Prazosin for the Treatment of Combat-Related Nightmares in Military Veterans with PTSD

Jess Calohan, DNP, MN, PMHNP-BC
Lieutenant Colonel, United States Army
Program Chair, Psychiatric Mental Health Nurse Practitioner Program
Daniel K. Inouye Graduate School of Nursing
Uniformed Services University of the Health Sciences

DISCLOSURES

- The opinions or assertions contained herein are the solely the views of the author and are not to be construed as official or reflecting the views of the Department of the Army or the Department of Defense.
- Discussion of use of medications include non-FDA or “off-label” indications; prescribers are advised to use their own clinical judgment in assessing risks, benefits, adverse effects and treatment alternatives when using medications “off-label.”
- The speaker has no conflicts of interest to disclose.

Learning Objectives

- Examine the impact of sleep disturbance on level of functioning in military veterans with Post-Traumatic Stress Disorder.
- Describe the standardized titration protocol for Prazosin in treating military veterans with combat-related nightmares.
- Identify standardized tools to evaluate outcomes in military veterans with combat-related nightmares receiving treatment with Prazosin.
“Sleep that knits up the raveled sleeve of care, the death of each day’s life, sore labor’s bath, balm of hurt minds, great nature’s second course, chief nourisher in life’s feast.”

― William Shakespeare, Macbeth

“A good laugh and a long sleep are the best cures in the doctor’s book.”

― Irish Proverb

“Some people talk in their sleep. Lecturers talk while other people sleep.”

― Albert Camus

http://www.quotegarden.com/sleep.html

Combat-Related Nightmares

- Sleep disturbance is a core symptom of PTSD
- A foundational component that significantly influences functional impairment
- Reported by 50-70% of Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF) combat veterans with PTSD1

Stress and HPA Axis

- Hippocampus, Amygdala & HPA axis involved in stress circuits
- Both may be sensitized in PTSD
- HPA axis normal response to stress: release of CRF $\rightarrow$ ACTH $\rightarrow$ glucocorticoids $\rightarrow$ negative feedback on CRF $\rightarrow$ stop stress response
- Resulting neurotransmitter cascade:
  - release of glutamate and norepinephrine $\rightarrow$ “fight or flight”
  - response $\rightarrow$ GABA attenuates Glutamate and Norepinephrine
  - “fight or flight” stops


Neurobiological Underpinnings of PTSD

- Hypothalamic-Pituitary-Adrenal Axis
  - Negative feedback loop is dysregulated
    - Hypercortisolism (near term) then, Hypocortisolism (chronic)
    - Cortico-Releasing Factor over activity in the brain leading to release of norepinephrine from the locus coeruleus
    - Anatomical changes in the brain region that inhibits the HPA axis
- Neurotransmitters alterations
  - Serotonin
  - Norepinephrine
  - GABA
  - Glutamate


Neurobiological Underpinnings of Combat-Related Nightmares

- The locus coeruleus “shuts down” during normal REM sleep
  - no norepinephrine release.
- In PTSD, locus coeruleus remains “active” norepinephrine is released during REM sleep, disrupting REM

Prazosin

- **Background**
  - One of the few lipid soluble alpha-1 antagonists
  - A non-sedating generic that has been used for decades to treat hypertension and BPH
  - Decreases/eliminates the effect of norepinephrine during REM sleep
  - Initially found effective for trauma nightmares in Vietnam veterans¹
  - Reports of improved sleep quality and duration
  - Marked decrease in frequency intensity of nightmares
  - Well tolerated; improvement is dose related
  - Discontinuing medications after improvement associated with return of nightmares
  - Potential to reduce co-morbid alcohol abuse


Evidence of Prazosin Efficacy for Trauma Nightmares and Global Function

- In Vietnam veterans, a crossover placebo-controlled study (n = 10)¹ and a parallel group placebo-controlled study (n = 34)² positive improvement in sleep duration and quality, reduction in nightmares

- In civilians, a crossover study (n = 13) positive and sleep duration 90 minutes longer than with placebo³


Evidence of Prazosin Efficacy for Trauma Nightmares and Global Function

- In OIF deployed in a combat zone, a prospective study (n = 13) positive improvement in sleep duration and quality, reduction in nightmares and improved overall level of functioning¹

- In OIF/OEF combat veterans, a double-blind placebo RCT (n = 56, 29 placebo and 27 prazosin) positive improvement in sleep duration and quality, reduction in nightmares and improved overall level of functioning²

¹Calohan, J. et al., (2010).
Nightmare Reduction Initiative

- Stigma of seeking help for PTSD
- Focus on sleep disturbance rather than PTSD
- Recruit for study participation
- Engage and coordinate care for Service Members

Kim, C. et al., (2009)

Prescribing Prazosin

- Prazosin (Minipress) 1mg-20mg
  - Dose initially at 1mg for two nights to assess for “first-dose effect.” Has been associated with orthostatic hypotension with first dose. Also possibility of reflex tachycardia in the AM upon exertion
  - If pt is tolerates medication and no improvement in nightmares, then increase dose to 2mg HS for four nights. Continue titrating dose upwards by 2mg q 4 days to effect
  - Monitoring: initial orthostatic and ongoing BP monitoring
  - Also can consider low-dose during the day (mid-AM) 2-6mg to address residual hyperarousal symptoms

Outcome Evaluation Tools
- Clinician Administered Post-Traumatic Stress Scale
- Clinical Global Impression of Change

CAPS Sleep Items (B2)

Frequency
How many times was bedtime problem?
0 Never
1 One a week
2 Two a week
3 Several times a week (3 or 4)
4 Daily or almost every day (5 or 6)

Sleep onset problems? Y N
Mid-sleep awakening? Y N
Early m. awakening? Y N

Total # hrs sleep/night
Desired # hrs sleep/night

Intensity
How much of a problem do you have with your sleep? (How long did it take you to fall asleep? How often did you wake up during the night? How often did you wake up earlier than you wanted to?)
0 No sleep problems
1 Mild, slightly longer latency, or minor difficulty staying asleep (e.g. 30 minutes loss of sleep)
2 Moderate, definite sleep disturbance, clearly longer latency, or clear difficulty staying asleep (30-90 minutes loss of sleep)
3 Severe, much longer latency, or marked difficulty staying asleep (90 minutes to 3 hrs loss of sleep)
4 Extreme, very long latency, or profound difficulty staying asleep (> 3 hrs loss of sleep)
### CAPS Nightmare Items (D2)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>Never</td>
</tr>
<tr>
<td>1 a week</td>
<td>Mild</td>
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<tr>
<td>2 a week</td>
<td>Moderate</td>
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<tr>
<td>3 a week</td>
<td>Severe</td>
</tr>
<tr>
<td>Daily</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

**Frequency**
- Have you ever had unpleasant dreams about (EVENT)?
- Describe a typical dream.
- How often have you had these dreams in the past month?

**Intensity**
- How much distress or discomfort did these dreams cause you? Did they ever wake you up?
- Did your dreams affect anyone else?

**Description/Examples**
- When you woke up?
- How long did it take you to get back to sleep?

### Clinical Global Impression of Change

- Prazosin is effective for treating combat-related nightmares, improving not only sleep, but overall quality of life and functioning.
- Can also be used during the day for residual hypervigilance symptoms.
- Potential secondary effects of reducing ETOH cravings and drinking days in patients with PTSD.
- Easy to use clinician-rated assessment and outcome tools.

### Summary

- CAPS Sleep and Nightmare Items
- Clinical Global Impression of Change
Questions?

Jess Calohan, DNP, MN, PMHNP-BC
Lieutenant Colonel, United States Army
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Daniel K. Inouye Graduate School of Nursing
Uniformed Services University of the Health Sciences
jess.calohan@usuhs.edu

References


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