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

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DISCLOSURES

• The opinions or assertions contained herein are the sole 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 PTSD

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 → ACTH → glucocorticoids → negative feedback on CRF → stop stress response
• Resulting neurotransmitter cascade:
  - release of glutamate and norepinephrine → "fight or flight" response → 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)
  - Cortic-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 veterans\(^1\)
  - 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 placebo\(^3\)

\(^3\)Taylor F. et al., (2008).

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 functioning\(^1\)

- 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 functioning\(^2\)

\(^1\)Calohan, 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

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 AN 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)

**Intensity**

- How often did you have any problems falling or staying asleep? What effect do these have on your daily functioning and quality of life?

**Severity**

- How much of a problem did you have with your sleep? (How many hours of sleep were lost?)
- How many days did you lose sleep over the past week?
- How many total hours did you lose each night?

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<table>
<thead>
<tr>
<th>Item</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often did you have a hard time falling asleep?</td>
<td>No sleep problems</td>
</tr>
<tr>
<td>How often did you have problems staying asleep?</td>
<td>Mildly delayed sleep latency, or minimal difficulty staying asleep</td>
</tr>
<tr>
<td>When did you start having problems sleeping?</td>
<td>Moderately delayed sleep latency, clear difficulty staying asleep</td>
</tr>
<tr>
<td>When did you start having problems sleeping?</td>
<td>Severe, much delayed latency, or marked difficulty staying asleep</td>
</tr>
<tr>
<td>When did you start having problems sleeping?</td>
<td>Extremely delayed latency, or profound difficulty staying asleep</td>
</tr>
<tr>
<td>How many total hours did you lose each night?</td>
<td>[Enter]</td>
</tr>
<tr>
<td>How many total hours did you lose each night?</td>
<td>[Enter]</td>
</tr>
</tbody>
</table>

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*Kim, C. et al., (2009)*
**CAPS Nightmare Items (D2)**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Description/Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Never</td>
<td></td>
</tr>
<tr>
<td>1 One a week</td>
<td></td>
</tr>
<tr>
<td>2 Two a week</td>
<td></td>
</tr>
<tr>
<td>3 Several times a week (3 or 4)</td>
<td></td>
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<tr>
<td>4 Daily or almost every day (5 to 7)</td>
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</tr>
</tbody>
</table>

**Clinical Global Impression of Change**

**Summary**

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

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References


References (Cont.)