and sleep disturbance (CAPS "sleep difficulty" item) and improving global clinical status. All Cohen's d effect sizes for prazosin were large at >1.0. Change in total CAPS score and all three CAPS PTSD symptom clusters (re-experiencing, avoidance and hyperarousal) also significantly favored prazosin.

In the second RCT, 40 veterans with chronic PTSD and distressing trauma nightmares were randomized to prazosin or placebo in a parallel group design [31]. Most had experienced combat trauma in the Vietnam War. A 4-week dose titration of prazosin or placebo was followed by 8 weeks of maintenance medication (maximum bedtime dose=15 mg; mean maintenance bedtime prazosin dose=13.3 mg). Prazosin again was significantly and substantially superior to placebo for reducing nightmares and sleep disturbance and improving global clinical status. Effect sizes again were large (Cohen's d all >0.9). Consistent with the effect of prazosin to increase duration and continuity of REM sleep, dream characteristics of prazosin subjects demonstrated a change from those typical of trauma nightmares toward those typical of normal dreaming.

The third RCT was a crossover study in participants with civilian trauma PTSD [32•]. This RCT was a collaboration with Fletcher Taylor, MD, a Puget Sound area private practice psychiatrist who had independently observed prazosin beneficial effects on PTSD trauma nightmares in his civilian psychiatry practice. This study is unique in that it measured effects of both drug and placebo on objective measure of sleep physiology. Thirteen civilian trauma PTSD participants with severe trauma nightmares and sleep disturbance were randomized to prazosin or placebo in a double-blind crossover trial. Prazosin or placebo was rapidly titrated to 3 mg in the evening during each 3-week treatment period. In the final three nights of each treatment condition, total sleep time, REM sleep time, and sleep latency were recorded at home with the two-lead portable REMView device, which distinguishes sleep from awake state and REM sleep from nonREM sleep [36]. In addition to

significant prazosin condition vs. placebo condition reductions in trauma nightmares and total PTSD symptom surges, there were marked improvements in objective sleep parameters. Total sleep time was 94 min longer in the prazosin than in the placebo condition (374±86 min vs. 280±105 min, $p<0.01$). Both REM time and mean REM period duration were significantly greater during prazosin, suggesting normalization of PTSD-disrupted REM sleep. In contrast, sleep latency (time to fall asleep) was actually several minutes longer in the prazosin condition, consistent with the nonhypnotic nature of prazosin. One interpretation of these data is that disruption of REM sleep by inappropriately elevated CNS noradrenergic activity contributes to the pathogenesis of PTSD trauma nightmares and distressed awakenings. Interestingly, normal REM sleep appears to contribute to removal of excessive emotional response to traumatic memories [37, 38].

The fourth RCT was performed by Germain and colleagues at the University of Pittsburgh [33•]. They randomized 50 veterans with chronic sleep disturbances to one of three conditions: prazosin (mean dose=9 mg at night); a behavioral sleep intervention (BSI) that included imagery rehearsal therapy, stimulus control, and sleep restriction or placebo pill treatment. Both prazosin and BSI were significantly more effective than placebo for sleep improvement, reduction in daytime PTSD symptoms, and improvement of global function. The efficacy of both prazosin and BSI raises the possibility that a combination of prazosin and BSI, two mechanistically different treatments, may be more effective for PTSD nighttime symptoms than either treatment alone.

The fifth RCT was performed in active duty American soldiers returned from combat deployments in Iraq and Afghanistan [30••]. This study is the first prazosin RCT to have prescribed a midmorning prazosin dose in addition to a larger bedtime prazosin dose to increase likelihood of reducing daytime PTSD symptoms. Prescribing prazosin two or three times daily is consistent with prazosin use in general medicine to treat hypertension and benign prostatic hypertrophy and its 6 to 10 h duration of action. Sixty-seven soldiers in garrison at Joint Base Lewis McChord, Washington, were randomized to prazosin or placebo for 15 weeks. Participants met criteria for PTSD with frequent and severe combat trauma nightmares that had started subsequent to their traumatic combat event(s) in Iraq and Afghanistan. Prazosin was titrated upward over 6 weeks until trauma nightmares were absent or maximum doses of 5 mg midmorning and 20 mg bedtime for men ($n=57$) and 2.0 mg midmorning and 10.0 mg bedtime for women ($n=10$) were achieved. Maintenance prazosin doses were 4.0±1.2 mg midmorning and 15.6±6.0 mg bedtime for men and 2.0±0.0 mg midmorning and 7.0±3.5 mg bedtime for women.

Prazosin was significantly more effective than placebo for reducing CAPS "recurrent distressing dreams of the event" item scores; Pittsburgh Sleep Quality Index [39] scores; and total 17 item CAPS scores (reduction from baseline=25.1±3.4 prazosin group and 13.8±3.3 placebo group ($p=0.02$)). Total CAPS score decrease remained significantly greater in the prazosin group ($p=0.04$) even after removing the nightmare item. The proportion of treatment "responders," defined as CGIC

ratings "moderately improved" or "markedly improved" in ability to function at home and at work, was 64 % for the prazosin group and 27 % for the placebo group ($p<0.001$). Even at the relatively high doses achieved, prazosin was well tolerated by these young soldiers. This study demonstrated that prazosin has clinically meaningful beneficial effects on both daytime and nighttime PTSD symptoms in active duty combat experienced soldiers when administered twice daily. Similar open label prazosin beneficial effects with good tolerability have been reported in soldiers performing combat operations in the dehydrating Iraq desert warfare environment [40] and in elderly World War II veterans and Holocaust survivors [41] (Fig. 1).

A chart review effectiveness study of prazosin vs. quetiapine for nighttime PTSD symptoms in military veterans

Quetiapine is a sedating second generation antipsychotic drug that has been widely prescribed for decades to treat nighttime PTSD symptoms in military veterans. It has the highest "prazosin-like" affinity for the alpha-1 AR among commonly used antipsychotic drugs. Byers et al. used a retrospective chart review method to evaluate differential effectiveness between quetiapine and prazosin in veterans treated with these drugs for nighttime PTSD symptoms at the Phoenix, Arizona VA Medical Center [34]. Two hundred thirty-seven veterans (mean age=54 years) were first prescribed prazosin ($n=62$, initial mean nighttime dose=1.4 mg) or quetiapine ($n=175$, mean nighttime dose=41 mg) between 2002 and 2006. Short-term benefit was estimated at 6 months after first prescription based on charting clinician's indication of symptom improvement. Long-term benefit and tolerability were estimated in 2008 (end study), by comparing percentage of patients remaining on their initially prescribed prazosin (end study mean dose=6 mg) or initially prescribed quetiapine (end study mean dose=135 mg). Tolerability was estimated by comparing adverse effects leading to drug discontinuation.

The two drugs produced equal rates of short term improvement (prazosin=61.3 % vs. quetiapine 61.7 %). However, prazosin was significantly superior to quetiapine on long-term effectiveness estimated by percentage remaining on original drug at end study (48 vs. 21 %, $p<0.001$). More veterans discontinued quetiapine than prazosin for adverse effects (35 vs. 18 %, $p<0.01$), or for lack of efficacy (13 vs. 2 %, $p=0.03$). In contrast, discontinuation for symptom resolution (drug treatment no longer necessary) was significantly greater for prazosin than quetiapine (29 vs. 10 %, $p=0.02$). When specific adverse effects leading to discontinuation were examined, sedation (23 vs. 1 %, $p<0.001$) and metabolic effects (8 vs. 0 %, $p=0.01$) were greater with quetiapine than prazosin. Hypotension and dizziness were infrequent and did not differ between groups. Substitution of one drug for the other also favored prazosin. Prazosin was substituted for quetiapine in 25 % of patients initiated on quetiapine whereas quetiapine was substituted for prazosin is only 8 % of patients initiated on prazosin.

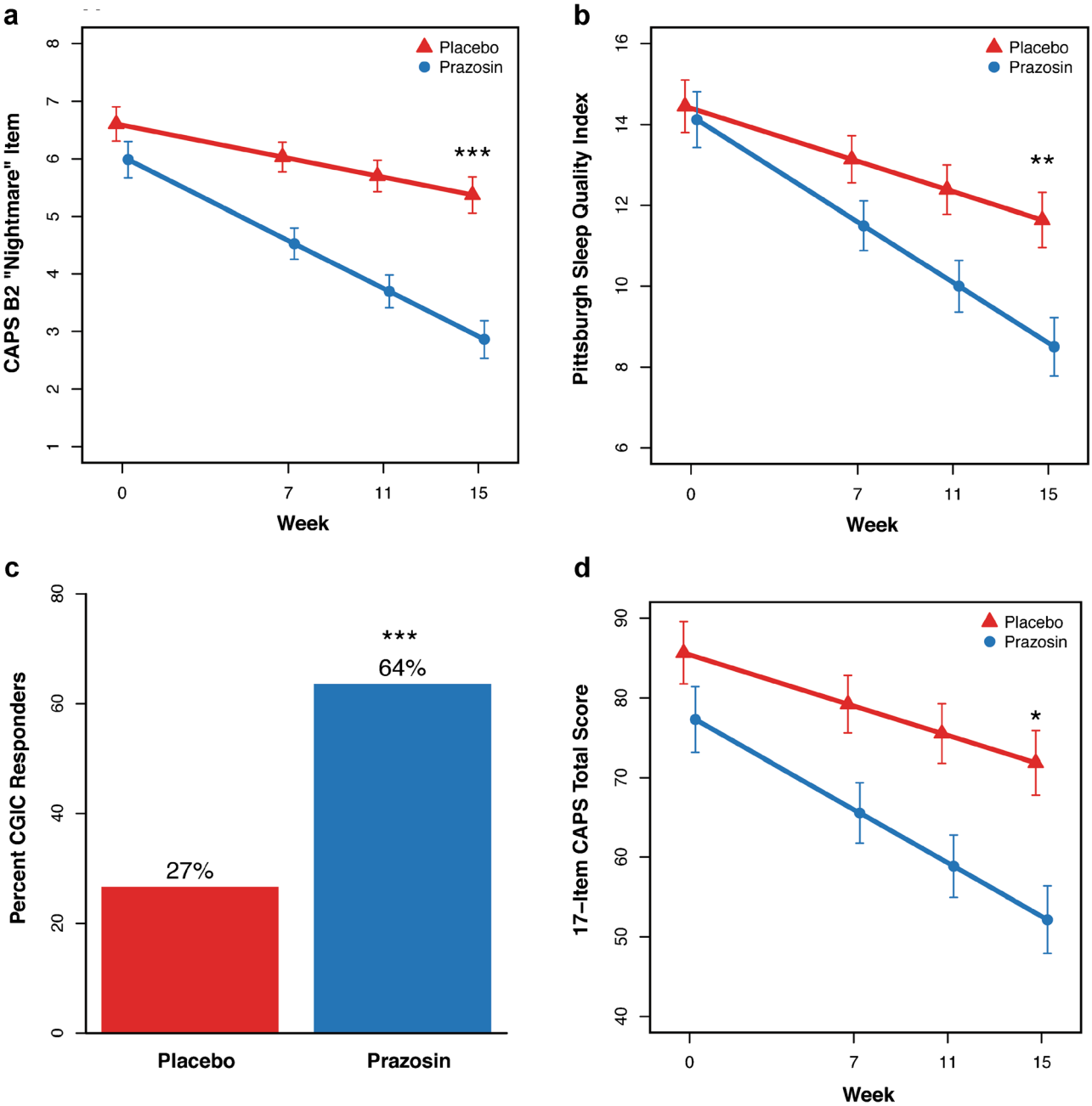

Fig. 1. Effects of prazosin and placebo on ratings of **a** CAPS B2 "nightmare" item, **b** Pittsburgh Sleep Quality Index, **c** Clinical Global Impression of Change (*CGIC*), percent responders (moderately or markedly improved), and **d** 17-item CAPS Total Score; based on linear mixed-effects models. *Error bars* indicate standard error (SE). Change from baseline to week 15 greater for prazosin than placebo: *$p<0.05$; **$p<0.01$; ***$p<0.001$.

These findings are consistent with increasing prazosin utilization for PTSD in the United States Veterans Health System every year since 2001. Although diffusion of prazosin treatment for PTSD in veterans initially was related to facility geographic proximity to Seattle, Washington [42], prazosin for PTSD

recently has become more widely and homogenously prescribed geographically across US Veterans Affairs Medical Centers [43].

Optimizing therapeutic effects and minimizing adverse effects of prazosin

Recommendations for the prescriber

- Prazosin must be initiated at a low dose (usually 1 mg at bedtime for 3 days) to avoid "first-dose" hypotension. Although some patients respond well to low doses (e.g., 2 to 4 mg HS), other patients require up to 40 mg at bedtime and 5 mg midmorning and mid-afternoon to achieve meaningful reduction or elimination of trauma nightmares, sleep disruption, and daytime hyperarousal symptoms [44] (and unpublished observations).
- Prazosin is recommended for treatment of PTSD associated nightmares by the American Academy of Sleep Medicine [45]. In our experience, prazosin is most effective for frequent trauma content nightmares that are highly distressing and accompanied by intense autonomic arousal. It also appears effective for PTSD distressed awakenings with intense autonomic arousal in the absence of recalled trauma content nightmares [46]. It does not appear effective for "normal" unpleasant anxious dreams with bizarre content.
- Although symptomatic orthostatic hypotension induced dizziness or fainting are unusual, especially after the first few weeks of prazosin titration, several factors increase risk for this adverse effect. These include: baseline orthostatic hypotension, erectile dysfunction medications, other maintenance antihypertensives, and inadequate hydration. Dizziness and syncope during early titration and in patients with hypotension risk factors are best avoided by instructing the patient to arise gradually from a supine to a sitting position, waiting 30 s without dizziness before standing, and an additional 30 s without dizziness before ambulating.
- If daytime hyperarousal symptoms persist despite bedtime prazosin elimination of nighttime PTSD symptoms, addition of prazosin 1 to 5 mg midmorning and mid-afternoon can reduce or eliminate persistent daytime hyperarousal PTSD symptoms.
- Prazosin is not a hypnotic and does not decrease seep onset latency [47].
- Prazosin generally is well tolerated. Adverse effects include orthostatic hypotension, nasal congestion, and reflex tachycardia perceived as uncomfortable or even frightening palpitations. Palpitations respond to adding low dose propranolol to the prazosin regimen. Priapism is an infrequent adverse event. Although propranolol alone can exacerbate trauma nightmares (as in the first veteran to receive prazosin described above), this does not occur when prazosin is already prescribed. In fact, addition of propranolol to prazosin (combined CNS beta AR and

alpha-1 AR antagonism) may reduce residual daytime irritability and low anger threshold (unpublished observations).
- Although prazosin often needs to be titrated upward aggressively during early treatment, once an effective dose is achieved that dose usually continues effective during long-term maintenance treatment. Why habituation to beneficial prazosin effects on PTSD is rare whereas habituation to prazosin hypotensive effects is common remains unclear.

Conclusion

Prazosin is a useful tool in the management of PTSD trauma content nightmares, sleep disruption, and daytime hyperarousal symptoms, particularly when these symptoms are frequent, severe, distressing, and accompanied by high autonomic arousal. The effective dose range is highly variable, so upward titration guided by elimination of target symptoms and emergence of troublesome adverse effects is necessary. Prazosin is generally well tolerated with gradual dose titration, and benefit usually continues for years once an effective dose is achieved. Prazosin may also prove beneficial for alcohol use disorder [48, 49] and persistent postconcussive headaches [50]. Clinical effectiveness of prazosin is supported by increased utilization every year among veterans with a PTSD diagnosis receiving care in the Veterans Health Care System since publication of the first case report series in 2000 [43, 51].

Compliance with Ethics Guidelines

Conflict of Interest
Murray Raskind declares no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Berridge CW. The locus ceruleus-noradrenergic system and stress: implications for posttraumatic stress disorder. In: Shiromani TKP, LeDoux JE, editors. Posttraumatic stress disorder: basic science and clinical practice. New York: Humana Press; 2009. p. 213–30.
2. Geracioti Jr TD et al. CSF norepinephrine concentrations in posttraumatic stress disorder. Am J Psychiatry. 2001;158(8):1227–30.
3. Mellman TA et al. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. Biol Psychiatry. 1995;38:174–9.
4. Bremner JD et al. Positron emission tomography measurement of cerebral metabolic correlates of yohimhine administration in combat-related posttraumatic stress disorder. Arch Gen Psychiatry. 1997;54:246–54.

5. Southwick SM et al. Abnormal noradrenergic function in posttaumatic stress disorder. Arch Gen Psychiatry. 1993;50:266–74.
6. Pietrzak RH et al. Association of posttraumatic stress disorder with reduced in vivo norepinephrine transporter availability in the locus coeruleus. JAMA Psychiatry. 2013;70(11):1199–205.
7. Westfall T, Westfall D. Adrenergic agonists and antagonists. In: Hardman J et al., editors. Goodman & Gilman's the pharmacological basis of therapeutics. New York: McGraw-Hill; 2006.
8. Lund-Johansen P et al. Selective alpha-1 inhibitors: first- or second-line antihypertensive agents? Cardiology. 1993;83(3):150–9.
9. Hieble JP, Ruffolo Jr RR. The use of alpha-adrenoceptor antagonists in the pharmacological management of benign prostatic hypertrophy: an overview. Pharmacol Res. 1996;33(3):145–60.
10. Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part II: physiological and pharmacological manipulations and pathological alterations of locus coeruleus activity in humans. Curr Neuropharmacol. 2008;6(3):254–85.
11. Pellejero T et al. Effects of methoxamine and alpha-adrenoceptor antagonists, prazosin and yohimbine, on the sleep-wake cycle of the rat. Sleep. 1984;7(4):365–72.
12. Cirelli C et al. Modulation of desynchronized sleep through microinjection of alpha 1-adrenergic agonists and antagonists in the dorsal pontine tegmentum of the cat. Pflugers Arch. 1992;422(3):273–9.
13. Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharmacol. 1997;11(2):151–62.
14. Neylan TC et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry. 1998;155(7):929–33.
15. Ross RJ et al. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry. 1989;146(6):697–707.
16. Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. J Trauma Stress. 2004;17(1):69–73.
17. Ravaris CL et al. A controlled study of alprazolam and propranolol in panic-disordered and agoraphobic outpatients. J Clin Psychopharmacol. 1991;11(6):344–50.
18. Famularo R, Kinscherff R, Fenton T. Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. Am J Dis Child. 1988;142(11):1244–7.
19. Kolb PE, Burns BS, Griffiths S. Propranolol and clonidine in the treatment of the chronic posttraumatic stress disorders of war. In: van der Kolk B, editor. Post traumatic stress disorder: psychological and biological sequelae. Washington DC: American Psychiatric Press; 1984.
20. Yamada Y et al. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. J Pharmacokinet Biopharm. 1995;23(2):131–45.
21. Day TA, Randle JC, Renaud LP. Opposing alpha- and beta-adrenergic mechanisms mediate dose-dependent actions of noradrenaline on supraoptic vasopressin neurones in vivo. Brain Res. 1985;358(1–2):171–9.
22. Medical Economics Company. Physicians desk reference. 62nd ed. Montvale: Medical Economics Company; 2008.
23. Kiss A, Aguilera G. Participation of alpha 1-adrenergic receptors in the secretion of hypothalamic corticotropin-releasing hormone during stress. Neuroendocrinology. 1992;56(2):153–60.
24. Birnbaum S et al. A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex. Biol Psychiatry. 1999;46(9):1266–74.
25. Southwick SM et al. Noradrenergic alterations in posttraumatic stress disorder. Ann N Y Acad Sci. 1997;821:125–41.
26. Woodward SH et al. Laboratory sleep correlates of nightmare complaint in PTSD inpatients. Biol Psychiatry. 2000;48(11):1081–7.
27. Hilakivi I, Leppavuori A. Effects of methoxamine, and alpha-1 adrenoceptor agonist, and prazosin, an alpha-1 antagonist, on the stages of the sleep-waking cycle in the cat. Acta Physiol Scand. 1984;120(3):363–72.
28. Pickworth WB et al. Sleep suppression induced by intravenous and intraventricular infusions of methoxamine in the dog. Exp Neurol. 1977;57(3):999–1011.
29. Raskind MA et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry. 2003;160(2):371–3.
30.•• Raskind MA et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afgahnistan. Am J Psychiatry. 2013;170(9):1003–10.

This study provides the strongest evidence for prazosin efficacy for overall PTSD, trauma nightmares, sleep disturbance and global function. This collaborative VA/Department of Defense study is the first ever completed randomized controlled trial of a medication for any behavioral disorder in active duty combat soldiers.

31. Raskind MA 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):928–34.
32.• Taylor FB et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008;63(6):629–32.

This placebo-controlled study objectively demonstrates prazosin improvement of sleep physiology in PTSD.

33.• Germain A 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.
This study demonstrates both prazosin and a behavioral sleep intervention were effective for sleep disturbance in military veterans.
34. Byers MG 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):225–9.
35. Blake DD et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8(1):75–90.
36. Ajilore O et al. Nightcap: laboratory and home-based evaluation of a portable sleep monitor. Psychophysiology. 1995;32(1):92–8.
37. van der Helm E et al. REM sleep depotentiates amygdala activity to previous emotional experiences. Curr Biol. 2011;21(23):2029–32.
38. Raskind MA. Pharmacologic treatment of PTSD. In: Shiromani PJ, Keane TM, LeDoux JE, editors. Posttraumatic stress disorder. New York: Humana Press; 2009. p. 337–61.
39. Buysse D et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric research and practice. Psychiatry Res. 1989;28(2):193–213.
40. Calohan J et al. Prazosin treatment of trauma nightmares and sleep disturbance in soldiers deployed in Iraq. J Trauma Stress. 2010;23(5):645–8.
41. Peskind ER et al. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. J Geriatr Psychiatry Neurol. 2003;16(3):165–71.
42. Hermes E, Harpaz-Rotem I, Rosenheck R. Diffusion of prazosin treatment for PTSD. Am J Psychiatry. 2014;171(1):117.
43. Bernardy NC et al. Prescribing trends in veterans with posttraumatic stress disorder. J Clin Psychiatry. 2012;73(3):297–303.
44. Koola MM, Varghese SP, Fawcett JA. High-dose prazosin for the treatment of post-traumatic stress disorder. Ther Adv Psychopharmacol. 2014;4(1):43–7.
45. Aurora RN et al. Best practice guide for the treatment of nightmare disorder in adults. J Clin Sleep Med. 2010;6(4):389–401.
46. Thompson CE et al. Nonnightmare distressed awakenings in veterans with posttraumatic stress disorder: response to prazosin. J Trauma Stress. 2008;21(4):417–20.
47. Taylor FB et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. Biol Psychiatry. 2006;59(7):577–81.
48. Simpson TL et al. A pilot trial of the alpha-1 adrenergic antagonist, prazosin, for alcohol dependence. Alcohol Clin Exp Res. 2009;33(2):255–63.
49. Simpson TL et al. Drinking motives moderate daily relationships between PTSD symptoms and alcohol use. J Abnorm Psychol. 2014;123(1):237–47.
50. Mayer CL, Huber BR, Peskind E. Traumatic brain injury, neuroinflammation, and post-traumatic headaches. Headache. 2013;53(9):1523–30.
51. Raskind MA et al. The alpha-1 adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. J Clin Psychiatry. 2000;61(2):129–33.