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TITLE:  A Placebo-Controlled Augmentation Trial of Prazosin for Combat Trauma PTSD

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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
This study consists of a 14-week, two parallel group, randomized placebo controlled trial to evaluate the efficacy and tolerability of the alpha-1 adrenergic antagonist, prazosin, for reducing trauma nightmares and sleep disturbance and improving global function and sense of well-being, in 210 OIF and OEF combat-exposed returnees with PTSD and persistent trauma-related nightmares and disrupted sleep. A secondary aim is to assess efficacy of prazosin for reducing total PTSD symptoms, reducing symptoms of depression, improving quality of life, and reducing alcohol craving.
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Introduction:
The objective of this randomized controlled trial (RCT) has been to evaluate the efficacy and
tolerability of the alpha-1 adrenergic antagonist prazosin compared to placebo for combat stress-
related nightmares, sleep disturbance, and global function in combat trauma-exposed Service
Members who are in garrison at Joint Base Lewis McChord (JBLM). The secondary objectives of
this trial are to assess the efficacy of prazosin for reducing total PTSD symptoms, reducing
symptoms of depression and improving quality of life.
Active duty soldiers who have experienced combat in OIF/OEF/OND and who have
persistent combat stress-related nightmares and sleep disturbance in the context of combat trauma
PTSD have been enrolled in the study. Participants undergo a flexible dose titration period followed
by optimal dose treatment for a total of 15 weeks including the titration period. Primary and
secondary outcome measures assess nightmares, sleep disturbance, PTSD severity by total CAPS
score, depression, global function, and quality of life and are administered every four weeks (weeks
7, 11 and 15).

Body:
We have successfully launched and brought to a halfway point preplanned interim
analysis what, to our knowledge, is the first ever medication randomized controlled trial for
PTSD (or any other behavioral disorder) performed in US active duty combat experienced
Service Members. Our active outreach approach to recruitment across JBLM has successfully
attracted volunteers for research participation, and also has provided support to the Psychiatry
Service mission at Madigan Army Medical Center (MAMC) and JBLM.

Key Research Accomplishments
- We performed a planned “halfway” interim analysis on the first 67 randomized subjects.
  54 had at least one full behavioral outcome (the evaluable sample) and 49 completed
  the entire 15-week trial. An Intent to treat linear mixed effects models analysis utilizing
data from all randomized subjects has been performed.

Reportable Outcomes
Prazosin was significantly superior to placebo for all three primary outcome measures. CAPS
B2 nightmare score decrease from baseline to end point was 3.1 ± 0.3 (mean ± SE) in the
prazosin group vs. 1.2 ± 0.3 in the placebo group (difference in change from baseline p < 0.001,
95%, CI for difference in change from baseline [1.0, 2.8]). PSQI decrease from baseline to
endpoint was 5.6 ± 0.7 in the prazosin group vs. 2.8 ± 0.6 in the placebo group (difference in
change from baseline p=0.004, 95% CI [0.9, 4.6]) adjusted per cent CGIC responders
(“markedly” or “moderately” improved for prazosin subjects was 64% (95% CI [44%, 79%]
compared to 26% (95% CI [14%, 44%] for placebo subjects (difference in per cent responders p
< 0.001, odds ratio 4.9, 95% CI [1.9, 12.3]. Prazosin was well tolerated. These data are
presented graphically in the attached poster presented 3 December 2012 at the American
College of Neuropsychopharmacology Annual Meeting. A manuscript describing these results is
under consideration by the American Journal of Psychiatry.

Conclusions
After review of the interim data analysis by the MAMC data monitoring officer and IRB, they
concluded that randomization should be halted because of clear efficacy and clinical availability
of prazosin. MAMC Psychiatry has requested that VA study personnel continue to follow
completed subjects for ongoing care. This will assist the MAMC clinical care mission and also
enable obtaining long-term follow-up (open label) data through June 2013 on service members
initially randomized to and continued on open label prazosin, as well as on service members
initially randomized to placebo and switched to open label prazosin for persistent PTSD
symptoms at end of double blind. We also plan a number of additional data analyses and manuscript preparation during the next 6 months. These include differential effects on prazosin response of a maintenance antidepressant, an analysis of concomitant non-psychotropic medications and medical conditions, and others.

References (for background)


Appendices
N/A

Supporting Data
Pending
A Placebo-Controlled Augmentation Trial of Prazosin for Combat Trauma PTSD

PI: Murray A. Raskind, MD  
Org: VA Puget Sound – Seattle Institute for Biomedical & Clinical Research

Problem, Hypothesis and Military Relevance

- **Problem**: Preliminary data in Vietnam Veterans suggested prazosin efficacy for PTSD nightmare, sleep disruption, global status, and overall PTSD.

- **Hypothesis**: Prazosin is more effective than placebo for PTSD nighttime symptoms, function, and overall PTSD in active duty soldiers returned from combat deployments to OEF/OIF/OND.

- **Outcome measures are**: CAPS, B-2 nightmare item, Pittsburgh Sleep Quality Index (PSQI), Clinical Global Impression of Change (CGI) anchored to function, and 17 item CAPS total score.

- **Military Relevance**: PTSD is a common cause of distress and disability in service members and Veterans.

Accomplishments

We have completed the efficacy phase of this study. Prazosin was significantly superior to placebo for all primary outcome measures. CAPS B2 nightmare score decrease from baseline to end point was $3.1 \pm 0.3$ (mean ± SE) in the prazosin group vs. $1.2 \pm 0.3$ in the placebo group (difference in change from baseline $p < 0.001$, 95% CI for difference in change from baseline [1.0, 2.8]). PSQI decrease from baseline to endpoint was $5.6 \pm 0.7$ in the prazosin group vs. $2.8 \pm 0.6$ in the placebo group (difference in change from baseline $p=0.004$, 95% CI [0.9, 4.6]). Per cent CGI responders (“markedly” or “moderately” improved) for prazosin subjects was 64% (95% CI [44%, 79%]) compared to 26% (95% CI [14%, 44%]) for placebo subjects (difference in per cent responders $p < 0.001$, odds ratio 4.9, 95% CI [1.9, 12.3]).

<table>
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<th>Activities</th>
<th>FY:</th>
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<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>Start-up activities</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Recruit, enroll, and perform all study procedures; double data entry, data cleaning. Prelim data analyses</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Long term open label clinical follow-up of randomized service members. Collection of long term data and secondary data analyses, manuscript preparation</td>
<td></td>
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<td>Total Budget (1,776,722)</td>
<td>355K</td>
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Prazosin is effective for overall PTSD (17 items CAPS) and Clinical Global Impression of Change (anchored to function at work and home) in active duty soldiers.
A Randomized Controlled Trial of Prazosin for Combat Trauma PTSD with Nightmares in Active Duty Soldiers Returned from Iraq and Afghanistan

Murray Raskind, MD; Elaine Peskind, MD; COL (RET) Kris Peterson, MD; COL Dallas Homas, MD; Kimberly Hart, PA-C; David Hoff, PA-C; Tammy Williams, LCSW; Hollie Holmes, BA
VA Northwest Network Mental Illness Research, Education and Clinical Center (MIRECC); Madigan Health Care System, Joint Base Lewis McChord, Washington

BACKGROUND

• Prazosin is a generically available (inexpensive) alpha-1 adrenoreceptor antagonist that easily enters the brain and reduces excessive norarenergic-mediated arousal.

• Prazosin at bedtime has been demonstrated effective for PTSD nightmares in Vietnam Veterans1 and civilians.2

QUESTIONS

• Is prazosin effective for PTSD with prominent trauma nightmares in active duty Soldiers returned from combat in Iraq/Afghanistan?

• Is twice daily prazosin effective for total PTSD symptoms in these Soldiers?

• Is prazosin dosing regimen well tolerated by active duty Soldiers?

METHODS

• Soldiers randomized to prazosin or placebo for 15 weeks (6 week titration, 9 week maintenance dose). Outcome ratings at weeks 7, 11, and 15.

Table 1. Titration Schedule

<table>
<thead>
<tr>
<th>AM Dose (1000-1100 hrs)</th>
<th>QHS dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Subjects</td>
<td>Female Subjects</td>
</tr>
<tr>
<td>Week 1</td>
<td>Days 1 and 2</td>
</tr>
<tr>
<td>Days 3-7</td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>1 mg</td>
</tr>
<tr>
<td>Week 3</td>
<td>2 mg</td>
</tr>
<tr>
<td>Week 4</td>
<td>2 mg</td>
</tr>
<tr>
<td>Week 5</td>
<td>5 mg</td>
</tr>
<tr>
<td>Week 6</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Table 2. Demographics

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Married (%)</th>
<th>Median rank</th>
<th>Maintenance SSRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 ± 7 years</td>
<td>26 (81%)</td>
<td>68%</td>
<td>E-5 (Sergeant)</td>
<td>9</td>
</tr>
<tr>
<td>31 ± 7 years</td>
<td>31 (89%)</td>
<td>62%</td>
<td>E-5 (Sergeant)</td>
<td>12</td>
</tr>
</tbody>
</table>

RESULTS

• 56 of 67 subjects completed at least one rating period, and 46 the entire 15-week study. Data analyzed with linear mixed effects models using data from all 67 randomized subjects.

• Average doses achieved in male soldiers:
  Prazosin (mg) | Placebo (mg)*
  4.0 ± 1.4 midmorning/15.6 ± 6.0 bedtime | 4.8 ± 0.8 midmorning/18.8 ± 3.3 bedtime
  *placebo > prazosin, p < 0.05

A. Prazosin Effects on Combat Trauma Nightmares in Soldiers

B. Prazosin Effects on Sleep Quality in Soldiers

C. Prazosin Effects on Global Function in Soldiers at End Study

D. Prazosin Effects on Overall PTSD in Soldiers

• Prazosin significantly superior for CAPS hyperarousal cluster and numerically superior for depression ratings (HAM-D, PHQ-9). No drug effect on blood pressure.

ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Prazosin</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
</tr>
<tr>
<td>Palpitations</td>
<td>4</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Prazosin prescribed twice daily at mid-morning and bedtime is an effective and well tolerated treatment for combat trauma nightmares, sleep disturbance, function and overall PTSD in Soldiers returned from Iraq and Afghanistan combat deployment(s).

• Substantial residual PTSD symptoms suggest that adding effective psychotherapy and/or other medications may further enhance efficacy.

REFERENCES


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Disclaimer: The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense or the U.S. Government.

This investigation has adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.