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NON-NIGHTMARE DISTRESSED AWAKENINGS IN VETERANS WITH POSTTRAUMATIC STRESS DISORDER: RESPONSE TO PRAZOSIN

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Abstract

Twenty-two veterans with posttraumatic stress disorder (PTSD) were assessed for trauma-related nightmares (NM) and non-nightmare distressed awakenings (NNDA) before and after treatment with the alpha-1 adrenoreceptor antagonist prazosin at an average bedtime dose of 9.6 mg/day. Ratings combining frequency and intensity dimensions of NM decreased from 3.6 ± 2.6 to 2.2 ± 2.4 ($p < 0.05$), NNDA from 5.2 ± 1.7 to 2.1 ± 2.4 ($p < 0.01$), and sleep difficulty from 7.2 ± 8 to 4.1 ± 2.3 ($p < 0.01$) per week. These results suggest that increased brain adrenergic activity may contribute to the pathophysiology of both NM and NNDA in PTSD.

INTRODUCTION

Sleep complaints are among the most common, troublesome and treatment resistant symptoms of posttraumatic stress disorder (PTSD) (Ross, Ball, Sullivan, & Caroff, 1989; Ohayon & Shapiro, 2000; Geuze & Vermetten, 2004). Recurrent distressing dreams (or “nightmares”) related to the traumatic event(s) are the sleep complaint most specific for PTSD in Vietnam veterans, but distressed awakenings with difficulty returning to sleep are even more frequently reported (Neylan, Marmar, Meltzer, Weiss, Zatzick, Delucchi, et al., 1998). Increased central nervous system (CNS) adrenergic activity during sleep time may contribute to these symptoms (Raskind, Dobie, Kanter, Petrie, Thompson, & Peskind, 2000; Mellman, Kumar, Kulick-Bell, Kumar & Nolan 1995a; Mellman, Knorr, Pigeon, Leiter & Akay, 2004). Although persons with PTSD often attribute distressed awakenings to frightening trauma-related nightmares (NM), distressed awakenings phenomenologically similar to those associated with NM frequently occur without dream recall (Mellman, Kulick-Bell, Ashlock & Nolan, 1995b). We use the term “non-nightmare distressed awakening” (NNDA) to describe this symptom.

Prazosin is a generic non-sedating alpha-1 adrenoreceptor (AR) antagonist used for many years to treat hypertension and the urinary symptoms of benign prostatic hypertrophy (Lund-

Johansen, Hjermann, Iverson & Thaulow, 1993; Hieble & Ruffolo, 1996). Prazosin is the only clinically available alpha-1 AR antagonist that crosses the blood brain barrier (Hardman, Limbird, Milinoff & Rudden, 1996) and specifically blocks CNS responses to adrenergic stimulation when administered peripherally (Menkes, Baraban & Aghajanian, 1981). Prazosin has been demonstrated substantially more effective than placebo for reducing PTSD trauma nightmares and sleep disturbance and improving global clinical status in both military veteran and civilian samples (Raskind, Peskind, Kanter, Petrie, Radant, Thompson, et al., 2003; Raskind, Peskind, Hoff, Hart, Holmes, Warren, et al., 2007; Taylor, Martin, Thompson, Williams, Mellman, Gross, et al., 2008). In the civilian PTSD study (Taylor et al., 2008) at home measurement of physiologic sleep parameters were obtained. These demonstrated significantly and substantially greater sleep duration (by 90 minutes) in the prazosin than the placebo condition without a hypnotic-like reduction of sleep latency (time to fall asleep) by prazosin. These sleep parameter data are consistent with a reduction of NNDA by prazosin having contributed to the observed increased sleep duration. However, NNDA were not specifically assessed in the Taylor et al. 2008 or other prazosin for PTSD studies.

As a first step in determining the effects of prazosin on NNDA in veterans with chronic PTSD we performed a chart review study of a consecutively treated sample of outpatients prescribed bedtime prazosin for PTSD trauma nightmares and sleep disturbance. For each patient, trauma nightmares, general sleep disturbance and specific NNDA had been quantified before prazosin was initiated and again after a clinically optimal dose of prazosin had been achieved.

METHODS

Participants

Following IRB approval, charts of 22 veterans who met DSM-IV (American Psychiatric Association, 1994) criteria for PTSD were anonymously reviewed. These veterans comprised a consecutive outpatient sample who were seen for initial evaluation (by author CT) between June 1, 2003 and August 1, 2003, and who endorsed troublesome trauma-related nightmares and sleep difficulty as presenting symptoms. Trauma exposures included combat (n=17), aircraft carrier flight deck accident (n=4), and life-threatening motor vehicle accident in a combat zone (n=1). Comorbidities included major depression or dysthymia (n=19), alcohol abuse or dependence all in sustained remission (n=11), generalized anxiety disorder (n=3) and panic disorder without nocturnal panic attacks (n=2). Two participants had sleep apnea responsive to maintenance CPAP treatment. None had a lifetime diagnosis of psychotic disorder or parasomnias including sleep terrors, REM sleep behavior disorder, restless leg syndrome, periodic limb movements in sleep or somnambulation. All 22 were maintained on at least one psychotropic medication (mean 3.3, range 1-6, SD = 1.58) prior to and during prazosin treatment including selective serotonin re-uptake inhibitors (SSRIs) (n=8), other antidepressants (n=16), atypical antipsychotics (n=6), hypnotics or benzodiazepines (n=18). All participants received supportive individual psychotherapy and 7 were in supportive group therapy. None had received formal exposure or cognitive-behavioral therapy.

Measures

All assessments of sleep symptoms were performed by author CT. Participants were based on participants' reports of symptom frequency and severity during the week prior to assessment. Trauma-related nightmares (NM) were quantified with Item B-2 "recurrent distressing dreams" of the Clinician Administered PTSD Scale (CAPS) (Blake, Weathers, Nagy, Kaloupek, Gusman, Chaney, et al., 1995). CAPS B-2 quantifies frequency of unpleasant dreams about the (traumatic) event(s) and intensity of distress and being awakened by these dreams. It is scored by combining frequency and intensity dimensions. The maximum score of 8 denotes "unpleasant dreams about the event daily or almost every day causing extreme incapacitating distress, did not return to sleep." Sleep difficulty was quantified with the CAPS D-1 item "difficulty falling or staying asleep." This item is scored by combining frequency of difficulty falling or staying asleep with the intensity of the difficulty. The maximum score of 8 denotes sleep difficulty "daily or almost every day with very long latency, or profound difficulty staying asleep." Because the CAPS D-1 item confounds prolonged sleep onset latency ("difficulty falling asleep") with awakening from already achieved sleep ("difficulty staying asleep") it is not appropriate for quantifying NNDA. We therefore adapted the CAPS item B-2 to quantify NNDA by substituting "NNDA" for "recurrent distressing dreams of the event" but otherwise leaving the CAPS B-2 frequency and intensity descriptors and scoring rules intact. Thus, the maximum score of 8 denotes "NNDA daily or almost every day with extreme incapacitating distress, did not return to sleep."

The clinical Global Impression of Change (CGIC) (Guy & Bonato, 1976) was completed at the follow-up prazosin maintenance dose visit by author CT. The CGIC is a 7-item scale that provides an estimate of change in overall clinical status operationalized as sense of well-being and ability to function. A score of 1 is "markedly improved," 2 is "moderately improved," 3 is "minimally improved," 4 is "unchanged," 5 is "minimally worse," 6 is "moderately worse" and 7 is "markedly worse."

The significance of differences in symptom ratings between baseline and prazosin condition within patients was determined by paired *t* tests. The relationships between change in distressed sleep and changes in nightmares or NNDA were estimated by Pearson Product Moment Correlations.

Treatment

Prazosin treatment was prescribed after 1 or 2 pretreatment evaluation sessions. NM, sleep difficulty and NNTE were rated by author CT at the visit at which prazosin was prescribed. Prazosin was initiated at 1 mg one hour before bedtime for three nights then increased to 2 mg before bedtime through night seven. If NM were not at least moderately reduced by participant report after night seven and there were no clinically significant adverse effects, prazosin was then increased by weekly 2 mg increments to a possible dose of 10 mg at bedtime. Dose increase was stopped and that dose maintained at a dose at which the participant reported at least moderately reduced NM. An additional increase by 5 mg to a maximum dose of 15 mg prazosin at bedtime could be prescribed if nightmares had not moderately improved and adverse effects were not problematic at one week after the 10 mg

dose had been achieved. Trauma-related nightmares were again rated by CT at a visit at least one week after maintenance prazosin dose had been achieved. Participants were seen approximately every two weeks and not all dose increases required a clinic visit. Mean number of visits after beginning prazosin was 3.4 ± 1.8 .

RESULTS

Mean maintenance prazosin dose was 9.6 ± 6.0 mg at bedtime. Ratings of trauma-related nightmares, sleep disturbance and NNDA before initiation of prazosin treatment and after achievement of maintenance prazosin dose are presented in Table 1. All three sleep symptom parameters were significantly reduced following prazosin treatment. There were significant correlations between change in ratings of sleep difficulties and both changes in ratings of NM ($r = 0.63$, $p < 0.05$) and changes in ratings of NNDA ($r = 0.55$, $p < 0.05$). Mean improvement in global clinical status (sense of well-being and ability to function) quantified by CGIC was 2.7 (SD = 1.0), falling between “minimally improved” and “moderately improved” using CGIC verbal descriptors.

DISCUSSION

These results suggest that NNDA are a common and distressing symptom among veterans with PTSD who present clinically with sleep complaints. They are consistent with a sleep diary and polysomnography sleep laboratory study in veterans (Mellman, Kulick-Bell, Achlock & Nolan, 1995b). Sleep diary data demonstrated NNDA to occur at a frequency comparable to NM. Of 18 awakenings in the sleep laboratory associated with startle or fear, only three had recalled NM content. Because recall of a NM is a variable and often transient phenomenon, it is difficult to determine if NM and NNDA represent the same neurobiologic phenomenon differently perceived or whether they are distinct types of sleep disorder. However, their common association with hyperarousal and startle and their similar reduction by prazosin suggest that increased brain responsiveness to norepinephrine at the postsynaptic alpha-1 adrenoceptor contributes to the pathophysiology of both symptoms.

Interpretation of the current results is limited by the lack of a placebo control or blinding of either participants or clinician raters. The psychopharmacology of PTSD is replete with positive uncontrolled studies of drugs that fail to demonstrate efficacy when evaluated in a randomized placebo-controlled trial (RCT) (Institute of Medicine, 2008). To extend demonstrated prazosin efficacy in PTSD to NNDA, larger controlled studies are needed in both veteran and civilian trauma samples.

Improvement in global sense of well-being and ability to function following prazosin suggests that NM and/or NNDA contribute substantially to reduced function and overall illness burden in PTSD. Reductions of distressing and dysphoric NM and NNDA themselves would certainly be perceived as beneficial. It also is possible that improved sleep had further beneficial effects on daytime PTSD symptoms such as poor concentration and irritability that may be related to impaired sleep (Mellman, Kulick-Bell, Ashlock & Nolan, 1995b).

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REFERENCES

- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed.. Author; Washington DC: 1994.
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a Clinician-Administered PTSD Scale. *Journal of Traumatic Stress*. 1995; 8:75–90. [PubMed: 7712061]
- Friedman MJ. Future pharmacotherapy for posttraumatic stress disorder: prevention and treatment. *Psychiatric Clinics of North America*. 2002; 25:427–441. [PubMed: 12136508]
- Geuze, E.; Vermetten, E. Disordered sleep in posttraumatic stress disorder: clinical presentation, research, findings, and implications for treatment.. In: Golbin, A.; Kravitz, H.; Keith, LG., editors. *Sleep psychiatry*. Taylor & Francis; New York, New York: 2004. p. 247-269.
- Guy, W.; Bonato, RR. US Department Health, Education and Welfare publication (ADM) 76-338. National Institute of Mental Health; Rockville, Maryland: 1976. ECDEU assessment manual for psychopharmacology..
- Hardman, JG.; Limbird, LE.; Milinoff, PB.; Ruddon, RW., editors. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th Ed.. McGraw-Hill; 1996. p. 229
- Hieble JP, Ruffolo RR Jr. The use of alpha-adrenoreceptor antagonists in the pharmacological management of benign prostatic hypertrophy: an overview. *Pharmacology Research*. 1996; 33:145–160.
- Institute of Medicine. Treatment of posttraumatic stress disorder: an assessment of the evidence. The National Academies Press; Washington DC: 2008.
- Lund-Johansen P, Hjermann I, Iverson BM, Thaulow E. Selective alpha-1 inhibitors: first- or second-line antihypertensive agents? *Cardiology*. 1993; 83:150–159. [PubMed: 7904230]
- Mellman T, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. *American Journal of Psychiatry*. 1995b; 152:110–115. [PubMed: 7802100]
- Mellman T, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biological Psychiatry*. 1995a; 38:174–179. [PubMed: 7578660]
- Mellman TA, Knorr BR, Pigeon WR, Leiter JC, Akay M. Heart rate variability during sleep and the early development of posttraumatic stress disorder. *Biological Psychiatry*. 2004; 55:953–956. [PubMed: 15110740]
- Menkes DB, Baraban JM, Aghajanian GK. Prazosin selectively antagonizes neuronal responses mediated by alpha-1 adrenoreceptors in brain. *Naunyn Schmiedebergs Archives of Pharmacology*. 1981; 317:273–275. [PubMed: 6119624]
- Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Wu RM, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *American Journal of Psychiatry*. 1998; 155:929–933. [PubMed: 9659859]
- Ohayon MM, Shapiro CM. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Comprehensive Psychiatry*. 2000; 41:469–478. [PubMed: 11086154]
- Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall ME. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *American Journal of Psychiatry*. 2003; 160:371–373. [PubMed: 12562588]
- Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma

nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. *Biological Psychiatry*. 2007; 61:928–934. [PubMed: 17069768]

Ross R, Ball W, Sullivan K, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. *American Journal of Psychiatry*. 1989; 146:697–707. [PubMed: 2658624]

Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma PTSD: a placebo-controlled study. *Biological Psychiatry*. 2008; 63:629–632. [PubMed: 17868655]

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Table 1
Posttraumatic Stress Disorder Sleep Symptom Ratings Before and After Prazosin ($N = 22$)

	<u>Baseline</u>		<u>Prazosin^a</u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Trauma nightmares (CAPS B-2 item)	3.6	2.6	2.2 [*]	2.4
Sleep difficulty (CAPS D-2 item)	7.2	0.8	4.1 ^{**}	2.3
Nonnightmare distressed awakenings	5.2	1.7	2.1 ^{**}	2.4

Note. CAPS = Clinician Administered PTSD Scale.

^aOne week after achieving maintenance evening prazosin dose ($M = 9.6$, $SD = 6$).

^{*} $p < 0.05$.

^{**} $p < 0.01$.