Prazosin for Mild Traumatic Brain Injury Comorbidities: Toward a Precision Medicine Approach

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The Story Begins in Vietnam and
The Black Veterans Support Group of Puget Sound
Enhanced Norepinephrine Activity Model of PTSD

• Acute brain “adrenaline (norepinephrine) rush” that increases arousal and vigilance and saves lives in combat becomes persistent.

• Persistent hyperarousal and hypervigilance are maladaptive in the civilian world.
Don in Vietnam During Tet Offensive
Don - Now
Prazosin Treatment of PTSD Grew from Clinical Observations

• The first veteran treated for severe treatment-resistant Vietnam combat PTSD nightmares (1996) was given the beta-blocker propranolol (case report suggesting benefit--Kolb, 1984).

• After two weeks the veteran said “Doc, we are going the wrong direction; my nightmares are even worse.”

• Intensifying dreams is an established adverse effect of beta-adrenergic blockade.
What to do Next?

• Brain alpha-1 adrenergic effects are often opposed to brain beta-adrenergic effects.

• Would blocking brain alpha-1 adrenergic receptors with prazosin suppress nightmares?
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.
Prazosin Appeared Helpful

• Prazosin was begun at 1 mg QHS to avoid “first-dose effect” of orthostatic hypotension.

• After two weeks of gradual prazosin dose increase to 6 mg QHS, nightmares disappeared!

• This Veteran continues nightmare-free, suicidal ideation-free, and alcohol-free for past 20 years on 5mg BID and 10mg QHS.

• Similar long-term benefit in many other Veterans.
Sleep Physiology of Trauma Nightmares and PTSD

• Trauma nightmares arise from disrupted REM sleep and light sleep (stages 1 and 2).

• In animals, alpha-1 stimulation with methoxamine disrupts REM sleep and lengthens light sleep. These effects are reversed by prazosin.

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

Prazosin RCTs for PTSD with Nightmares and/or Sleep Disturbance

• Positive:
  » M. Raskind et al, 2007, *Biol Psychiatry*
  » F. Taylor et al, 2008, *Biol Psychiatry*
  » M. Ahmadpanah et al, 2014, *Neuropsychobiology*

• Failed:
  » M. Raskind et al (CSP #563), NEJM (in press).
VA Cooperative Study #563 (NEJM in press)

• A six month randomized control trial of prazosin for combat theatre PTSD in 304 Veterans (70% Vietnam)
• Maximum dose 5mg QAM, 15 mg QHS
• Prazosin not superior to placebo
Failed VA Cooperative Study #563

• Provider reluctance to refer distressed/unstable Veterans

• Relatively low BP and low alcohol and benzodiazepine use in referred Veterans

• Psychosocially unstable Veterans were excluded

• Therefore, likely selected against the “adrenergic” subtype of PTSD
• Incident suicidal ideation significantly lower in prazosin condition (p<0.05)
  ▶ 15 in placebo group
  ▶ 9 in prazosin group
Acceptance of Prazosin Effectiveness for PTSD within VA Health Care System

• Prescribed to approximately 15% of all Veterans in VA health care system with a PTSD diagnosis (approximately 100,000 Veterans).
GOT NIGHTMARES?
Combat Nightmare Reduction Initiative
(253) 968-4735
MAMC
Prazosin RCT in Active Duty OEF/OIF Soldiers (N=67)

- 15-week parallel group RCT (1:1) at Joint Base Lewis-McChord, WA
- Maximum dose prazosin 5 mg QAM + 20 mg QHS for men and 2 mg + 12 mg QHS in women (in flexible dose titration)
- 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

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

Seeking a Biomarker That Predicts PTSD Response to Prazosin in Active Duty Combat Soldiers

Randomized to Prazosin (N=32)

- Prazosin responders did not differ from nonresponders in CAPS symptom severity or prazosin dose achieved.

- Is there an accessible biologic variable ("biomarker") that helps predict therapeutic response to prazosin?

Pretreatment Standing Blood Pressure (BP) is a Rational Candidate Biomarker for Predicting Therapeutic Response to Prazosin

• Excessive brain alpha-1 AR activity contributes to PTSD hyperarousal and trauma nightmare symptoms.
  » Unfortunately, brain alpha-1 AR activity cannot be measured.

• Peripheral vascular alpha-1 AR activity contributes to BP regulation, particularly in the standing position.
  » Standing BP is easily measured.

• Hypothesis: Higher standing pretreatment BP predicts greater PTSD symptom reduction by prazosin.
Pretreatment Standing Systolic BP Strongly Predicted PTSD Response to Prazosin

• Prazosin Group: For every 10mm Hg increase in pretreatment systolic BP, there was an additional 14 point reduction in total CAPS score (p=0.002):
  » Standing systolic of 130mm Hg → 36 point CAPS reduction
  » Standing systolic of 120mm Hg → 22 point CAPS reduction
  » Standing systolic of 110mm Hg → 7 point CAPS reduction

• Placebo Group: No effect of pretreatment standing systolic BP on total CAPS score response.
• Higher pretreatment standing BP for a PTSD or AUD patient’s demographic group is an accessible biomarker that helps predict therapeutic response to prazosin or doxazosin.
Candidate Syndromal Predictors of Prazosin Response

- Trauma Associated Sleep Disorder*
  - Disruptive nocturnal behavior (distressed vocalizations, somnambulism, combative behaviors)
  - REM without atonia
- Trauma nightmares and/or distressed awakenings with autonomic arousal (sweating, rapid heart rate, vigilance)

*V. Mysliwiec et al, 2014, J Clin Sleep Med
The Alpha-1 Adrenoreceptor Antagonist Prazosin for Alcohol Use Disorder

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Prazosin for Alcohol Dependence: Results from a Randomized Controlled Trial

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Participants and Methods

- 24 (19 men) participants without PTSD entering treatment for alcohol dependence
- Prazosin or placebo titrated over two weeks to 4mg BID and 8mg QHS and maintained for additional 4 weeks.
Mean Standard Drinks per Week: *Daily Self-report via IVR*

Intent to treat analysis, adjusting for gender (N=30, X²= 21.6; p=0.002).
Completer analysis, adjusting for gender (n=21, X²=17.6; p=0.008).
Three Positive, 1 Negative Prazosin RCTs for Alcohol Use Disorder

• The most consistent effect of prazosin for alcohol use disorder is on heavy drinking days

• Combining prazosin with naltrexone or propranolol likely more effective than prazosin alone
Pretreatment Diastolic Blood Pressure (BP) Predicts Greater Alcohol Reduction in Alcohol Dependent Patients Treated with Doxazosin

• Doxazosin is an alpha-1 AR antagonist with longer duration of action than prazosin

• Higher standing pretreatment diastolic BP (>80 mmHg) predicted significant reductions in heavy drinking days and drinks/week

Ongoing RCT of prazosin and naltrexone for alcohol use disorder.
The strongest effect on alcohol misuse in rats is prazosin plus naltrexone plus propranolol.
Prazosin for Persistent Postconcussive Headaches: A Placebo-Controlled Clinical Trial

Cynthia L. Mayer, DO
Recipient, Career Development Award, RR&D

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This research is supported by the Department of Veterans Affairs and Department of Defense Congressionally Directed Medical Research Programs
Does the PTSD Drug Prazosin Reduce Blast mTBI Headaches in OEF/OIF Veterans?

• OEF/OIF Veterans with blast concussion PTHA have a high prevalence of comorbid PTSD trauma nightmares and sleep disturbance\textsuperscript{1,2,3}

• Robert Ruff, MD, former VA Director of Neurology and former acting Director of Rehabilitation Medicine, used prazosin open label to treat comorbid PTSD in OEF/OIF Veterans with blast mTBI manifested by PTHA and other post concussive symptoms\textsuperscript{4}

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

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<th>Baseline</th>
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<td>Headaches per month</td>
<td>12.4 ± 8.1</td>
<td>4.8 ± 2.9</td>
<td>&lt; 0.001</td>
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<td>Headache intensity</td>
<td>7.1 ± 1.4</td>
<td>4.1 ± 1.6</td>
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<td>Daytime sleepiness</td>
<td>16.1 ± 2.4</td>
<td>7.3 ± 2.9</td>
<td>&lt; 0.001</td>
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<tr>
<td>Daytime sleepiness</td>
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<td>(Epworth Sleepiness</td>
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<td>Scale)</td>
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<td>% subjects with</td>
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<td>87.8%</td>
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<td>restorative” sleep</td>
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<tr>
<td>Cognition</td>
<td>24.1 ± 2.0</td>
<td>28.1 ± 2.2</td>
<td>&lt; 0.001</td>
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<td>(Montreal Cognitive</td>
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<td>Assessment)</td>
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Prazosin for Postconcussive Headache Clinical Trial

• Results of these studies provided the rationale for a placebo-controlled trial of prazosin for blast concussion PTHA

• This study is funded by:
  » VA Career Development Award (C. Mayer)
  » DoD CDMRP Award (M. Raskind)
Study Objectives

• Evaluate efficacy and safety of prazosin for prophylaxis of chronic postconcussive headaches following mTBI through a randomized double-blind placebo-controlled clinical trial
Titration of Prazosin using Therapeutic Response and Adverse Effects as Guides

- Gradually increase dose until target symptoms are at least moderately improved and there are no problematic adverse effects.
- Instruct patient arising from lying position to sit on edge of bed for 30 seconds; if not dizzy, stand by bed for 30 seconds; if not dizzy, “good to go”.
- Not necessary to measure BP in office if patient reports no dizziness upon standing during dose titration.
Other Prazosin Adverse Effects Often Resolve with Time or can be Treated Symptomatically

• Nasal congestion interfering with sleep – judicious use of nasal decongestants

• Palpitations – low dose propranolol, reassurance
Drugs and Other Factors that can Lower Threshold for Prazosin Symptomatic BP Drop

• Viagra and other ED drugs (also may slightly increase priapism risk)
• Other antihypertensives
• Dehydration
• Hot tub, hot bath
• Exercise supplements containing “muscle blood flow enhancers”
• Priapism is rare but instruct to receive ER evaluation if erection persists for excessive period of time

• Trazodone may slightly increase priapism risk
Prazosin Effect on Trauma Nightmares and Dreaming Phenomena

• As trauma nightmares disappear with prazosin treatment, long absent “normal” dreams with typical bizarre content (pleasant or unpleasant) reappear.

• Because trauma nightmares likely are “retraumatizing”, benefit of prazosin eliminating of trauma nightmares and distressed awakenings may be more than “just symptomatic”.
• Adding low dose midmorning or BID prazosin to larger bedtime dose can substantially reduce daytime PTSD hyperarousal symptoms
• QUESTIONS/COMMENTS?

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