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

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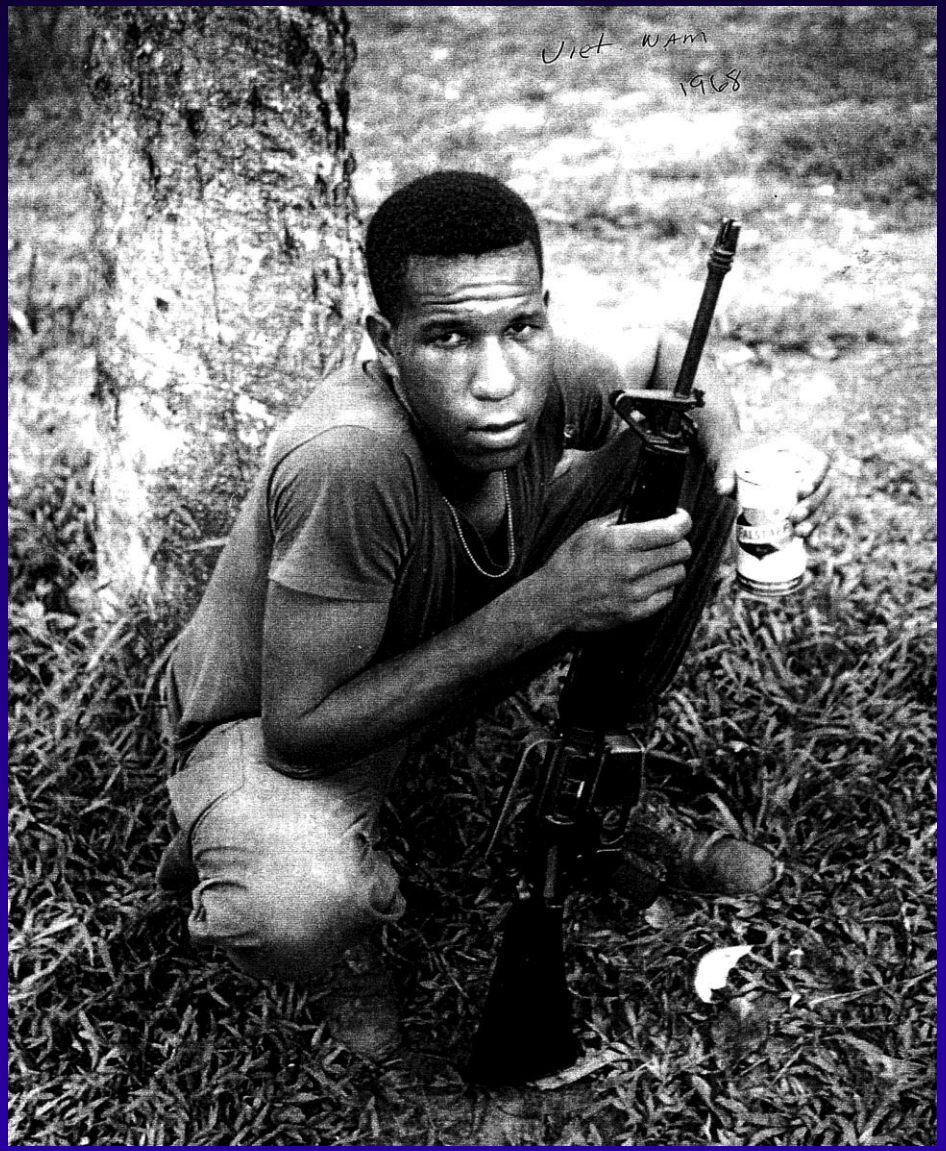
# The Story Begins in Vietnam and The Black Veterans Support Group of Puget Sound

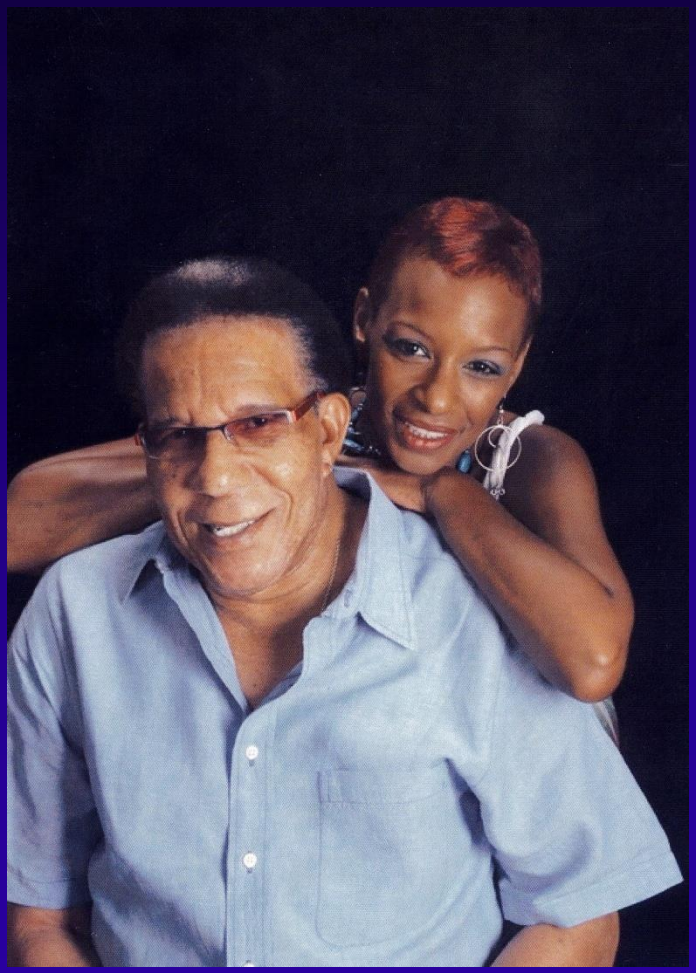
# Enhanced Norepinephrine Activity Model of PTSD

- 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

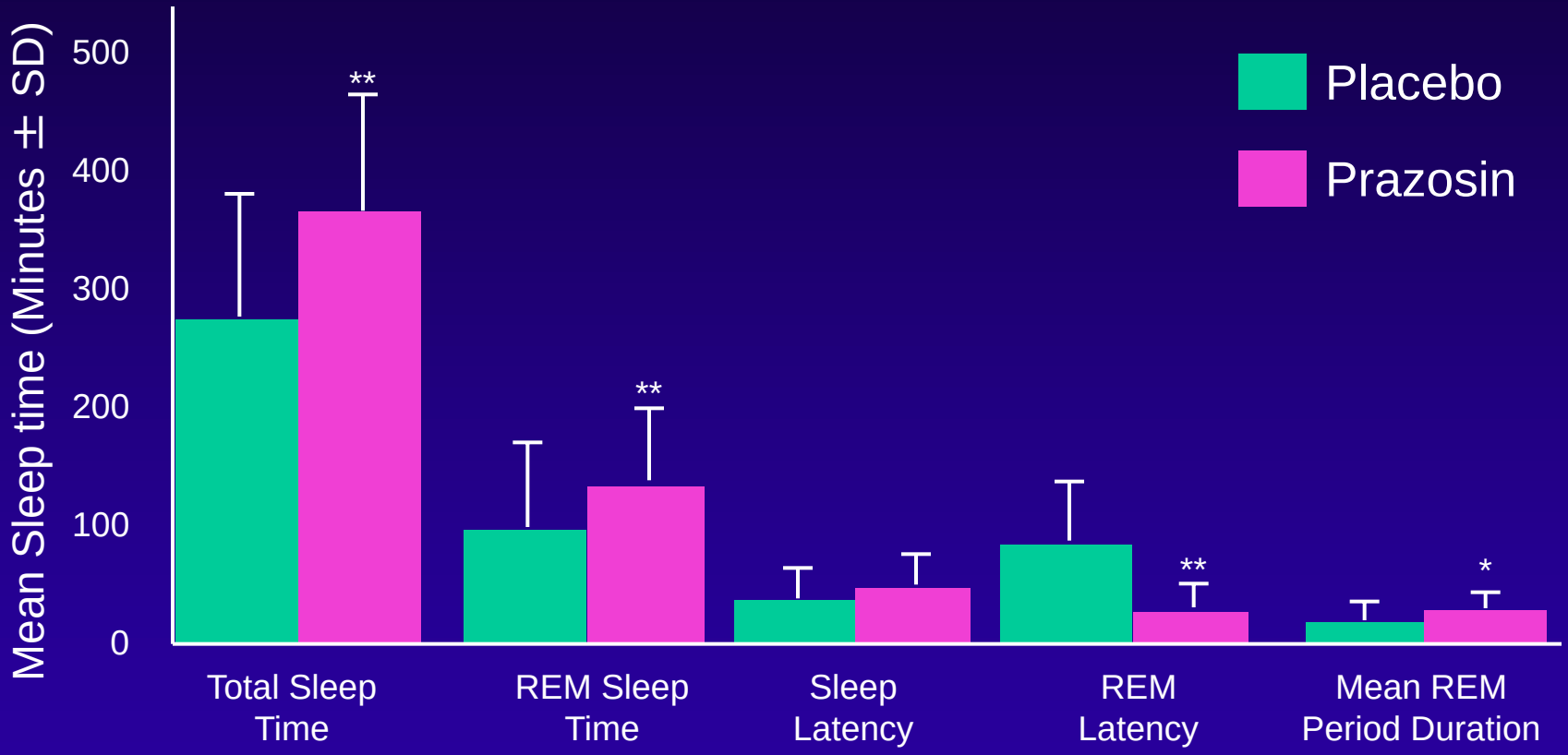
- Prazosin was begun at 1 mg QHS to avoid “first-dose effect” of orthostatic hypotension.
- After two weeks of gradual prazosin dose increase to 6 mg QHS, nightmares disappeared!
- This Veteran continues nightmare-free, suicidal ideation-free, and alcohol-free for past 20 years on 5mg BID and 10mg QHS.
- 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.

**Taylor FB, et al., *Biol Psychiatry* 63:629-32, 2008.**

# 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 FB, et al., *Biol Psychiatry* 63:629-32, 2008.**

# Prazosin RCTs for PTSD with Nightmares and/or Sleep Disturbance

- Positive:
  - M. Raskind et al, 2003, *Am J Psychiatry*
  - M. Raskind et al, 2007, *Biol Psychiatry*
  - F. Taylor et al, 2008, *Biol Psychiatry*
  - A. Germain et al, 2012, *J Psychosomatic Res*
  - M. Raskind et al, 2013, *Am J 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

# Failed VA Cooperative Study #563

- 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

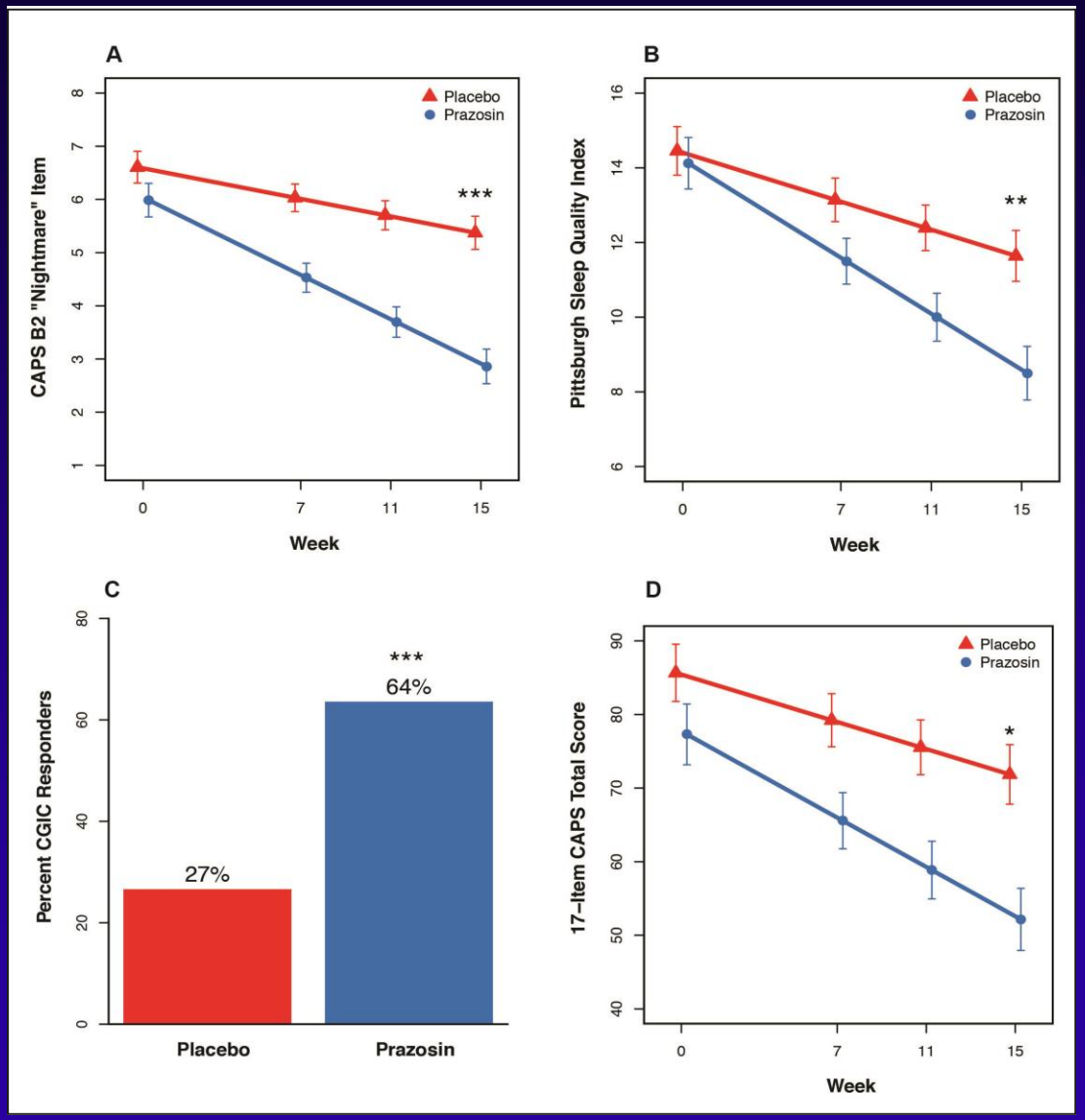
MAMC

# 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

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

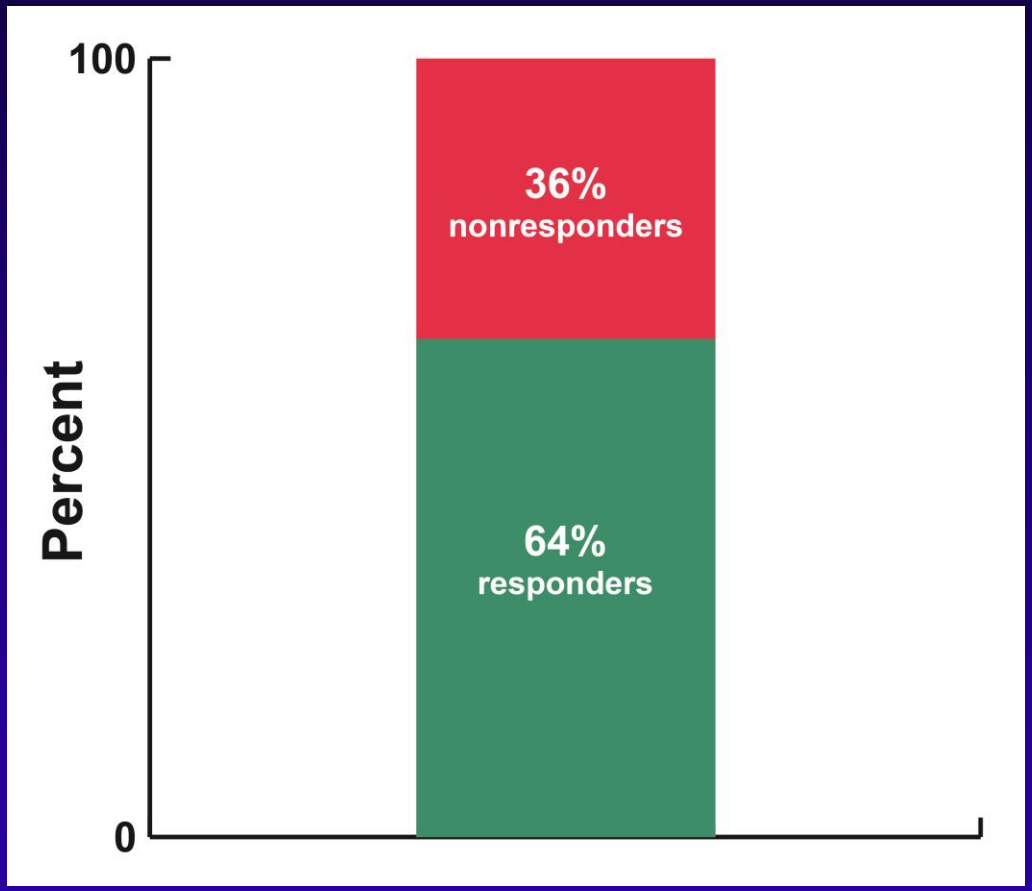
# Effects on PTSD Outcome Parameters in Combat Soldiers Randomized to Prazosin (n=32) or Placebo (n=35)




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

# 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?

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

# 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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# Rodent Studies Relevant to Prazosin Effects on Alcohol Drinking

Dennis Rasmussen, et al.


1. Rasmussen DD, Alexander LL, Raskind MA, Froehlich JC. The alpha-1 adrenergic antagonist, prazosin, reduces alcohol drinking in alcohol-preferring (P) rats. Alcohol Clin Exp Res 2009 33(2):264-72.
2. Froehlich JC, Hausauer BJ, Rasmussen DD. Combining naltrexone and prazosin in a single oral medication decreases alcohol drinking more effectively than does either drug alone. Alcohol Clin Exp Res 2013 37(10)1763-70.

# Prazosin for Alcohol Dependence: Results from a Randomized Controlled Trial

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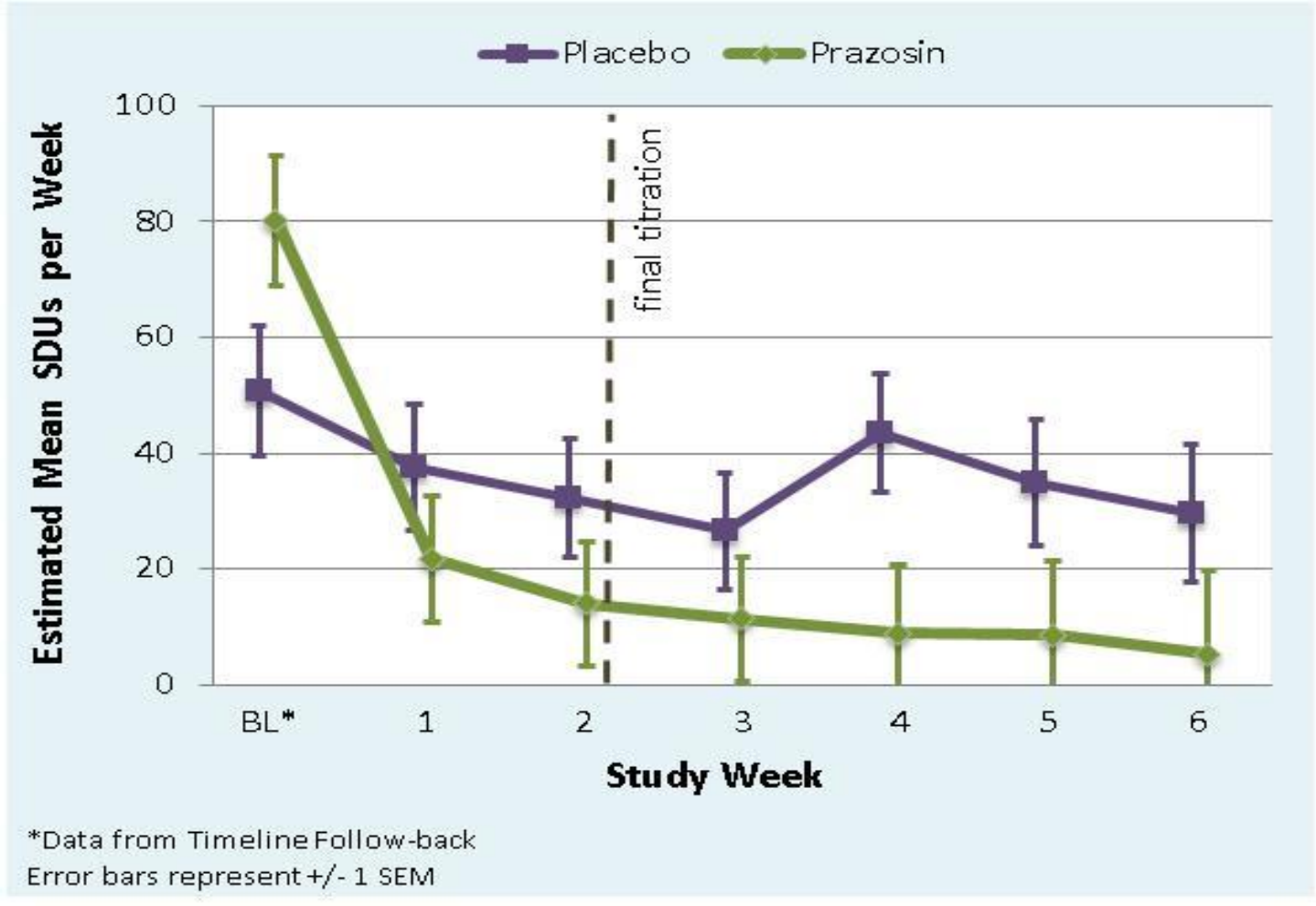
Simpson et al, Alcohol Clin Exp Res 2009 33(2):255-63

# 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

**Haass-Koffler et al, 2017. Drug and Alcohol Dependence 177, 23-28**

- 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

**Murray A. Raskind, MD**

Director, VA Northwest Network Mental Illness Research, Education, and Clinical Center

**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[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[4]


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

# An Open Label Prazosin and Sleep Hygiene Trial for OIF/OEF Veterans with Blast mTBI and 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 Sleepiness Scale) | 16.1 ± 2.4 | 7.3 ± 2.9 | < 0.001 |
| % subjects with “restful and restorative” sleep | 7.0% | 87.8% | < 0.001 |
| Cognition (Montreal Cognitive Assessment) | 24.1 ± 2.0 | 28.1 ± 2.2 | < 0.001 |

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

# 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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