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BRIEF REPORTS

The α_1-Adrenergic Antagonist Prazosin Improves Sleep and Nightmares in Civilian Trauma Posttraumatic Stress Disorder

FLETCHER TAYLOR, MD*†, AND MURRAY A. RASKIND, MD†‡

**Rainier Associates, Tacoma, Washington; †Department of Psychiatry and Behavioral Sciences, University of Washington; ‡VA Puget Sound Health Care System Northwest Network VA Mental Illness Research, Education and Clinical Center (MIRECC), Seattle, Washington*

Heightened noradrenergic reactivity may be a contributing factor in the pathophysiology of posttraumatic stress disorder (PTSD). Prazosin is an α_1-adrenoceptor antagonist commonly used as an antihypertensive agent. Because α_1-adrenergic activity has been associated with fear and startle responses, a drug that blocks central α_1-adrenergic activity may be useful in the treatment of PTSD symptoms. An outpatient who had been exposed to civilian trauma and had subsequent chronic refractory PTSD was thus prescribed prazosin. The marked reduction in PTSD symptoms, particularly sleep and nightmares, prompted the following open-label feasibility trial. Five outpatients with non–combat-related PTSD were consecutively identified and received prazosin in a 6-week open-label trial. In each case, the prazosin doses were slowly increased until optimal benefit was achieved. Change was assessed with the Clinician-Administered PTSD Scale for DSM-IV, One Week Symptom Version (CAPS-SX), the Clinical Global Impression of Change Scale (CGIC), and the Clinical Impression of Change-Nightmares (CIC-Nightmares) score. All five patients experienced moderate to marked improvement on the CGIC. The CAPS-SX PTSD nightmare and sleep PTSD categories showed at least a four-point reduction of those symptoms. All patients reported at least moderate improvement on the CIC-Nightmare score. Optimal doses of prazosin ranged from 1 to 4 mg/day. The drug was reasonably tolerated, and there were no drug discontinuations. These preliminary findings provide a rationale for blind placebo-controlled efficacy trials of the α_1 antagonist prazosin for PTSD. (J Clin Psychopharmacol 2002;22:82–85)

SEVERAL MODELS OF posttraumatic stress disorder (PTSD) pathophysiology suggest a role for central nervous system noradrenergic hyperresponsiveness.[1, 2] There are α_1- and α_2-adrenergic postsynaptic receptors distributed in structures relevant to PTSD, such as the prefrontal cortex, hippocampus, and amygdala.[3] They play opposing roles in the control of behavior during aversive stress paradigms at the level of the cortex[4] and the locus ceruleus.[5] Activation of the α_1 receptor has been associated with fear response behaviors[6] and activation of the α_2 receptor with quiet concentration[7]; α_1 receptors are also important in the modulation of startle and sleep responses.[6, 8] That activation of α_{2a} receptors may be beneficial for PTSD symptoms by down-regulation of noradrenergic outflow (Southwick, personal communication, 2000) implies that postsynaptic blockade of α_1 receptors might have similar effects.

Prazosin is a centrally and peripherally acting α_1-adrenergic antagonist with a long and established history as an antihypertensive medication. To this end, F.T. began prescribing prazosin for those outpatients with PTSD after civilian trauma. The first patient reported a reduction of PTSD symptoms, particularly sleep and trauma-related nightmares. This encouraging result prompted further clinical use of prazosin for PTSD. Subsequently, the primary author discovered that M.A.R. had observed similar positive effects of prazosin in combat veterans with chronic PTSD,[9] hence

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Address requests for reprints to: Fletcher Taylor, MD, Rainier Associates, 5909 Orchard West, Tacoma, WA 98467.

this collaborative report with an emphasis on the effects of prazosin on PTSD-related nightmares and sleep patterns.

Methods

After University of Washington human subjects review board approval of a prazosin trial for PTSD, five consecutively identified outpatients consented to open-label treatment with prazosin for their PTSD symptoms. They were assessed before and after 2 and 6 weeks of receiving prazosin. The inclusion criteria were (1) DSM-IV criteria for PTSD; (2) a score of at least 80 on the Clinician-Administered PTSD Scale (CAPS)[10]; (3) PTSD symptoms as the motive for seeking treatment; (4) no alcohol or substance abuse within the last 6 months; and (5) a score of at least 4 (maximum of 8) on the nightmare item of the CAPS One Week Symptom Version (CAPS-SX). This measure combines a four-point nightmare frequency scale based on the response to the question "In the past week have you had unpleasant dreams about (EVENT)?" ranging from 0 (never) to 4 (daily or almost every day), and a four-point nightmare intensity scale based on the response to the question "How much distress or discomfort did these dreams cause you?" ranging from 0 (no distress) to 4 (extreme, incapacitating distress, did not return to sleep).

All patients were treated and rated by F.T. All measures were performed at baseline and after 2 and 6 weeks of prazosin treatment. All patients were assigned a Clinical Global Impression of Change (CGIC) score and a Clinical Impression of Change-Nightmares (CIC-Nightmares) score.[11] Prazosin doses were started at 1 mg at bedtime. If there was no improvement after 2 weeks, the dose was increased to 2 mg at bedtime, and a morning dose was added for daytime symptoms when necessary. If patients reported dizziness, sitting and standing blood pressures with pulse rates were recorded.

Results

After 6 weeks of prazosin therapy, all five patients as rated by the CGIC had achieved at least a "moderate improvement" rating of their PTSD symptoms. Cases 1, 3, and 5 had "marked improvement" CGIC ratings. All cases had at least a "moderate improvement" rating on the CIC-Nightmares measure. Table 1 presents the overall CAPS-SX severity scores and insomnia and nightmare severity subscores. The following case descriptions and details of clinical management are presented to further characterize PTSD symptoms and their response to prazosin.

Case 1

A 53-year-old unemployed woman experienced repeated childhood traumas from age 6 until adolescence. At age 6, both parents unexpectedly left without arrangements for her care, so she presumed that she had been left to die. She then lived in six different homes in as many years, experiencing verbal abuse, physical abuse, and neglect, such as being forced to sleep in an unlit basement. She experienced intrusive recollections, severe nightmares, guardedness, apprehension, and emotional distancing. Her traumatic memories interfered with her concentration, and she was often unable to balance her checkbook and cook basic meals. Ongoing medications included buspirone and nefazodone. Within 24 hours of beginning prazosin (which she called "praise the sun"), she reported a normal sleeping pattern, "fun adventure dreams instead of nightmares," and that "I can put aside my bad memories." She remarked feeling more relaxed and "a part of the picture" instead of feeling removed from events. She drew up a resume and applied for jobs. She was without side effects and continued to benefit from prazosin 13 months later. She reported that if she missed a dose, her PTSD symptoms would begin to return within 24 hours.

Case 2

A 35-year-old carpenter sustained third-degree hot tar burns to 40% of his body. Not expected to live, he required painful skin grafts. By the sixth month of hospitalization, he was experiencing insomnia, nightmares, flashbacks of the incident, extreme irritability, and hypervigilant behaviors. His arousal symptoms precluded social activities because he feared that he would "lose control and hurt somebody." He made several attempts to return to work but was unable to function. His ongoing medications

TABLE 1. The reduction of PTSD symptoms in five civilians over 6 weeks of prazosin treatment[a]

			CAPS-SX Nightmare Frequency + Severity			CAPS-SX Insomnia Frequency + Severity			CAPS-SX Total Score		
Case	Age	Optimum Prazosin Dose	Baseline	Week 2	Week 6	Baseline	Week 2	Week 6	Baseline	Week 2	Week 6
1	53	1 mg hs	6		2	6		2	103		81
2	35	1 mg a.m. and hs	7	2	0	7	0	2	107	83	87
3	53	1 mg hs	6	1	1	6	0	0	97	53	43
4	58	2 mg a.m. and hs	8	6	3	7	0	3	102	82	71
5	40	1 mg hs	7	6	3	7	5	3	106	54	49

[a]hs, at bedtime.

included insulin (for diabetes), lithium, paroxetine, fluoxetine, and buspirone. Seven months after the trauma, he began receiving prazosin. Within several days of beginning prazosin, the insomnia and nightmares were gone ("I don't dream about hot anymore"), and he was less irritable and less easily startled. When he missed two or more consecutive doses of prazosin, his nightmares began to return. He reported transient morning sedation that resolved within several days of beginning prazosin. He has remained on 1 mg twice daily and has retained its benefits 9 months after beginning treatment.

Case 3

A 53-year-old woman flight attendant was raised in a satanic cult community, where she was drugged, forced into prostitution, and forced to witness ritual violence. Her accounts were independently corroborated by reports from other family members. Escaping at age 16, she has received treatment for symptoms of PTSD since. Ten different psychotropic drug trials failed to reduce her PTSD symptoms. She reported repeated nightmares of her traumatic experiences, usually awakening her "in a sweat" and "feeling like I had been fighting a war all night." Flashbacks, hyperarousal, and avoidance were daily distressing occurrences in social and work settings. Her ongoing medications included paroxetine 20 mg/day and temazepam 10 mg at bedtime. Within several days of beginning the prazosin, she noted reduced hyperarousal symptoms during the day, resumption of normal sleep patterns, and disappearance of nightmares. She reported no side effects while receiving prazosin. After 2 months of prazosin treatment, she ran out, and has continued to do well without it for 6 months after treatment.

Case 4

A 58-year-old claims adjuster had no prior psychiatric history before her life-threatening pulmonary embolus. Other stressors included the diagnosis of hypertension, a close friend's dying of cancer, and losing her job of 15 years. Within 4 weeks of the pulmonary embolus, she began "feeling very vulnerable indeed," and she experienced frequent nightmares of the recent events from which she would awake "in a cold sweat." During flashbacks, she experienced some of the symptoms of the pulmonary embolus, including shortness of breath, palpitations, tachycardia, and other hyperarousal symptoms. She reported extreme social withdrawal, avoidance of reminders of the recent events, depersonalization, and irritability. By several days into the prazosin trial, she described some improvement of her hyperarousal symptoms, insomnia, and nightmares. After a dose increase to 2 mg twice daily, she reported a more substantial improvement of her PTSD symptoms overall. The content of her dreams was the same, but they were no longer frightening and were "funny and goofy in a sad sort of way, like a cartoon." Other than a transient dry mouth, no side effects were reported. Her hypertension remained unimproved. She continued to report benefit from prazosin 8 months later.

Case 5

This 40-year-old psychiatric nurse was the only child of abusive alcoholic parents, and she bears scars from their beatings. When the patient was 8 years old, the family escaped from their burning home after her intoxicated mother set fire to a pile of her father's magazines indoors. Under the threat of her life, she was forced to tell the authorities that she had set the fire. A year before the patient's treatment, her supervisor was indirectly responsible for the death of a patient and unsuccessfully tried to shift the blame onto her. Childhood PTSD symptoms re-emerged, and she experienced dissociation, nightmares, and vivid flashbacks of the house fire incident and of her childhood beatings. She described extreme vigilance, startle responses, irritability, and avoidance of the people at her workplace despite her ongoing medication, fluoxetine. Two days after beginning 1 mg of prazosin at bedtime, she had one episode of syncope after a nocturnal micturition. The following morning her sitting blood pressure was 120/65 with a pulse of 75 bpm, and her standing blood pressure was 115/65 with a pulse of 80 bpm. Her dose was decreased to 0.5 mg at bedtime for a week before reinstating the 1-mg dosage, and neither syncope nor dizziness recurred. By the third day of beginning prazosin, she noted that her nightmares were gone and the insomnia much improved. She reported markedly reduced hyperarousal, irritability, and dissociation and noted an improved ability to function in social settings. She continued to benefit from prazosin 4 months later.

Discussion

Prazosin therapy resulted in the reduction of non–combat-related PTSD symptoms in five consecutive outpatients. It was well tolerated and seemed particularly helpful for PTSD-associated insomnia and nightmares, with variable improvement of other PTSD symptoms. Several qualitative observations are of note. First, in all cases, the response to prazosin was within several days, and with the exception of one case, missing a dose resulted in the rapid return of PTSD-related nightmares. This suggests that the rapid reduction of PTSD symptoms by prazosin may be the result of direct antagonist effects on α_1-adrenergic receptors. An analogy would be the rapid effects of propranolol on somatic manifestations of anxiety, such as tremor and tachycardia, by direct antagonist effects on β-adrenergic receptors. Second, there was one patient in whom the nightmares did not return

upon discontinuation of prazosin. Her nightmares tended to be episodic, falling on the anniversary dates of past traumas. This patient's nightmares could have spontaneously resolved irrespective of being on prazosin, thus accounting for her absence of relapse nightmares upon discontinuation. Alternatively, she may have been a placebo responder. Third, in four of the five cases, there were other ongoing psychotropic medications, any of which could have augmented the effect of prazosin on PTSD symptoms. For example, the α_1-antagonist activity of nefazodone (case 1) may have had additive effects with prazosin in reducing PTSD symptoms. Patient 4 was taking no other medications at the time of prazosin treatment and required the highest dose of prazosin for optimal benefit. This is consistent with the idea that prazosin and other drugs may have additive effects. Finally, the five PTSD cases reported varied greatly in both the duration of their PTSD symptoms and the nature of the precipitating stressors. This makes the overall interpretation of our observations particularly complex.

Noradrenergic effects on sleep physiology suggest possible mechanisms by which central α_1-adrenergic receptor blockade by prazosin could reduce nightmares and improve sleep quality in PTSD. The reduction of noradrenergic activity observed during normal sleep[12] seems not to occur in PTSD.[13] Preclinical observations demonstrate that α_1-noradrenergic stimulation disrupts rapid eye movement (REM) sleep and increases stage 1 light sleep. These are the sleep stages during which PTSD trauma content nightmares seem most likely to occur.[14] In dogs, the α_1-adrenergic agonist methoxamine disrupts REM sleep, an effect reversed by prazosin.[8] In cats, REM sleep is disrupted by the indirect noradrenergic agonist desipramine.[15] This desipramine effect is reversed by prazosin but not by the β-adrenergic antagonist propranolol. These animal studies suggest that REM sleep is disrupted by excessive α_1-adrenergic stimulation. In our PTSD patients, blockade of α_1-adrenergic receptors by prazosin may have normalized REM sleep, producing the reported reduction of trauma content nightmares and the emergence of more normal dreaming. However, the prominent motor activity often reported to occur in association with PTSD nightmares implies that at least some PTSD nightmares are not REM sleep phenomena. Furthermore, a recent study of nightmare complaints in PTSD inpatients found no relationship between nightmare complaints and REM sleep architecture.[16] It has been suggested that phasic noradrenergic outflow might contribute to non-REM nightmares that emerge preferentially during stage 1 sleep.[14] α1-Adrenergic stimulation increases stage 1 sleep, and this effect is reversed by prazosin.[8] Thus, excessive nocturnal stimulation of central α_1-receptors could contribute to PTSD sleep disturbance arising during either REM or stage 1 sleep. Blocking α_1-adrenergic receptors with prazosin may have restored normal sleep physiology in these patients.

Open-label clinical treatment with prazosin was associated with reduced PTSD symptoms, particularly nightmares and insomnia. The drug was well tolerated, with only one occurrence of dizziness possibly attributable to the blood pressure–reducing property of prazosin. These clinical observations provide a rationale for placebo-controlled trials of prazosin for PTSD.

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