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Improving sleep: Initial headache treatment in OIF/OEF veterans with blast-induced mild traumatic brain injury

Robert L. Ruff, MD, PhD;[1–2*] Suzanne S. Ruff, PhD;[3] Xiao-Feng Wang, PhD[4]
[1]Neurology Service and Polytrauma System of Care, Louis Stokes Cleveland Department of Veterans Affairs Medical Center (LSCVAMC), Cleveland, OH; [2]Department of Neurology, Case Western Reserve University, Cleveland, OH; [3]Psychology Service and Polytrauma System of Care, LSCVAMC, Cleveland, OH; [4]Department of Quantitative Health Sciences, The Cleveland Clinic, Cleveland, OH

Abstract—This was an observational study of a cohort of 126 veterans with mild traumatic brain injury caused by an explosion during deployment in Operation Iraqi Freedom or Operation Enduring Freedom (OIF/OEF); 74 of the 126 veterans had comorbidities including frequent, severe headaches and residual deficits on neurological examination, neuropsychological testing, or both. Of these veterans, 71 had posttraumatic stress disorder and only 5 had restful sleep. We examined whether treatment with sleep hygiene counseling and oral prazosin would improve sleep, headaches, and cognitive performance. Nine weeks after providing sleep counseling and initiating an increasing dosage schedule of prazosin at bedtime, 65 veterans reported restful sleep. Peak headache pain (0–10 scale) decreased from 7.28 +/– 0.27 to 4.08 +/– 0.19 (values presented as mean +/– standard deviation). The number of headaches per month decreased from 12.40 +/– 0.94 to 4.77 +/– 0.34. Montreal Cognitive Assessment scores improved from 24.50 +/– 0.49 to 28.60 +/– 0.59. We found these gains maintained 6 months later. This pilot study suggests that addressing sleep is a good first step in treating posttraumatic headaches in OIF/OEF veterans.

Key words: combat, concussion, explosion, headache, mild traumatic brain injury, OIF/OEF, pain, prazosin, PTSD, sleep.

INTRODUCTION

Traumatic brain injury (TBI) is an important health issue for military personnel serving in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) [1–4]. Headache is a frequent sequel to head trauma [5–6]. Headache usually resolves within 6 months for civilians with mild TBI, which is also called concussion [6–9]. However, pain, including headache associated with mild TBI, has a high prevalence among OIF/OEF veterans treated in Department of Veterans Affairs (VA) medical centers (VAMCs) even though these veterans are often seen several years after their episodes of combat-associated head trauma [10].

Several features distinguish mild TBI occurring in a setting of military combat associated with explosions from mild TBI occurring in a civilian setting. Combat TBI is more commonly associated with posttraumatic stress

Abbreviations: ANOVA = analysis of variance, CI = confidence interval, ESS = Epworth Sleepiness Scale, LMM = linear mixed model, LSCVAMC = Louis Stokes Cleveland Department of Veterans Affairs Medical Center, MOCA = Montreal Cognitive Assessment, OEF = Operation Enduring Freedom, OIF = Operation Iraqi Freedom, OR = odds ratio, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury, VA = Department of Veterans Affairs, VAMC = Department of Veterans Affairs Medical Center, VHA = Veterans Health Administration.

[*]Address all correspondence to Robert L. Ruff, MD, PhD; Neurology Service, 127(W), Louis Stokes Cleveland VA Medical Center, 10701 East Blvd, Cleveland, OH 44106; 215-791-3800, ext 5230; fax: 216-707-6401.
Email: robert.ruff1@va.gov
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disorder (PTSD), visual disturbances, impaired hearing, and impaired sleep [1]. OIF/OEF veterans with a history of mild TBI due to exposure to explosions were more likely to have prolonged postconcussive symptoms compared with civilians with a history of mild TBI [1,4].

We developed this study when OIF/OEF veterans who had been in the U.S. National Guard and Military Reserves became aware of their eligibility for medical treatment within the VA and joined the continuous influx of discharged former active-duty military personnel in seeking VA healthcare. Combat veterans with histories of TBI faced challenges reintegrating into society [4,11–12]. Readjusting to civilian life presents challenges because behavior patterns that are useful in a combat setting, referred to as Battlemind, are often not appropriate for civilian life [13–15]. A specific challenge faced by veterans with mild TBI and PTSD, but with no other physical injuries, was that family members and others could not understand why the veterans were having problems resuming their predeployment lives [4]. The veterans looked the same but did not act the same. Family discord, including divorce, was common. Frequent veteran complaints included headaches, impaired memory, poor attention, low frustration tolerance, and impaired sleep with nightmares. These veterans were reluctant to take medications that could compromise cognitive processing. Treatment that could compromise sexual performance was also undesirable to male patients.

The Neurology Service at the Louis Stokes Cleveland VAMC (LSCVAMC) in Cleveland, Ohio, part of the Veterans Integrated Service Network 10 Polytrauma Center, was responsible for evaluating veterans with TBI and developing treatment strategies for their headaches. The Neurology Service established a Quality Assurance Monitor to collect information about the OIF/OEF veterans with histories of TBI exposures and evaluate the utility of interventions [16]. Data were collected in the course of providing treatment. Therefore, the data were collected unblinded because the treatment providers were also the data collectors. We found that in a group of 126 OIF/OEF veterans who had histories of combat-associated mild TBI resulting from exposures to explosions, 63.5 percent continued to have headaches [16]. The interval from the final blast exposure to time of evaluation was 8 months to 4.5 years. Consequently, many in this group of OIF/OEF veterans with mild TBI due to blast exposures continued to have headaches after the 6-month period when most civilian posttraumatic headaches would be expected to resolve [6–7,9]. We found that 63.5 percent of the 126 veterans had abnormalities on neurological examinations, neuropsychological testing, or both that were consistent with residual cerebral dysfunction [16]. Among these 80 veterans who had abnormalities on neurological examination or neuropsychological testing, 74 (92.5%) had headaches. In contrast, only 6 (13.0%) of the 46 veterans who did not have residual neurocognitive deficits had headaches. Among the 80 veterans with posttraumatic headaches, the veterans with residual neurocognitive deficits had more frequent headaches, experienced greater headache pain, and were more likely to have headaches with migraine features [16].

This study describes the findings of the initial intervention we used to address headache treatment for the 74 veterans described with residual neurocognitive deficits and headaches. We addressed impaired sleep as the initial intervention for the OIF/OEF veterans because we felt that the veterans would likely accept this initial treatment strategy. We provided sleep hygiene counseling as part of the initial intervention because it is a standard educational intervention provided to patients to improve sleep and it enabled the veterans to have an active role in their healthcare. We chose prazosin as the pharmaceutical agent to improve sleep for several reasons:

1. Prazosin is an alpha-adrenergic blocking agent that penetrates into the central nervous system and is able to block nightmares associated with stress disorders [17].
2. Placebo-controlled clinical trials demonstrated that prazosin reduced nightmares and improved sleep in veterans with PTSD [18] and in civilians with PTSD [19].
3. In addition to improving sleep, prazosin may improve cognitive function by reducing the anxiety associated with PTSD. Subjects with PTSD have impaired cognitive function that can be attributed in part to anxiety [20]. Prazosin may reduce anxiety in veterans with PTSD by reducing central nervous system noradrenergic activity [21].
4. Our OIF/OEF study group members were reluctant to take medications that would cloud their consciousness or alter their mood. They were willing to take prazosin because it does not induce sleepiness and is not considered an agent that will cloud consciousness or directly alter mood.
5. Prazosin is now being used by active-duty military personnel to treat nightmares associated with combat experiences.
6. Prazosin is not known to cause erectile dysfunction [17].

The objective of this study was to determine whether treating impaired sleep would reduce headache frequency and severity. The three hypotheses explored in this manuscript were that (1) OIF/OEF veterans would tolerate prazosin with a low incidence of side effects, (2) prazosin combined with sleep hygiene counseling would improve sleep among OIF/OEF veterans with mTBI, and (3) veterans who took prazosin and received sleep hygiene counseling would have less severe headache pain and fewer headaches. This article reports the effect of addressing impaired sleep on the frequency and intensity of posttraumatic headaches. We also report the effect of sleep hygiene counseling and prazosin treatment on cognitive function and daytime sleepiness.

METHODS

Veterans

This was an observational study of a cohort of 126 veterans with mild TBI caused by exposure to an explosion during deployment in OIF/OEF. The veterans in this cohort had comorbidities including frequent, severe headaches and residual deficits on neurological examination, neuropsychological testing, or both and often experienced PTSD associated with impaired sleep. This study was part of a Quality Assurance Monitor of the evaluation of OIF/OEF veterans at a regional VA Polytrauma Center. We assessed the veterans that we followed in a uniform manner. The veterans did not sign consent forms and we had no parallel control group. We collected information from the veterans in a prospective manner. Mental health professionals treated the veterans for PTSD and mood disorders at the same time that we treated the veterans for headaches. We evaluated all veterans at LSCVAMC, a second level Veterans Health Administration (VHA) Polytrauma Center responsible for most of Ohio. This study was approved and continuously reviewed by the Quality Assurance Committee of the Neurology and Quality Assurance Services and the Medical Executive Committee of the LSCVAMC. The LSCVAMC Institutional Review Board reviewed the data in this study, approved a waiver of Health Insurance Portability and Accountability Act authorization, approved a waiver of informed consent, and approved the data for submission for publication.

We drew the cohort of 74 veterans described in this study from a study group that consisted of 126 OIF/OEF veterans with mild TBI due to exposure to a combat-associated explosion, usually produced by an improvised explosive device. These veterans did not have a penetrating head injury. The criteria for mild TBI were that for each episode of TBI, the duration of loss of consciousness was <30 minutes, the duration of any alteration in mental state (e.g., confusion, disorientation, slowed thinking) following the TBI was <24 hours, and the period of any posttraumatic amnesia was <24 hours. These criteria are consistent with existing criteria for mild TBI [8,22–25]. The veterans were seen within 1 month of the time that they initially visited the LSCVAMC [16].

Each of the 126 veterans had a detailed neurological examination, neuropsychological testing, and an assessment for PTSD. The elements of the neurological examination were previously described [16]. Neuropsychological testing consisted of a battery of 21 tests that assessed (1) intelligence; (2) executive functioning, including attention and tracking, short term and working memory, and initiating, sustaining, and retrieving information; (3) language; (4) planning and problem solving; (5) visuospatial memory; (6) secondary memory and learning; (7) tests of effort to assess for malingering; (8) depression; (9) anxiety; and (10) personality and symptom validation. We considered neuropsychological testing results to be abnormal if a veteran demonstrated impaired performance on two or more tests. For tests that evaluated several aspects of cognitive performance, an individual needed to demonstrate impaired function on two or more elements for the test to be considered to support impaired performance. The specific neuropsychological tests were described previously [16].

We screened every veteran for PTSD using a four-question instrument described previously [16]. We referred veterans who acknowledged three questions on the PTSD screen, reported flashbacks, reported a history of hyperarousal or hypervigilance, or manifested hyperarousal or hypervigilance during the examination for further evaluation to a mental health professional trained and qualified to recognize and diagnose PTSD. The criteria for formal recognition of PTSD were previously described [16].

We described previously that 80 of the 126 veterans in the overall study group had abnormalities on neurological examination, neuropsychological testing, or both [16]. The veteran cohort that is described in this study consists of the 74 veterans who had headaches from within this group of 80 veterans.

In this study, 71 of the 74 veterans had PTSD. Mental health professionals treated this condition during the time of the study. The pharmacological treatment for PTSD consisted of citalopram (55 veterans), quetiepine (15 veterans), or trazadone (1 veteran). The medication dosages for

PTSD did not change during the 9-week intervention period. The most common medication and dosage were citalopram, 20 mg/day (51 veterans). During the interval between the end of the intervention period and the 6-month follow-up evaluation, mental health professionals caring for 22 veterans changed the dosage of the PTSD medication or changed the PTSD medication.

Characterization of Headaches

We queried each veteran about the presence of headaches. If the veteran had OIF/OEF deployment-associated headaches, we recorded the headache pattern, character, frequency, and severity. The highest pain level that a patient experienced during a headache was scored on a numerical pain rating scale from 0 to 10, where 0 = no pain and 10 = unbearable pain [26]. Close agreement exists between the 11-point numerical pain rating scale that we used here and visual analog pain rating scales [27–28]. The International Headache Society classification for headaches includes a distinct category for posttraumatic headaches [5]. The three usual patterns of headache associated with TBI are muscle tension headaches, migraines, or mixed tension and migraine headaches [1]. As previously described, we characterized each veteran's headaches as being tension-like, migraine-like, or mixed tension and migraine headaches based on whether the characteristics of the headaches fit the International Headache Society criteria for tension headaches, migraine headaches, or had features of both headache types [5,16]. The baseline distribution of headache types among the 74 veterans was 40.54 percent tension-like headaches, 18.92 percent migraine-like headaches, and 40.54 percent mixed-type headaches [16].

Repeated Cognitive Assessment

We used the Montreal Cognitive Assessment (MOCA) to repeatedly assess cognitive function. It was not part of the battery of neuropsychological tests described earlier. MOCA scores range from 0 to 30. The MOCA has been used to attain serial measures of cognitive function [29–30].

Sleep Assessment

We queried all veterans as to whether they had impaired sleep and the nature of the sleep impairment. We specifically questioned veterans about the restfulness of their sleep and the presence of nightmares. We asked each veteran whether their sleep was impaired and whether it was restful. The specific questions were (1) "Is your sleep impaired due to nightmares or for any other reason?" and (2) "When you awake from sleep at the end of your sleeping period, do you feel rested?" In addition, we used the Epworth Sleepiness Scale (ESS) to assess daytime sleepiness. ESS scores range from 0 to 24. The ESS is a subjective measure of sleepiness that has been validated and has high sensitivity and specificity [31].

Intervention

Because of the high frequency of sleep disorders and the veterans' desire to avoid medications that would compromise cognition or sexual function, we chose to address impaired sleep as the initial headache treatment. The initial intervention consisted of counseling the veterans about sleep hygiene [32–33] and using prazosin to address nightmares associated with PTSD [18]. Sleep hygiene counseling included the following instructions: (1) adopt a fixed bedtime; (2) avoid activities that may trigger flashbacks, including violent/graphic video games (such as "shooter games" or combat simulations), video or audio programs/movies about combat, or violent programs, particularly within 6 hours of bedtime; (3) stop watching television 1 hour before bedtime and engage in calming activities, such as reading or engaging in intimacy with your partner; (4) sleep only when sleepy or engage in a boring activity if not sleepy at bedtime; (5) avoid caffeinated beverages (veterans were counseled about beverages that contain caffeine such as coffee, sodas, and "power drinks"), nicotine, and alcohol within 6 hours of bedtime; (6) avoid sleeping during the day; (7) exercise during the day, but not within 4 hours of bedtime; (8) take a hot bath or shower about an hour before bedtime; and (9) if obesity is not an issue, eat a light snack before bedtime. We contacted the veterans every 2 weeks during the 9-week intervention period to reinforce sleep hygiene for a total of 5 counseling sessions.

The study group members were given headache education during clinic visits and invited to participate in group sessions involving other OIF/OEF veterans with pain issues. In the group sessions, we educated veterans about headaches and encouraged them to identify headache triggers. The sessions reinforced sleep hygiene education. We also educated veterans on activity management for maintaining physical activity and social interactions and reducing the physical and social isolation that can occur in association with pain. The sessions were interactive. We encouraged veterans to ask questions and share coping strategies. Of the 74 veterans in this study, 60 attended at least one group session. We encouraged the veterans to keep headache diaries that identified headache occurrence, character, and duration. When possible, we provided

education to family members and significant others identified by the veteran. We provided the headache education described previously to all veterans treated at the LSCVAMC.

Prazosin at bedtime was used to improve the quality of sleep. We began the dose at 1 mg QHS (at bedtime) and then increased the dose weekly to 2 mg, 4 mg, 5 mg, and 7 mg at bedtime. The treatment dose of prazosin was 7 mg at bedtime. We monitored the veterans for potential adverse reactions to prazosin, including abnormalities in laboratory tests of liver function, reductions in white blood cell counts, changes in bowel habits, and the development of a skin rash or pruritis. We monitored the following liver function tests at baseline, the end of the 9-week intervention period, and the end of the 6-month follow-up period: alkaline phosphatase, aspartate aminotransferase (AST or SGOT), alanine aminotransferase (ALT or SGPT), total bilirubin, direct bilirubin, total serum protein, and serum albumin. We counseled veterans about possible dose-dependent side effects of prazosin, including daytime somnolence, light-headedness, and postural hypotension. We instructed them that if light headedness or daytime somnolence developed, they should return to the previous dose for a week and then return to the weekly dose escalation.

Statistical Methods

The independent variables were presence of PTSD and whether a veteran took prazosin. The dependent variables were (1) number of headaches per month, (2) severity of headache pain, (3) MOCA score, (4) whether sleep was restful, (5) whether sleep was impaired, and (6) ESS score.

To examine the three hypotheses, we considered the following statistical methods in data analysis. For hypothesis 1, we simply used descriptive statistical methods by summarizing data numerically so that they can be better understood (**Table 1**) [34]. For hypothesis 2, we used the chi-square test to analyze the association of restful sleep with sleep hygiene counseling and prazosin [35]. For hypothesis 3, we assessed the dependent variables at baseline, 9 weeks after providing the initial sleep hygiene counseling and starting prazosin, and 6 months later. Linear mixed models (LMMs) were fitted for the repeated measures data. The conventional repeated measures analysis of variance (ANOVA) can be viewed as a special case of LMMs. We constructed ANOVA *F*-type tests [36] based on the LMMs to evaluate the effect of sleep hygiene counseling and prazosin on the dependent variables at the 0.05 significance level.

The **Figure** is a flow chart of this observational study. Within the study group of 74 veterans, 60 were taking prazosin at the completion of the 9-week evaluation period and during the 6-month follow-up period and 8 were not taking prazosin at the end of the evaluation period or at the end of the 6-month follow-up period. We used chi-square tests to examine the association of veteran's reporting of restful sleep or impaired sleep at baseline compared with the end of the 6-month follow-up period for the 60 veterans who took prazosin for the entire period and the 8 veterans who did not take prazosin [37]. To compare the effect of intervention between veterans who did or did not complete the dosing of prazosin, we fitted an LMM using only the baseline and 9-week data. We performed pairwise comparisons with associated ANOVA *F*-tests for headache pain, number of headaches, MOCA score, and ESS score.

We compared the veterans who were or were not taking prazosin 6 months after intervention period completion using the LMM. For the two subgroups of veterans who did (60 veterans) or did not take (8 veterans) prazosin for did entire period, we did pairwise comparisons of the headache pain, number of headaches, MOCA score, and ESS score at baseline versus the end of the 9-week intervention period, baseline versus the end of the 6-month follow-up, and the end of the 9-week intervention period versus the end of the 6-month follow-up period using

Table 1.
Effect of intervention consisting of sleep hygiene counseling and prazosin on daytime sleepiness, cognitive function, and headaches. We calculated *p*-values based on mixed-model analysis of variance (ANOVA).

Performance of Veterans ($N = 74$)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Baseline (mean ± SE)	16.10 ± 0.28	24.50 ± 0.49	7.28 ± 0.27	12.40 ± 0.94
After Intervention (mean ± SE)	7.28 ± 0.34	28.60 ± 0.59	4.08 ± 0.19	4.77 ± 0.34
p-Value by ANOVA *F*-Test	<0.001	<0.001	<0.001	<0.001

ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, SE = standard error of the mean.

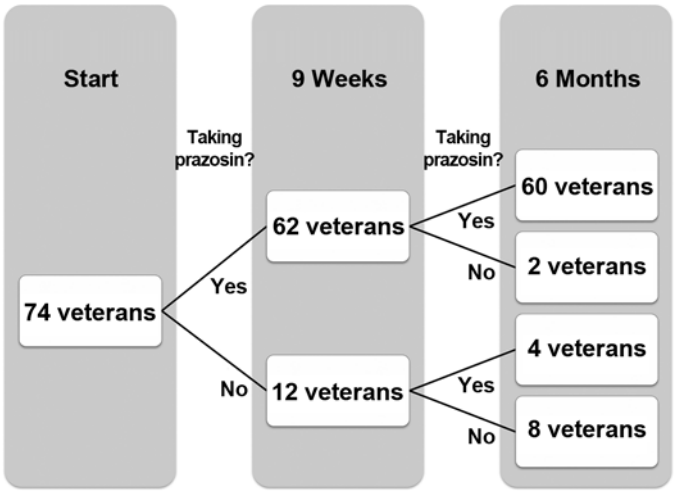

Figure.
Flow chart for veterans in this observational study. There were three study periods: baseline (Start), 9-week intervention period when veterans were initially introduced to prazosin and received sleep hygiene counseling (9 Weeks), and 6-month follow-up period (6 Months). Figure shows number of veterans taking prazosin or not taking prazosin at end of each study period and tracks prazosin usage histories of veterans.

ANOVA *F*-tests based on the LMM. Where applicable, we used an odds ratio (OR) and a 95 percent confidence interval (CI) to compare results. We chose the values used for comparing the veterans who did or did not take prazosin by using an OR either for clinical importance (pain score >6 associated with severe pain) or because that value permitted calculation of an OR. We used two-sample Kolmogorov-Smirnov tests to compare the distribution of headache types between groups of veterans who did or did not take prazosin [37]. In the tables, we reported statistical results as mean ± standard error of the mean with *p*-values from ANOVA *F*-tests.

RESULTS

Baseline

The **Figure** shows the distribution of patients in each phase of this observational study (baseline [Start], the end of the 9-week intervention period [9 Weeks], and the end of the 6-month follow-up period [6 Months]). We collected baseline demographic data on the veterans in the study group. The veterans were aged 29.4 ± 2.9 years (mean ± standard deviation) with a range of 20 to 62 years. There were five women (7%). All veterans had at least a high school education. Of the veterans, seven (9%) had graduated from college with a bachelor's degree, an additional four (5%) had an associate's degree, and five (7%) had taken some college courses without obtaining a degree. Thus, 21 percent had some college experience. None reported histories of episodes of TBI before military service. The interval from the final episode of TBI to the initial assessment was 124 ± 5 weeks with a range of 40 to 212 weeks.

Among our study group of 74 veterans with mild TBI and posttraumatic headaches caused by an explosion during deployment in OIF/OEF, 71 had PTSD and only 5 had restful sleep. Each of the 69 veterans who did not have restful sleep had PTSD with nocturnal arousals associated with nightmares, agitated sleep, or both. Among the five veterans who stated that their sleep was restful, three had nightmares occurring 1 to 3 times per week and a sleep partner noted that a fourth veteran was agitated during sleep. The veterans' baseline ESS scores indicated excessive daytime sleepiness (ESS > 8, **Table 1**). The baseline MOCA scores indicated a mild degree of cognitive impairment (**Table 1**).

At baseline, the veterans were experiencing an average of more than 12 headaches per month (**Table 1**). In addition, 96 percent had more than 4 headaches per month, 42 percent had more than 10 headaches per month, and 14 percent had daily headaches. The mean value of peak headache pain was >7 (**Table 1**).

Intervention

During the 9-week intervention period when prazosin was introduced, all of the veterans' other medications were kept the same. Mental health assessments occurred during this 9-week intervention period and medications for mood disorders or PTSD began after this period. In the 6-month follow-up period after the 9-week intervention period, 26 veterans received additional medications for their headaches, usually choline magnesium trisalisylate or another nonsteroidal anti-inflammatory medication to treat tension-like components of headache pain; zolmitriptan to abort migraine headaches; and an agent such as topirimate, metoprolol, tricyclic antidepressant medication, or divalproex sodium to prevent headaches. We explained the anticipated benefits and side effects associated with each medication and allowed the veterans to select specific medications based on the type of residual headache pain they were experiencing. PTSD treatment

continued after the 9-week intervention period for all veterans with PTSD. Medications and counseling session frequency for PTSD were adjusted according to the opinion of the treating mental health professional and with agreement from the veteran. During the 6-month follow-up evaluation, mental health professionals changed the dosage of PTSD medication or changed the medication for 22 veterans.

Side Effects Associated with Prazosin

All veterans received sleep hygiene counseling and initiated treatment of oral prazosin at bedtime. Hypothesis 1 was that the veterans would tolerate prazosin with a low incidence of side effects. The side effects that we assessed for were (1) postural hypotension or light-headedness, (2) increase in daytime sleepiness, (3) development of a skin rash, (4) change in bowel habits, (5) leucopenia, or (6) abnormalities of liver function. Of the 74 veterans, 62 (84%) completed the prazosin dosage schedule and remained on the medication through the end of the 9-week intervention period. None of the 62 veterans who took prazosin during the 9-week intervention period noted a side effect. The reasons that 12 veterans did not complete the prazosin dosage schedule were (1) prazosin was not perceived as beneficial (4 veterans), (2) prazosin increased daytime somnolence (4 veterans), (3) light-headedness (2 veterans), and (4) a desire to be vigilant at night and not wanting to sleep at night (2 veterans). Among the four veterans who did not complete the course of prazosin because they felt the medication was not useful, three (75%) reported restful sleep. The two veterans who wanted to be vigilant at night had PTSD and were not compliant with their medication treatment for PTSD during the intervention period. Thus, 6 of the 74 veterans (8%) experienced the side effects of excessive daytime sleepiness or light-headedness. An additional six veterans did not complete the initial titration of prazosin because they did not perceive a benefit from prazosin or because they wanted to remain vigilant at night.

During the 6-month follow-up period, the two veterans who experienced light-headedness agreed to be restarted on prazosin at 0.5 mg by mouth at night and increased the nighttime dose by 1 mg per week. They did not re-experience light-headedness or experience any other side effect. After the two veterans who wished to remain vigilant at night began to respond to treatment for PTSD, they were willing to take prazosin. The nightmares experienced by two veterans stopped in response to prazosin and they did not experience any adverse side effects. Two other veterans who did not have PTSD and did not feel that prazosin was beneficial, but who completed the initial prazosin dosing, stopped taking prazosin after the intervention period. At the end of the 6-month follow-up period, 64 (86%) out of 74 veterans were taking prazosin. Two of the veterans experienced light-headedness that resolved and four experienced excessive daytime sleepiness. No veteran taking prazosin developed a rash, reported a change in bowel habits, developed leucopenia, or had elevation of liver function tests.

Improvement in Sleep Associated with Intervention

Hypothesis 2 was that prazosin combined with sleep hygiene counseling would improve sleep. Among the 62 veterans who continued taking prazosin for the entire intervention period, 60 (97%) reported at baseline that their sleep was not restful and they had nightmares. Among these 62 veterans, 60 (97%) felt that the prazosin provided benefit in terms of their sleep. These 60 veterans reported that after reaching a nighttime prazosin dose of 7 mg, their sleep was restful and nightmare frequency was reduced or that they no longer had nightmares. For the two veterans who continued to take prazosin and did not note any benefit for sleep, both reported unimpaired sleep at baseline. **Table 1** demonstrates that the entire 74-veteran study group had a reduction in daytime sleepiness at the end of the intervention period.

Among the 12 veterans who did not complete the prazosin dosage schedule during the 9-week intervention period, 9 (75%) reported impaired, nonrestful sleep at baseline that did not improve during the 9-week intervention period. The other three veterans reported restful, unimpaired sleep that did not change during the 9-week intervention period. **Table 2** compares the ESS scores for the veterans who did or did not complete the upward dosing schedule of prazosin during the intervention period. The veterans who took prazosin had a reduction of the mean ESS score to below 8, a value indicating that they did not have excessive daytime sleepiness. The veterans who did not take prazosin showed improvement in the group ESS scores, but the mean remained above 8, indicating excessive daytime sleepiness.

Each of the 64 veterans who were taking prazosin at the end of the 6-month follow-up period reported that their sleep was restful and that they were having <1 nightmare per month. In contrast, only 4/10 veterans who were not taking prazosin reported restful sleep and 5/10 reported >1 nightmare per week. The proportion of veterans

reporting restful sleep increased from 2 percent at baseline to 100 percent ($p < 0.001$) at the end of the 6-month follow-up period among the veterans who were taking prazosin, while the fraction remained at 40 percent for those not taking prazosin at the end of the 6-month follow-up period. **Table 3** shows that the mean of the ESS scores for the 64 veterans taking prazosin was below the threshold value of 8 that indicates excessive daytime sleepiness. **Table 4** compares the performances of the 60 veterans who were taking prazosin at the end of the intervention period and during the entire 6-month follow-up period with the performances of the 8 veterans who were not taking prazosin at the end of the intervention and follow-up periods. The veterans taking prazosin had mean ESS scores below the threshold for excessive daytime sleepiness at the end of the intervention and follow-up periods and they had a reduction in their ESS scores between the ends of the intervention and follow-up periods. In contrast, the veterans who did not take prazosin had mean ESS scores above the excessive sleepiness threshold and did not improve between the ends of the intervention and follow-up periods.

Improvement in Cognitive Performance

At the end of the 9-week intervention period, the mean MOCA scores of the entire study group improved (**Table 1**). The veterans who took prazosin during the intervention period showed improvement in their MOCA scores, whereas the veterans who did not complete the prazosin dosing schedule did not improve their MOCA scores (**Table 2**). Similarly, at the end of the follow-up period, the veterans who took prazosin continued to have improved MOCA scores compared to baseline, whereas the veterans who did not take prazosin did not improve their MOCA scores (**Table 3**). The veterans who took prazosin during the intervention and follow-up periods had improved MOCA scores relative to their baseline values. The veterans who did not take prazosin did not improve their MOCA scores (**Table 4**).

Effect of Sleep Hygiene and Prazosin on Headaches

At the completion of the 9-week intervention period, the headache symptoms for the entire study group improved (**Table 1**). The veterans who completed the prazosin dosage schedule had reductions in headache

Table 2.
Comparison of effect of intervention between veterans who did or did not complete dosing of prazosin. We calculated *p*-values based on mixed-model analysis of variance (ANOVA).

Performance of Veterans ($N = 74$)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Completed Prazosin ($n = 62$)				
Baseline (mean ± SE)	16.10 ± 0.33	24.10 ± 0.26	7.18 ± 0.18	13.40 ± 1.07
After Intervention (mean ± SE)	6.37 ± 0.26	28.90 ± 0.15	3.58 ± 0.13	4.26 ± 0.35
p-Value by ANOVA *F*-Test	<0.001	<0.001	<0.001	<0.001
Did Not Complete Prazosin ($n = 12$)				
Baseline (mean ± SE)	15.90 ± 0.42	24.70 ± 0.53	6.50 ± 0.45	7.17 ± 0.66
After Intervention (mean ± SE)	12.00 ± 0.55	24.20 ± 0.53	6.67 ± 0.48	7.42 ± 0.72
p-Value by ANOVA *F*-Test	<0.001	NS	NS	NS

ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, NS = not significant, SE = standard error of the mean.

Table 3.
Comparison done at end of 6-month follow-up period of performance of veterans who were or were not taking prazosin. We calculated *p*-values based on mixed-model analysis of variance (ANOVA).

Performance of Veterans ($N = 74$)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Taking Prazosin ($n = 64$, mean ± SE)	3.97 ± 0.18	29.00 ± 0.13	2.39 ± 0.12	1.88 ± 0.14
Not Taking Prazosin ($n = 10$, mean ± SE)	10.50 ± 0.58	24.80 ± 0.51	5.80 ± 0.29	7.00 ± 0.54
p-Value by ANOVA *F*-Test	<0.001	<0.001	<0.001	<0.001
All Veterans	4.85 ± 0.31	28.40 ± 0.21	2.85 ± 0.17	2.57 ± 0.25

ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, SE = standard error of the mean.

Table 4.
Comparisons done at end of 6-month follow-up period of outcomes of veterans who were or were not taking prazosin at end of both 9-week intervention period and 6-month follow-up period. Analysis results are based on linear mixed models.

Performance of Veterans (*N* = 68)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Taking Prazosin (*n* = 60)				
Baseline (mean ± SE)	16.20 ± 0.20	24.00 ± 0.24	7.21 ± 0.20	13.60 ± 1.10
End of 9-Week Intervention (mean ± SE)	6.56 ± 0.22	28.60 ± 0.19	3.73 ± 0.22	4.60 ± 0.29
End of 6-Month Follow-Up (mean ± SE)	4.00 ± 0.19	28.90 ± 0.26	2.48 ± 0.21	2.26 ± 0.29
Significance of Comparisons	A, B, C	A, B	A, B, C	A, B, C
Not Taking Prazosin (*n* = 8)				
Baseline (mean ± SE)	16.00 ± 0.44	24.60 ± 0.55	6.55 ± 0.51	7.19 ± 0.72
End of 9-Week Intervention (mean ± SE)	12.50 ± 0.59	24.10 ± 0.55	6.75 ± 0.50	8.19 ± 0.79
End of 6-Month Follow-Up (mean ± SE)	10.90 ± 0.72	24.60 ± 0.62	5.65 ± 0.51	6.89 ± 0.71
Significance of Comparisons	A, B	—	—	—

Note: A = comparisons between baseline and 9-week values significant at 0.05 level, B = comparisons between baseline and 6-month values significant at 0.05 level, C = comparisons between 9-week and 6-month values significant at 0.05 level.
ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, SE = standard error of the mean.

frequency and intensity (**Table 2**). In contrast, the veterans who did not take prazosin did not have improvements in their peak headache pain or headache frequency (**Table 2**). At the end of the 9-week intervention period, 9 out of 12 veterans who were not taking prazosin had severe headache pain (pain score 6), compared with only 1 out of 62 veterans who took prazosin (OR = 183, 95% CI = 17.1 to 1,960.0). In addition, at the end of the 9-week intervention period, 10 out of 12 veterans who were not taking prazosin had 3 headaches per month compared with 15 out of 62 veterans who took prazosin (OR = 15.7, 95% CI = 3.08 to 79.60). There were no significant differences in headache pain levels or headache frequencies at baseline between the veterans who did or did not continue taking prazosin during the 9-week intervention period. Among the 62 veterans who took prazosin, the distribution of headache patterns at the beginning/end of the 9-week intervention period was 42 percent/58 percent had tension-like headaches, 19 percent/19 percent had migraine-like headaches, and 39 percent/23 percent had mixed-type headaches. During the 9-week intervention period for the veterans taking prazosin, 12 veterans who initially had mixed-type headaches lost the migraine features of their headaches and had only tension-like headaches at the end of the intervention period. Among the 12 veterans who did not continue taking prazosin, the distribution of headache patterns was (1) 33 percent had tension-like headaches, (2) 17 percent had migraine-like headaches, and (3) 50 percent had mixed-type headaches. The headache patterns for the veterans who did not take prazosin did not change during the intervention period. We performed a two-sample Kolmogorov-Smirnov test to compare the initial distributions of headache types for veterans who did or did not take prazosin during the intervention period. The resulting *p*-value was 0.67, indicating that the initial headache distributions were not significantly different.

The 64 veterans who took prazosin during the 6-month follow-up period had less intense headache pain and less frequent headaches compared with the 10 veterans who did not take prazosin (**Table 3**). Only 4 out of 64 veterans who were taking prazosin had peak headache pain that was >3. Those four veterans reported peak headache pain levels of 4. In contrast, every veteran who was not taking prazosin had a peak pain level of 5. Among the veterans taking prazosin at the end of the follow up period, 3 had no headaches, 51 had <3 headaches per month, 5 had 3 headaches per month, 6 had 4 headaches per month, and 2 had 5 headaches per month. Every veteran who was not taking prazosin had 5 headaches per month. The distribution of headache types at the end of the follow-up period for veterans taking prazosin was 6 percent no headaches, 53 percent tension headaches, 19 percent migraine headaches, and 22 percent mixed-type headaches. The headache distribution for veterans not taking prazosin was 40 percent tension headaches, 20 percent migraine headaches, and 40 percent mixed-type headaches. If one considered only those veterans who had headaches, the distributions of headache types between veterans who did or did not take prazosin were not different.

Table 4 shows that the veterans who took prazosin during the intervention and follow-up periods had progressive reductions in the intensities and frequencies of their headaches. The veterans who did not take prazosin did not improve their headache frequency or intensity.

DISCUSSION

We must consider the findings reported here in light of this being an observational report. This was not a controlled study. Several potential biases exist that may have influenced the findings. First, this is not a random sample of soldiers who sustained mild TBI during deployment in OIF/OEF. Not all veterans seek care with VHA after OIF/OEF deployment. Veterans who sustained TBI without residual manifestations or PTSD would be less likely to seek treatment through VA. In addition, the group of veterans reported here were all symptomatic with headaches and most had PTSD and impaired sleep. Second, the history of TBI was based on self-report of a remote event. In a combat environment, medical personnel focus on the seriously injured. Consequently, non-life-threatening events such as mild TBI are not well documented. As we noted before, some of the veterans in our study group may have underestimated the duration of changed consciousness [16]. Consequently, some veterans may have had moderate rather than mild TBI. Third, the data were not collected in a blinded manner. Some of the veterans who took prazosin may have reported lower headache pain intensity or headache frequency in an attempt to please the data collector, who was also one of their care providers. However, it seems unlikely that some of the veterans who took prazosin could have performed better on the MOCA simply because they wanted to please the data collector. We suggest that the results of this study serve as preliminary data to support a controlled study of sleep hygiene counseling and prazosin treatment for veterans with residual headaches following mild combat TBI and impaired sleep associated with PTSD.

The data supported the three hypotheses explored in this study. Hypothesis 1 was that OIF/OEF veterans would tolerate prazosin with a low incidence of side effects. Only 8 percent of veterans experienced a side effect, none of which was life threatening. The side effects were daytime somnolence (four veterans) and light headedness (two veterans). The light-headedness in the two veterans resolved when prazosin was reintroduced with a starting dose of 0.5 mg at bedtime. Two veterans, who initially were not complaint with treatment for PTSD, did not initially want to take prazosin because they wanted to remain vigilant at night. After these veterans accepted prazosin, their nightmares resolved and they reported restful sleep.

Hypothesis 2 was that prazosin combined with sleep hygiene counseling would improve sleep among OIF/OEF veterans with mild TBI. Several tools can be employed to assess an individual's sleep hygiene [38]. The ESS is an easy-to-administer questionnaire to assess daytime sleepiness and is a good indicator of the quality of nighttime sleep [31]. **Table 1** shows that ESS scores were improved after the intervention. **Tables 2** to **4** compare veterans who did or did not take prazosin. Veterans who received sleep hygiene counseling but did not take prazosin showed improvement in ESS scores, but they did not improve in terms of the perception of restful and unimpaired sleep. In contrast, the veterans who took prazosin had improvement in fraction with restful and unimpaired sleep and showed reduction in ESS scores. The data may indicate that sleep hygiene counseling alone can reduce daytime sleepiness. However, this was not a controlled study, so it is possible that improvement in ESS scores among the veterans who received only sleep counseling was due to something other than sleep hygiene counseling.

Hypothesis 3 was that veterans who took prazosin and received sleep hygiene counseling would have less severe headache pain and fewer headaches. **Tables 2** and **4** demonstrated that veterans who took prazosin had reductions in headache frequency and pain intensity. In contrast, the veterans who did not take prazosin showed no improvement in headache pain or headache frequency.

An additional benefit associated with prazosin usage was improvement in MOCA scores. The MOCA scores of the veterans who did not complete the prazosin dosage schedule did not improve. The improvement in sleep associated with prazosin possibly contributed to the improvement in MOCA scores. However, because this was not a controlled study, the improvement in MOCA scores may have been due to an effect not related to prazosin usage, such as improvement in scores associated with retesting after 9 weeks or again 6 months later. The lack of improvement in MOCA scores among the veterans who did not take prazosin argues against appreciable improvement resulting from repeating the testing after several months.

All veterans in this study received sleep hygiene counseling. Veterans who received sleep hygiene counseling but did not take prazosin did not have improvements in their headaches or MOCA scores (**Tables 2–4**). In this study, even though the veterans who received sleep hygiene counseling and took prazosin did better than the smaller group of veterans who did not take prazosin, it is not possible to clearly distinguish the beneficial effect of the sleep hygiene counseling compared with the prazosin treatment. Sleep hygiene counseling is beneficial in terms of improving sleep duration and reducing the time it takes for a person to fall asleep [39]. However, sleep hygiene counseling alone is often less effective than other interventions to improve sleep combined with sleep hygiene counseling [40–41]. In this study, sleep hygiene counseling and prazosin may have had complementary effects to improve sleep. By blocking nightmares in people with PTSD, prazosin prolongs sleep duration by preventing sleep interruptions [18–19]. Thus the two interventions may have synergized, with sleep hygiene counseling reducing the time it took for veterans to fall asleep and prazosin prolonging sleep. In studies of chronic headaches, behavioral interventions combined with pharmaceutical treatments have benefits that exceed the benefits obtained with either treatment alone [42–43].

At the completion of this study, 10 veterans were not taking prazosin. Four reported restful sleep, three of these four did not have PTSD, and none reported recurrent nightmares. A fifth veteran had excessive daytime sleepiness and was unaware that he snored. This fifth veteran had obstructive sleep apnea and his sleep improved in response to treatment with continuous positive airway pressure treatment at night. The remaining five veterans had nightmares that did not resolve on prazosin doses up to 7 mg at bedtime. Two of these five veterans with persisting nightmares agreed to treatment with higher doses of prazosin. One had resolution of her nightmares and restful sleep at a prazosin dose of 15 mg at bedtime; the other had nightmare resolution and restful sleep when he received 20 mg of prazosin at bedtime. Raskind et al. noted that some veterans required higher doses of prazosin at bedtime to stop nightmares [18].

An interesting question is whether the veterans who did not take prazosin did not do as well as the veterans who took prazosin because the veterans who did not take prazosin had more severe headaches at baseline. As stated in the “Results” section, the baseline distributions of headache types were not different when we compared the veterans who did or did not take prazosin during the 9-week intervention period or when we compared the veterans who did or did not take prazosin during the 9-week intervention period and during the 6-month follow-up period. The veterans who did or did not complete the prazosin dosage schedule during the 9-week intervention period had similar baseline values for ESS scores, MOCA scores, and pain levels (**Table 2**). **Table 2** shows that the veterans who did not take prazosin during the 9-week intervention period had fewer headaches per month ($p < 0.001$). Comparing the veterans who took or did not take prazosin during both the intervention and follow-up periods, the two groups had similar baseline values for ESS scores, MOCA scores, and headache pain (**Table 4**). **Table 4** shows that the veterans who did not take prazosin during the intervention and follow-up periods had fewer headaches per month ($p < 0.001$). Therefore, it does not appear that the veterans who did not take prazosin had more severe headaches at baseline.

There are complex interactions between chronic pain and sleep. Chronic pain is often associated with impaired sleep [44–50]. However, impaired sleep can also alter pain perception, which can heighten the perceived pain severity [51]. Sleep deprivation can trigger migraines and other headaches and increase their perceived pain intensity [49–50,52]. We previously noted that veterans with impaired sleep reported more severe pain [16].

In addition to intensifying headache pain, sleep deprivation can compromise cognitive function [47,53]. Disruption of a normal sleep-wake cycle can desynchronize hormones that are usually synchronized with the circadian cycle. People who develop desynchronization of circadian hormones associated with disruption of a regular sleep-wake cycle developed cognitive impairment with impaired attention and reduced capacity to learn [53]. Pain combined with sleep deprivation will compromise several aspects of cognitive performance. Even if one considers the adverse effect of impaired sleep in cognitive performance, chronic pain itself has an adverse effect on cognitive performance [47].

There has been controversy as to whether prolonged symptoms in combat veterans who had sustained mild TBI were the result of residual damage to the brain or due solely to other conditions such as PTSD [54–55]. The veterans in this study had minor neurological deficits that might be missed by a physical examination that did not focus on neurological function and did not include formal testing of olfaction [16]. The mild neurological deficits were markers

of cerebral injury that had not completely resolved. That the veterans had appreciable improvements with interventions to improve sleep that were delivered in parallel with psychiatric treatment for PTSD indicates that the initial symptoms our veterans had were not due to irreversible neurological injury [55]. As suggested above, improving sleep may have improved cognitive performance and improved headaches. It is possible that by improving their sleep, the veterans in our study became more responsive to other treatments for headaches and stress. We feel that the prolonged symptoms seen in veterans with mild TBI due to combat exposure to explosions can be amenable to treatment, provided that the neurological, psychological, and sleep issues are simultaneously addressed in a manner that engages the veterans in their treatment.

CONCLUSIONS

We found that prazosin combined with sleep hygiene counseling was an effective initial treatment for a group of OIF/OEF veterans with headaches associated with histories of mild TBI from exposure to an explosion in combat. Prazosin was well tolerated. In association with prazosin treatment, veterans had reduced headache intensity and frequency, reduced daytime sleepiness, and improved performance on the MOCA. We believe that the prazosin and sleep hygiene counseling improved sleep by reducing the amount of time it took to fall asleep and preventing nocturnal arousals due to nightmares. This was not a placebo-controlled clinical trial. We must consider the findings in this study with caution until they are supported in a controlled clinical trial.

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Author Contributions:

Performed neurological examinations and cognitive screens: R. L. Ruff.

Collected data on sleep and headache type, frequency, and pain level: R. L. Ruff.

Prescribed prazosin and queried veterans about subjective side effects: R. L. Ruff.

Ordered tests to evaluate alteration in blood counts of liver function associated with prazosin usage: R. L. Ruff.

Provided sleep hygiene counseling and headache education: S. S. Ruff.

Analyzed data: X.-F. Wang.

Drafting of manuscript: R. L. Ruff, S. S. Ruff, X.-F. Wang.

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