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

Murray A. Raskind, MD

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

Professor
Dept. of Psychiatry & Behavioral Sciences
University of Washington School of Medicine

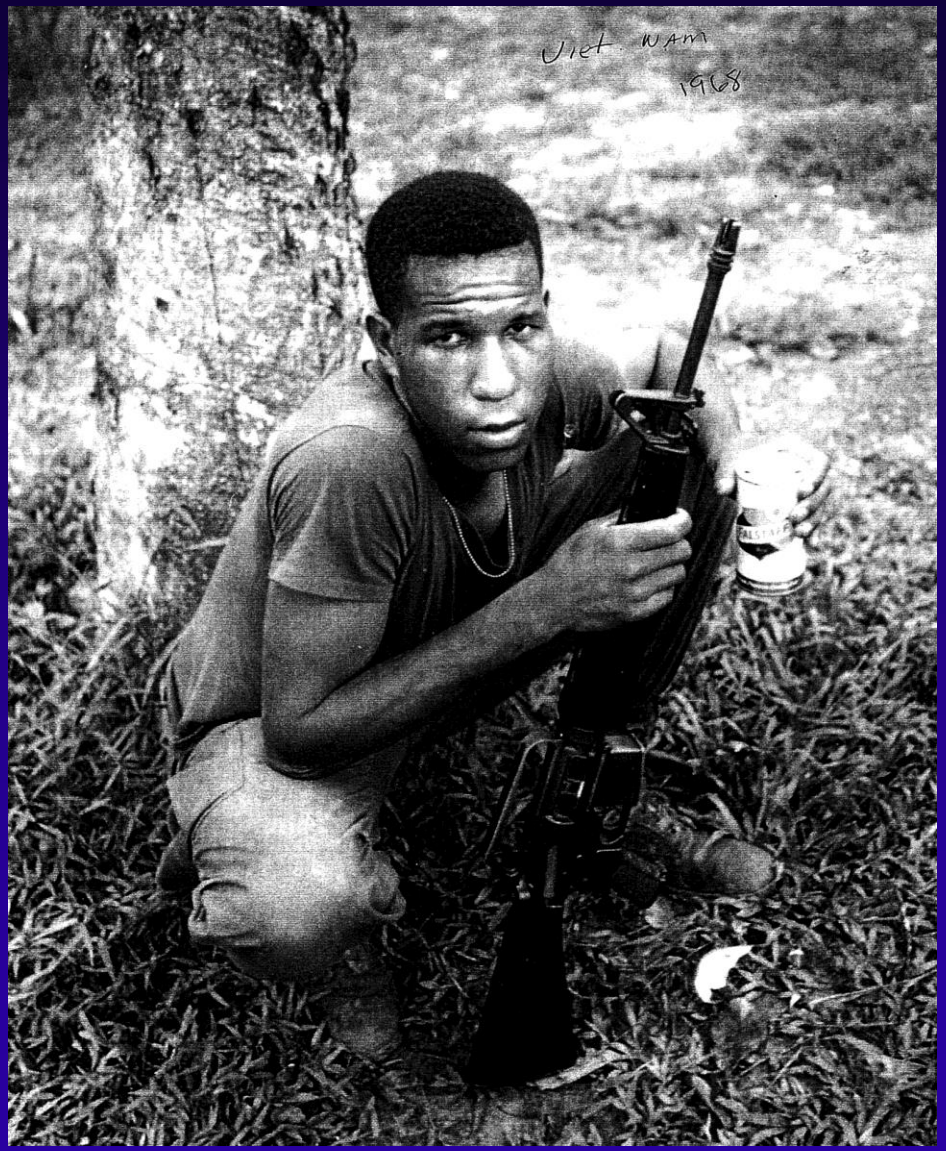
Staff Psychiatrist
Madigan Army Medical Center

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

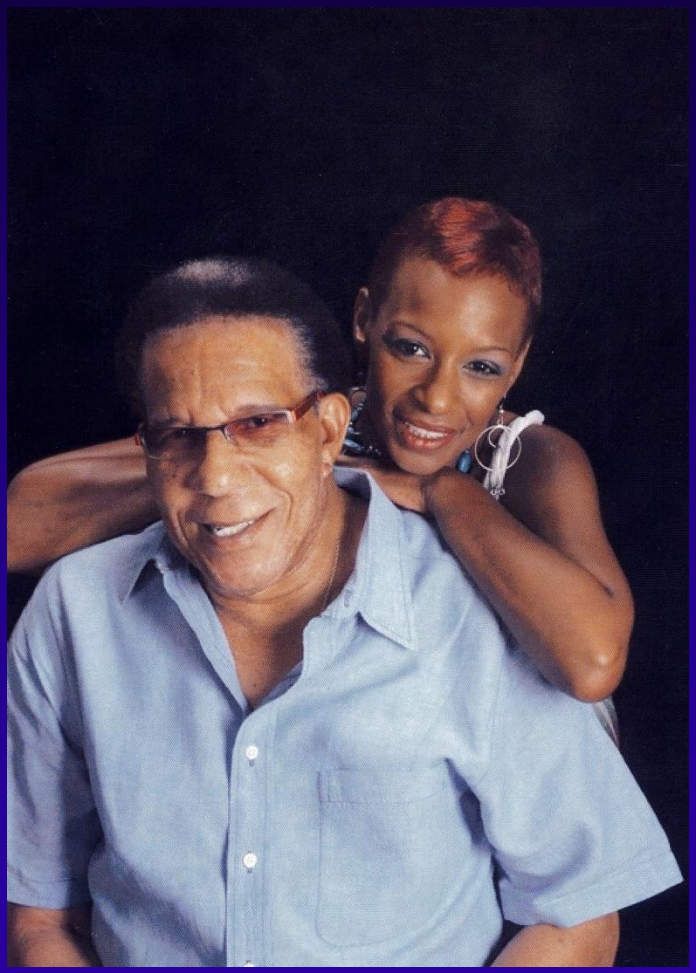
Enhanced Norepinephrine Activity Model of PTSD

- 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

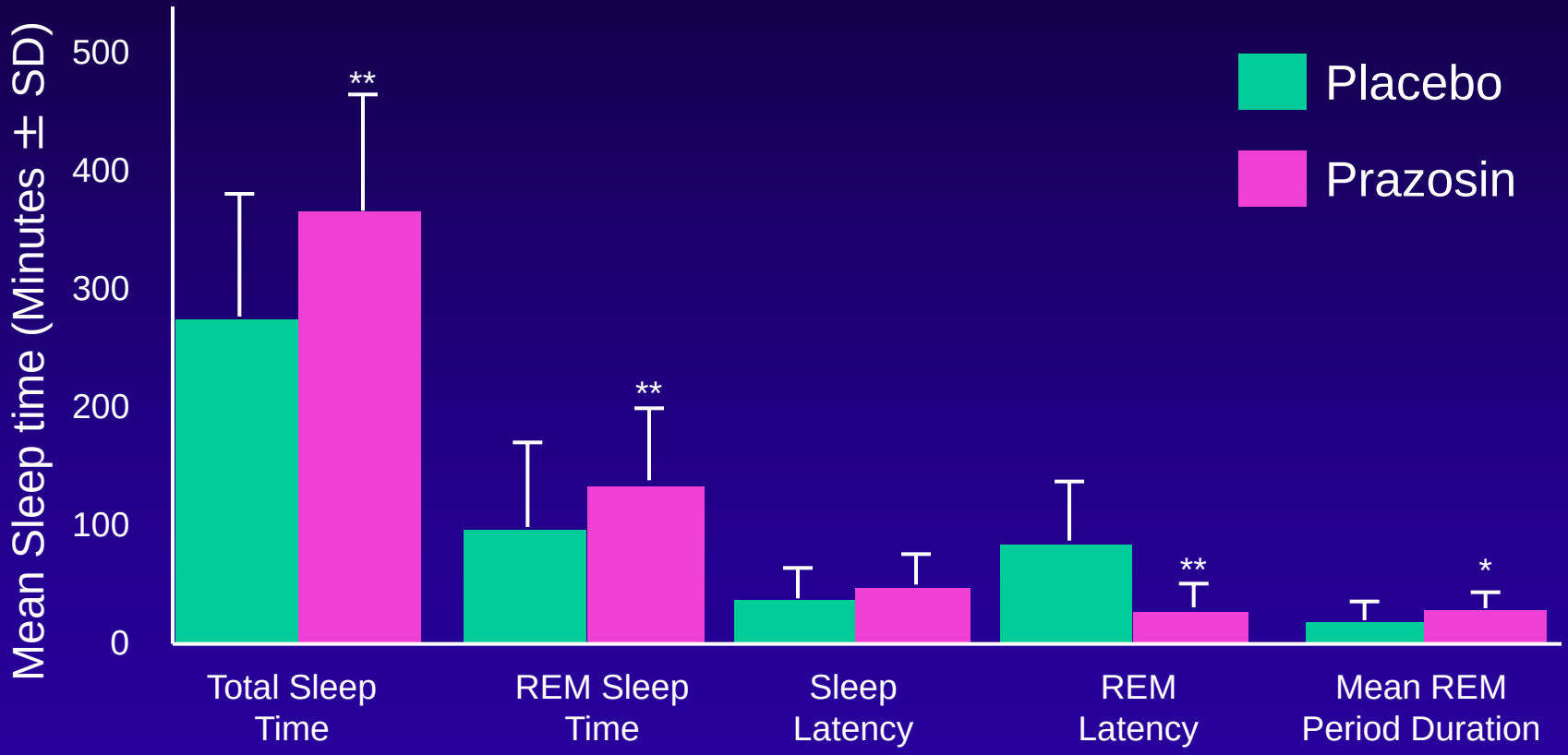
- Prazosin was begun at 1 mg QHS to avoid “first-dose effect” of orthostatic hypotension.
- After two weeks of gradual prazosin dose increase to 6 mg QHS, nightmares disappeared!
- This Veteran continues nightmare-free, suicidal ideation-free, and alcohol-free for past 20 years on 5mg BID and 10mg QHS.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

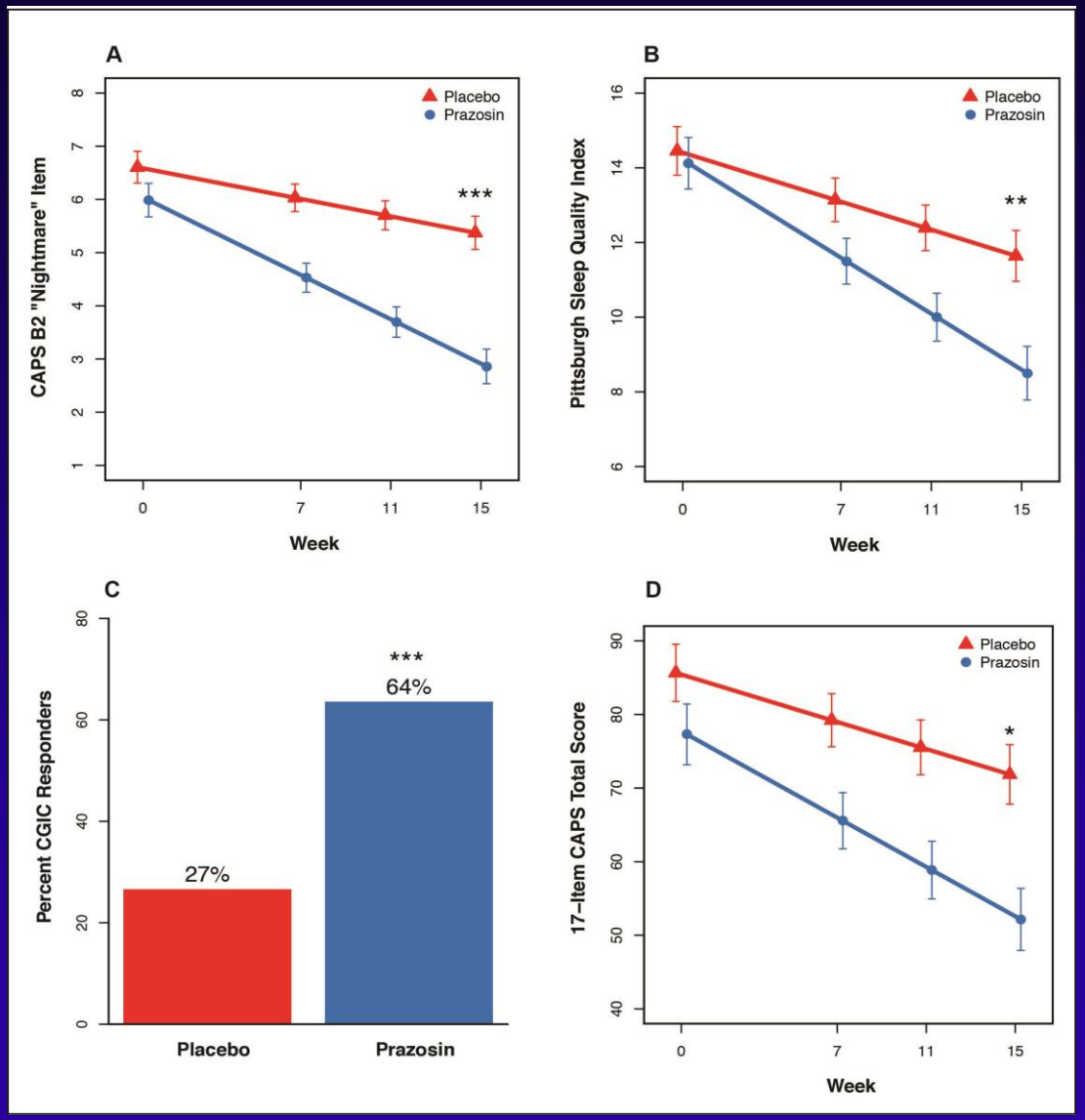
MAMC

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.

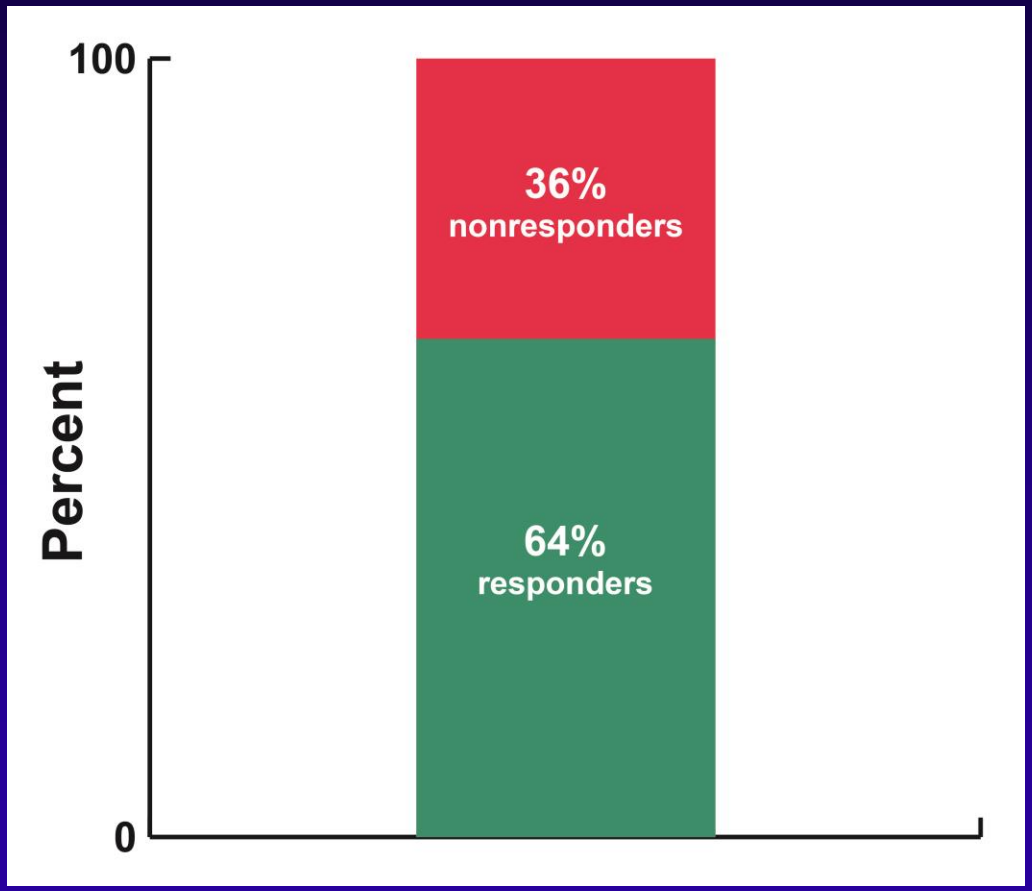
Effects on PTSD Outcome Parameters in Combat Soldiers Randomized to Prazosin (n=32) or Placebo (n=35)



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

Tracy L. Simpson, PhD

Andrew J. Saxon, MD

Dennis D. Rasmussen, PhD

Murray A. Raskind, MD

VA Puget Sound Health Care System
MIRECC – CESATE
Department of Psychiatry and Behavioral Sciences
University of Washington
Seattle, WA

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

Tracy Simpson, PhD
Andrew Saxon, MD
Charles Meredith, MD
Brittney McBride, MA
Carol Malte, MSW
Murray Raskind, MD

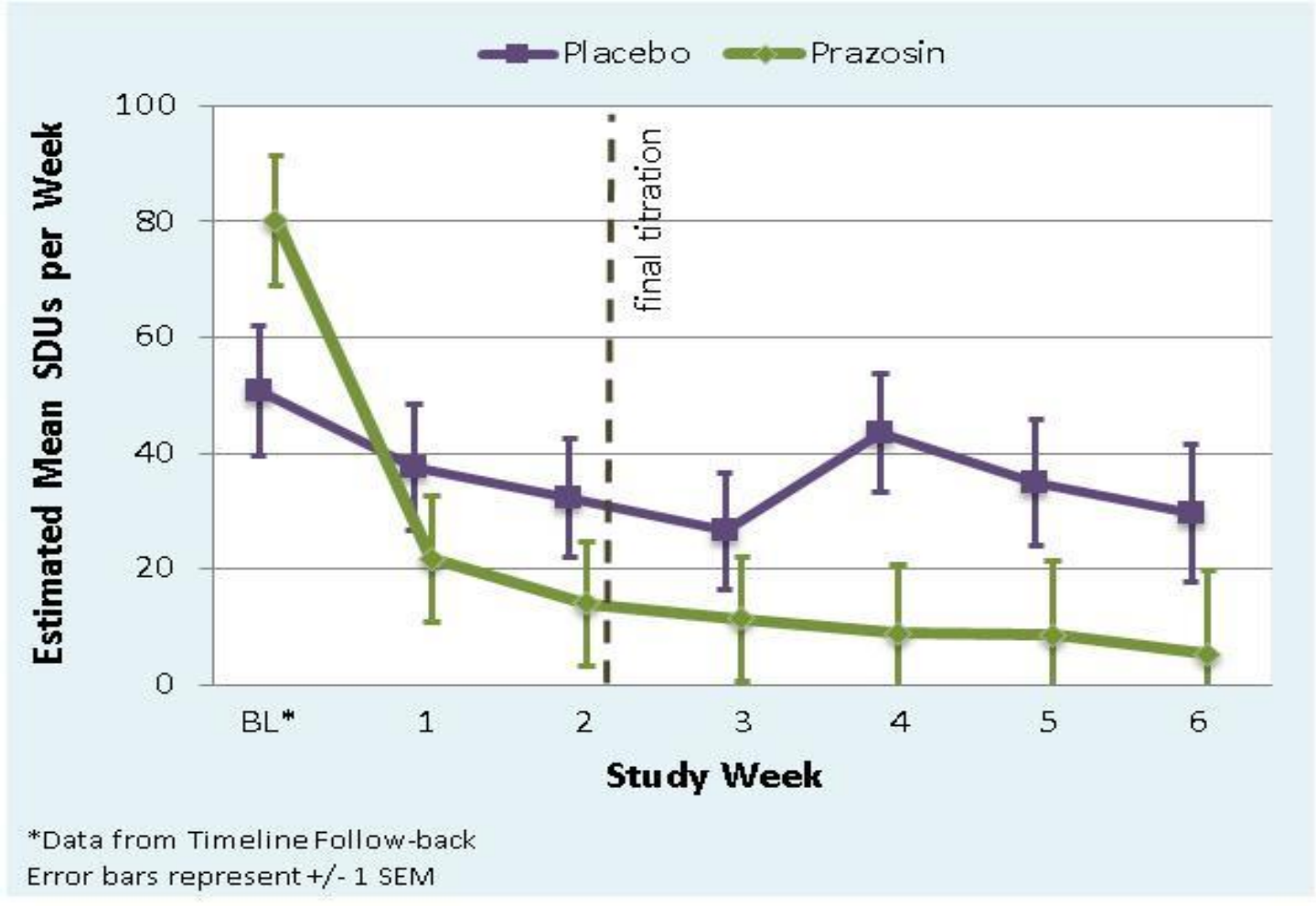
MIRECC-CESATE
VA Puget Sound Health Care System
Department of Psychiatry and Behavioral Sciences
University of Washington

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?

- Murray Raskind
- murray.raskind@va.gov