Management of mTBI Persistent Postconcussive Symptoms: Focus on Headache and Sleep Disturbance

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The Nature of an Emerging and Unprecedented Problem

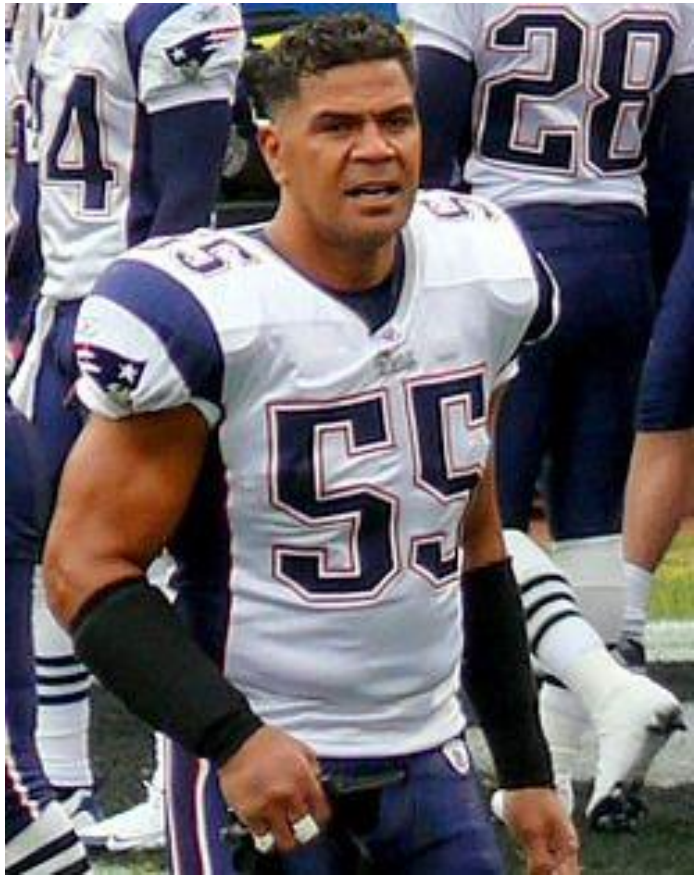
Helmand Province, Afghanistan. July 13, 2009. (*MSNBC*)

2.5 million Service Members have been deployed to

Iraq and Afghanistan

Los Angeles Times

Junior Seau had degenerative brain disease when he committed suicide



POLL SLIDE #1

- Do you provide clinical care for Veterans, service members, or civilians with mild traumatic brain injury?
  - YES
  - NO

POLL SLIDE #2

- What is your professional discipline:
  - Social Worker
  - RN
  - ARNP
  - PA
  - Clinical Psychologist
  - Physician
  - PhD Research Scientist

Chronic Postconcussive Headache in OEF/OIF/OND Veterans

- Estimated 19% of OEF/OIF/OND Veterans have sustained deployment-related mTBI
- Majority of mTBIs are result of blast concussion
- Prevalence of post-traumatic headaches (PTHAs) is approximately 40%

Chronic Postconcussive Headache

- International Classification of Headache Disorders defines PTHA:
  - Secondary HA precipitated by head trauma
  - In practice, new onset HAs within months of trauma

- Postconcussive headaches that persist for 3 months or more are considered chronic

Chronic Postconcussive Headache

- Tendency for PTHAs to become chronic is increased by:
  - Sleep deprivation
  - PTSD
  - Depression

Chronic Postconcussive Headache

- In a recent cross sectional study of 978 soldiers with deployment-related concussion, 20% met criteria for chronic daily headaches (15 days or more/month)
  - 4-5-fold higher than in general population
  - 66% had headaches with migraine features

Theeler et al, Headache 52(5):732-738, 2012.

Characteristics of Chronic Postconcussive Headache

- Considered to be one of most disabling and difficult to treat headache syndromes
- Injudicious use of opioids or other analgesics can provoke superimposed rebound ("medication over-use") headaches, particularly in those with frequent headaches at baseline
- "Medication over-use" headaches occur in 19-42% of patients with PTHA

Chronic Postconcussive Headache in Iraq/Afghanistan Veterans

- In civilian TBI population, PTHA tends to be tension-type, migraine or mixed

- In military combat population, headaches with migraine features predominate
- Migraine results in significantly more functional impairment and more sick call days than other types of headaches
  - 77% of migraine attacks interfered with duty performance on a mean of 2.4 days per month

Treatment Outcomes of Chronic Post-Traumatic Headaches After Mild Head Trauma in US Soldiers: An Observational Study

- Retrospective cohort study of 100 soldiers treated with migraine prophylaxis for chronic PTHA at Madigan Army Medical Center Neurology Clinic
  - 77 had blast PTHA
  - 23 had non-blast (impact) PTHA
  - Multiple concussions significantly more common in those with blast PTHA (51% vs. 23%)

Erickson et al, Headache 51(6):932-944, 2011.

Treatment of Blast Concussion Migraine is Challenging

- Blast concussion migraine was usually responsive to acute abortive therapy with a triptan
  - 77% reported reliable headache relief within 2 hours
  - Triptans equally effective in blast and non-blast PTHA

- However, compared to impact postconcussive migraine, blast postconcussive migraine was poorly responsive to standard migraine prophylaxis (TCAs, propranolol, valproate, topiramate)

Erickson et al, Headache 51(6):932-944, 2011.

Change at 3 Months in Headache Frequency in Response to Migraine Prophylaxis in Blast vs. Impact PTHA

	Headache (Days/Months)				
	Baseline Mean (SD)	Follow-Up Mean (SD)	Change Mean (%)	*P* Value	Responders*
Blast PTHA (n=77)	17.3 (9.2)	15.8 (10.4)	-1.5 (-9.1%)	0.21	22/77 (29%)
Impact PTHA (n=23)	16.5 (9.2)	9.8 (8.7)	-6.7 (-41%)	0.003	13/23 (57%)

*Defined as ≥ 50% decline in headache frequency at follow-up compared to baseline.

Erickson et al, Headache 51(6):932-944, 2011.

Sleep Disruption by Norepinephrine at CNS Alpha-1 Adrenoreceptors

- Disrupts REM sleep
- Increases light sleep
- Shortens total sleep time.

Prazosin

- A generic lipid-soluble alpha-1 adrenoreceptor (AR) antagonist introduced in 1973 as "Minipress" for treatment of hypertension
- Short duration of action (6-10 hours)
- Costs pennies per day
- In 2012, prescribed to 17% of all Veterans in VA health care systems with a PTSD diagnosis.

Does the PTSD Drug Prazosin Reduce Blast PTHA in OEF/OIF Veterans?

- OEF/OIF Veterans with blast concussion PTHA have a high prevalence of comorbid PTSD trauma nightmares and sleep disturbance
- Robert Ruff, MD, VA Director of Neurology, used open label prazosin to treat comorbid PTSD in OEF/OIF Veterans with blast mTBI manifested by PTHA and other postconcussive symptoms[1]
- Prazosin is a CNS-active alpha-1 adrenoreceptor antagonist demonstrated effective for combat PTSD trauma nightmares, sleep disruption, and global clinical status[2,3,4]

[1]Ruff et al, J Rehabil Res Dev 46:1071-1084, 2009.
[2]Raskind et al, J Clin Psychiatry 63:565-568, 2002.
[3]Raskind et al, Biol Psychiatry 61:928-934, 2007.
[4]Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

An Open Label Prazosin and Sleep Hygiene Trial for OIF/OEF Veterans with Blast mTBI with Comorbid PTSD (N=74)

	Baseline	Week 9	p value
Headaches per month	12.4 ± 8.1	4.8 ± 2.9	< 0.001
Headache intensity	7.1 ± 1.4	4.1 ± 1.6	< 0.001
Daytime sleepiness (Epworth)	16.1 ± 2.4	7.3 ± 2.9	< 0.001
% subjects with “restful and restorative” sleep	7.0%	87.8%	< 0.001
Montreal Cognitive Assessment	24.1 ± 2.0	28.1 ± 2.2	< 0.001

Ruff et al, J Rehabil Res Dev 46:1071-1084, 2009.

- Data from our recent positive RCT of prazosin for PTSD combat trauma nightmares in active duty combat soldiers is consistent with beneficial effects of prazosin on PTHA and sleep

Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Homas D, Hill J, Daniels C, Calohan J, Millard SP, Rohde K, O'Connell J, Pritzl D, Feiszli K, Petrie EC, Gross C, Mayer CL, Freed MC, Engel C, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry 170:1003-1010, 2013.

Active Duty OEF/OIF Prazosin RCT

- Parallel group RCT (1:1) at Joint Base Lewis McChord, WA
- Active duty OIF/OEF soldiers with combat operations PTSD (CAPS > 50) and distressing trauma nightmares (at least two nights/week)
- Majority of participants had comorbid mTBI

Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

Design Methodology

- 6-week dose titration to maximum 20 mg qhs and 5 mg midmorning (mean achieved dose 15 mg qhs and 4 mg midmorning)
- Study duration 15 weeks
- Outcome measures:
  - Total Clinician Administered PTSD Scale (CAPS)
  - CAPS “recurrent distressing dreams” item
  - Pittsburgh Sleep Quality Index
  - Clinical Global Impression of Change
  - Adverse Events (including headache)

Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

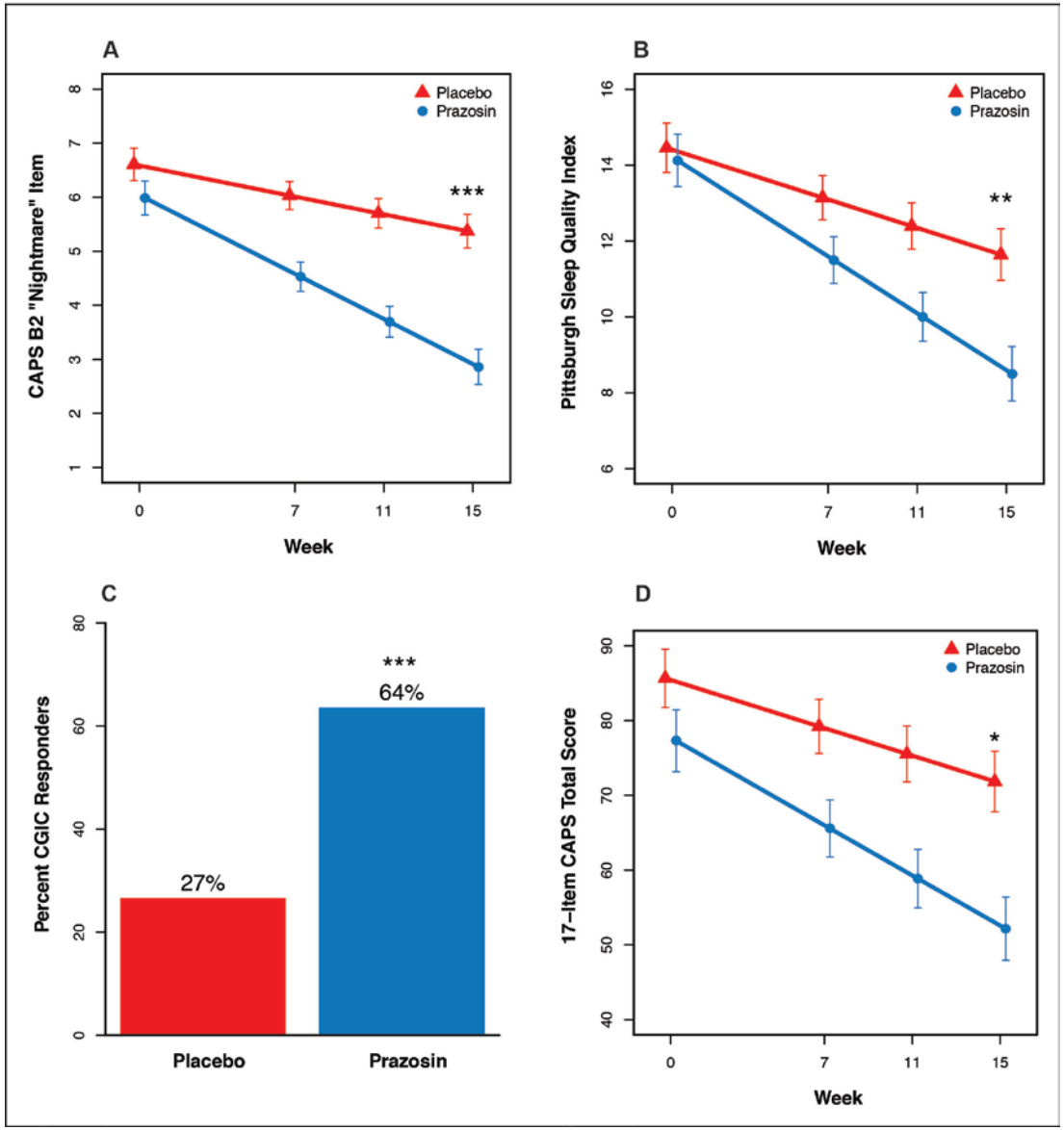
GOT NIGHTMARES?

Combat Nightmare Reduction Initiative

(253) 968-4735

MAMC

Effects on PTSD Outcome Parameters in Combat Soldiers Randomized to Prazosin (n=32) or Placebo (n=35)



Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

Emergent and Clinically Worsening Adverse Events

	Prazosin (n=32)	Placebo (n=35)
Syncope	2	0
Dizziness	6	6
Drowsiness	1	2
Depressed mood	0	2
Headache*	1	7
Nasal congestion	5	2
Nausea	2	5
Palpitations	4	1

*more frequent in placebo condition, $p < 0.05$

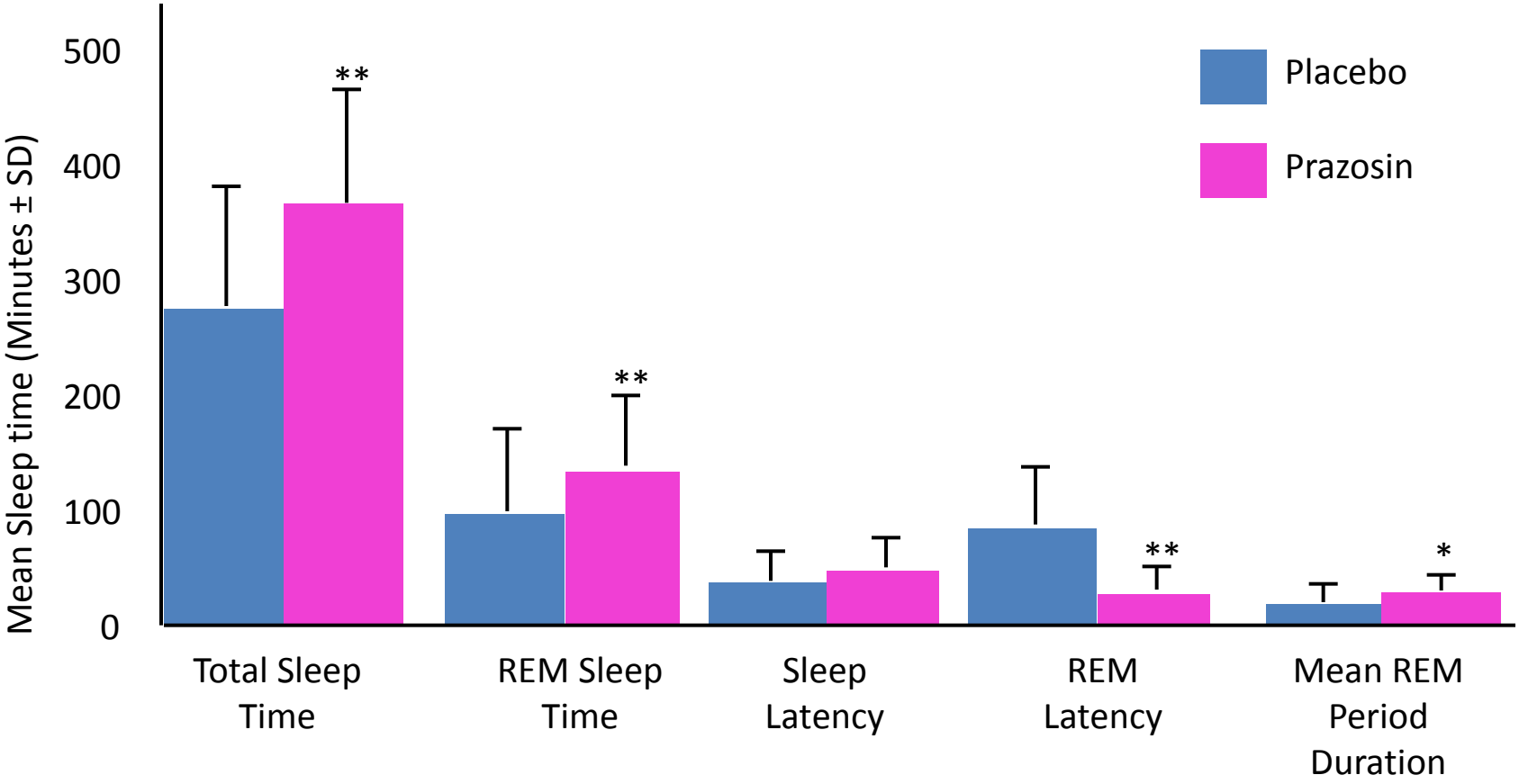
Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

Participants with Chronic Headaches at Baseline

- Of participants who had headaches prior to randomization:
  - 20% in placebo group had improvement or resolution of headache
  - 50% in prazosin group had improvement or resolution of headaches

Raskind et al, Am J Psychiatry 170:1003-1010, 2013.

Effects of Prazosin vs. Placebo on Sleep Measures in PTSD Subjects with Nocturnal Symptoms



*Significant difference between prazosin and placebo group by repeated measures ANOVA

*$p < 0.05$, **$p < 0.01$

Taylor et al, Biol Psychiatry 63:629-632, 2008.

Prazosin: Adverse Effects

- Generally, very well tolerated.
- “First dose” hypotension avoided with low dose initiation - but some vets need titration to 20 mg or more.
- Orthostatic dizziness more common in young women and persons already on a beta-blocker or ED drug.
- Concurrent use with trazodone may slightly increase priapism risk.
- Nasal congestion, peripheral edema, palpitations.

Conclusion

- Results of these studies provide rationale for a placebo-controlled trial of prazosin for blast concussion PTHA
- This study should evaluate relationship between sleep and PTHA