Prasozin for Posttraumatic Headache Randomized Controlled Trial in Veterans and Active Duty Service Members

HSR&D Cyberseminar

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Presentation Outline

- Background
  - Posttraumatic headaches (PTH) – the problem in context
  - Why prazosin?
    - Prior observations
    - Theoretical mechanism(s) of action
- Prazosin for PTH Randomized Controlled Trial (RCT)
  - Methods
  - Results of planned interim analysis of primary outcome measure and selected secondary outcome measures
  - PTH participant case presentation
- Future directions

Posttraumatic Headaches

- = Most common symptom following concussion
- Most resolve within 6 months following injury
- In Veterans up to 60% persist for a year or more
- Co-morbid postconcussive symptoms may include sleep impairments, cognitive issues, photophobia, autonomic disfunction, anxiety, depression, PTSD symptoms

Theeler B et al 2013. Post-traumatic headaches in civilians and military personnel: a comparative, clinical review. Headache;53:881-900

Posttraumatic Headaches

- Phenotypically similar to primary headaches, most commonly migraine, but recent imaging and other evidence suggests different structural and functional brain changes
- Currently no FDA-approved treatments specifically for PTHs
- Treated as the primary headache type they most resemble
- Medical management includes
  - as-needed “rescue” medications to interrupt onset or treat headache pain and other symptoms
  - scheduled prophylactic medications

Posttraumatic Headaches

- Acute (lasting <3 mo) – tend to be tension-type or have less well-defined features, which may reflect acute brain injury effects vs

- Persistent (lasting ≥3 mo) – tend to have more migraine features; more resistant to treatment; more likely to transform from occasional (episodic) to frequent (chronic) and become more difficult to treat

Episodic vs Chronic Headaches

- Both tension-type and migraine headaches can transform from episodic to chronic
- Chronic tension-type:
  - ≥15 days/month lasting hours to days or unremitting; may have mild nausea
- Chronic migraine:
  - ≥15 days/month which on ≥8 days/mo have migraine features
- Chronic tension-type and migraines can co-occur

Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. (2018) 38:1–211

Chronic Daily Headaches

- Inadequate treatment or poor response can lead to headaches becoming more frequent, severe, and chronic
- The transformation from episodic to chronic may represent progression in pathology and/or central pain sensitization
- Brain imaging shows structural and functional changes between episodic and chronic headaches
- Can be disabling and difficult to treat

Pathologic Pain: Central Sensitization

- A manifestation of plasticity of the somatosensory nervous system in response to inflammation, neural injury (e.g., by CGRP, synthesized by small-diameter sensory neurons)
- Results in uncoupling of pain sensation from noxious peripheral stimuli
- Net effect - previously subthreshold inputs generate increased outputs (facilitation; potentiation) resulting in sensory hypersensitivity

Latremolier and Woolf. J Pain. 2009 Sep; 10(9):895-926

Central Sensitization

- Features of central sensitization:
  - Allodynia – normally painless stimuli become painful, for example wearing glasses, earrings, hats, combing hair
  - Hyperalgesia – heightened response to painful stimulus

- Possible alteration of endogenous pain inhibition pathways

Latremolier and Woolf. J Pain. 2009 Sep; 10(9):895-926

Pathophysiology of PTH

- In addition to alterations in pain processing, patients can develop emotional and affective responses to chronic pain, impacting daily function, relationships, and overall quality of life
- The longer PTHs persist, the greater the chances for developing medication over-use habits that may be rooted in anticipatory anxiety, which can further add to the headache burden

Medication Over-use

- Regular overuse for >3 months of one or more acute symptomatic drugs:
  - Simple analgesics (acetaminophen, aspirin, or other NSAID) on ≥15 days/month
  - Triptans, ergotamines, opioids, combination headache medications, or combined use of multiple drug classes on ≥10 days/month on a regular basis
- May lead to “medication over-use” headaches indistinguishable from the original headaches
- Occurs in up to 40% of patients with PTH

Pathophysiology of PTH

- Direct damage to brain structures
- Blood/brain barrier dysfunction
- Neuroinflammation
  - Microglial activation in the brain parenchyma
  - Immune cell-mediated effects
  - Dural inflammation related to mast cell degranulation with sensitization of pain pathways
- Injury to extracranial tissues with activation of trigeminal and cervical afferents

Pathophysiology of PTH

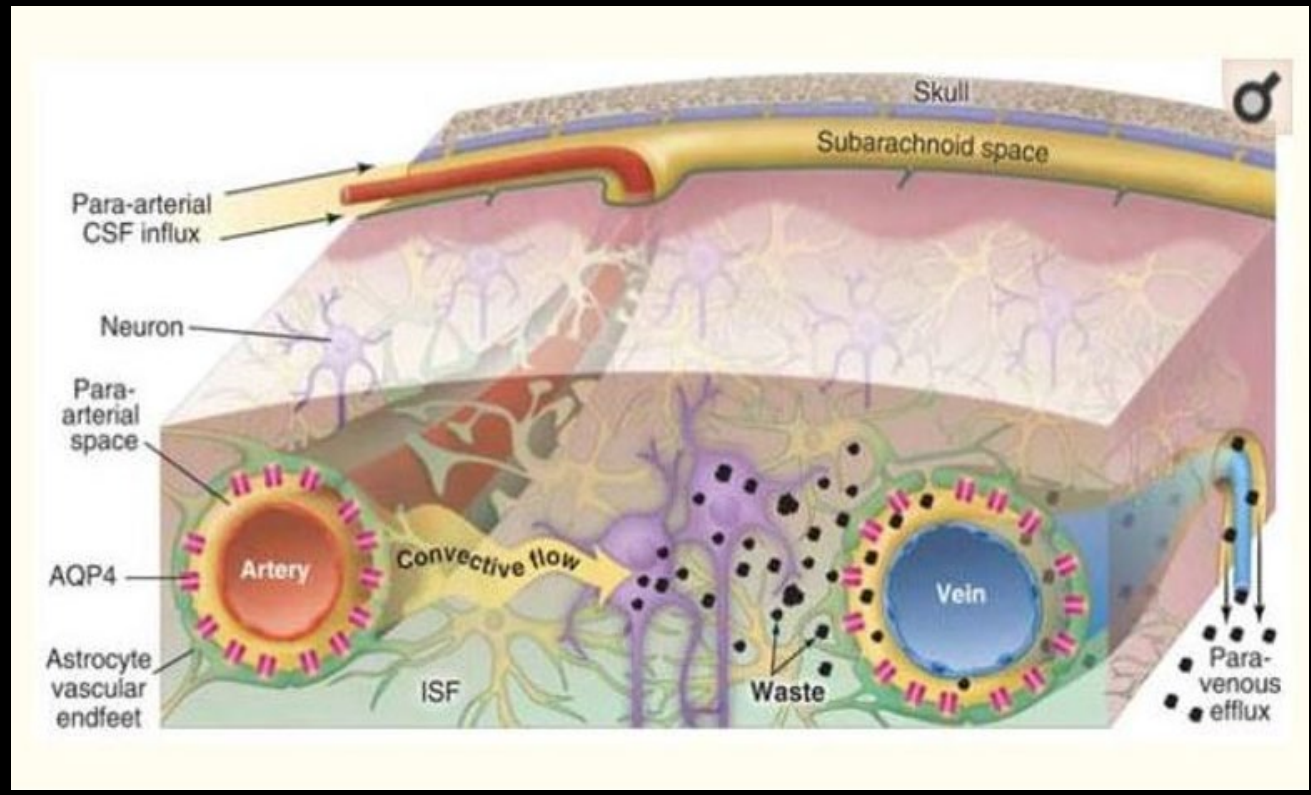
- Neurometabolic changes
- Cortical spreading depression
- Calcitonin gene-related peptide (CGRP) and other mediator-dependent mechanisms
- Aberrant neurogenesis, synaptogenesis
- Disrupted neural networks
- Impaired descending pain modulation
- Altered astrocyte function
- Glymphatic dysfunction
- Genetic vulnerability

Why Prazosin for PTH?

- Decreases CNS sympathetic tone – sympathetic outflow into the meninges involving noradrenaline (NA) release has been shown to contribute to pro-nociceptive (i.e., pain) signaling through actions on dural afferents
- May help facilitate restorative sleep
- May directly or indirectly increase brain glymphatic clearance of perivascular migraine-associated neuropeptides

Glymphatic System

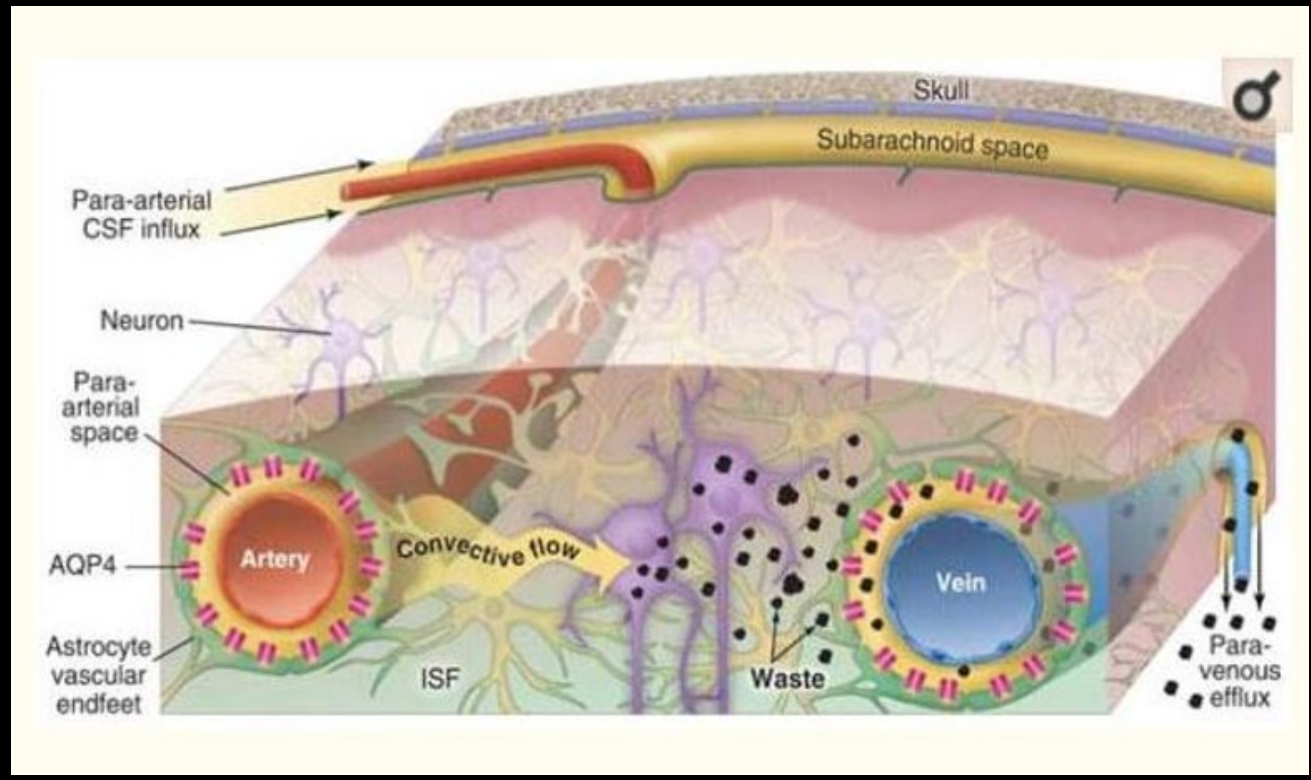
- Functions to clear toxic metabolites from the CNS via convective exchange of CSF and ISF
- CSF influx along arteries; ISF efflux along veins. Function depends on perivascular channels formed by astroglial end-feet, which express AQP-4 water channels.
- During sleep, interstitial space increases by 60%, resulting in a striking increase in convective exchange of CSF with ISF and clearance of toxic metabolites.



Iliff et al. Sci Transl Med. 2012. 4(147):147ra111; Xie et al. Science. 2013. 342(6156):373-77; Mestre 2017.

Glymphatic System

- The wake/sleep state → interstitial space volume – ↑ in sleep, ↓ in wakefulness
- Wakefulness is driven in large part by LC–derived NA signaling
- Administration of AR antagonists, including prazosin, increased interstitial volume in awake mice to levels similar to the sleep/anesthetized state
- Adrenergic signaling appears to be important in modulating both cortical neuronal activity and the volume of the interstitial space
- The restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate during wakefulness



Iliff et al. Sci Transl Med. 2012. 4(147):147ra111; Xie et al. Science. 2013. 342(6156):373-77; Mestre 2017.

Alpha $_1$ Adrenergic Blockers and Headaches

- Personal experience of a neurologist with migraines who was started on terazosin for hypertension, with resolution of headaches
- He treated 11 of his headache patients with terazosin or doxazosin
- 10 of 11 patients had complete resolution or decreased frequency and/or severity of headaches
- "The alpha$_1$adrenergic blockers may have a place in the prophylaxis of migraines, especially if other agents have failed".

Vatz, K Headache 1997; 37:107-108

Alpha $_1$ Adrenergic Blockers and Headaches

- Others had previously postulated that the target structure for alpha$_1$adrenergic blockers may be the trigeminal innervation of the extracranial and/or dural vessels.

- “This anecdotal experience with the alpha$_1$adrenergic blockers warrants a controlled double-blind study of this class of drugs for prophylaxis of migraines”.

Vatz, K Headache 1997; 37:107-108

Open-Label Trial of Prazosin for PTH and Sleep Disturbance in Veterans with Blast-induced mTBI

- Robert Ruff, MD, former VA Director of Neurology, used prazosin open label and sleep hygiene counseling to treat OEF/OIF Veterans with blast mTBI, sleep disturbances, and PTH, many also with PTSD
- Prazosin was titrated over 5 weeks to a maximum dose of 7 mg at bedtime

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

Open-Label Trial of Prazosin for PTH and Sleep Disturbance in Veterans with mTBI

Comparisons done at end of 6-month follow-up period of outcomes of veterans who were or were not taking prazosin at end of both 9-week intervention period and 6-month follow-up period. Analysis results are based on linear mixed models.

Performance of Veterans (*N* = 68)	**ESS Score (0–24)**	**MOCA Score (0–30)**	**Headache Pain Intensity (0–10)**	**Headache Frequency (No./Month)**
Taking Prazosin (*n* = 60)				
Baseline (mean ± SE)	16.20 ± 0.20	24.00 ± 0.24	7.21 ± 0.20	13.60 ± 1.10
End of 9-Week Intervention (mean ± SE)	6.56 ± 0.22	28.60 ± 0.19	3.73 ± 0.22	4.60 ± 0.29
End of 6-Month Follow-Up (mean ± SE)	4.00 ± 0.19	28.90 ± 0.26	2.48 ± 0.21	2.26 ± 0.29
Significance of Comparisons	A, B, C	A, B	A, B, C	A, B, C
Not Taking Prazosin (*n* = 8)				
Baseline (mean ± SE)	16.00 ± 0.44	24.60 ± 0.55	6.55 ± 0.51	7.19 ± 0.72
End of 9-Week Intervention (mean ± SE)	12.50 ± 0.59	24.10 ± 0.55	6.75 ± 0.50	8.19 ± 0.79
End of 6-Month Follow-Up (mean ± SE)	10.90 ± 0.72	24.60 ± 0.62	5.65 ± 0.51	6.89 ± 0.71
Significance of Comparisons	A, B	—	—	—

Note: A = comparisons between baseline and 9-week values significant at 0.05 level, B = comparisons between baseline and 6-month values significant at 0.05 level, C = comparisons between 9-week and 6-month values significant at 0.05 level.
ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, SE = standard error of the mean.

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

Incidental Headache Improvement in Positive Prazosin Trial for PTSD in Active Duty Soldiers Study

- Parallel group RCT (1:1) at Joint Base Lewis McChord
- Active duty OIF/OEF soldiers with PTSD and trauma nightmares
- Majority of participants had comorbid mTBI
- Headaches were assessed as a potential side effect of prazosin

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

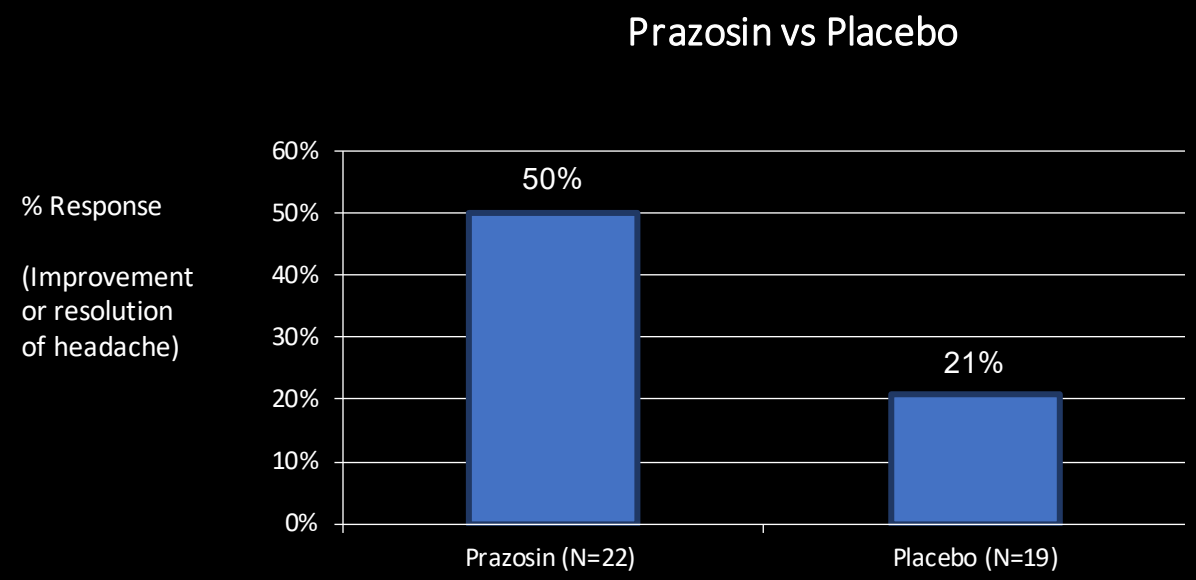
Prazosin for PTSD Study Participants with Headaches at Baseline

Of those with headaches prior to randomization, % with improvement or resolution of baseline headaches:

50% in prazosin group

vs

21% in placebo group



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

Summary of Adverse Events, Prazosin for PTSD Study

	Prazosin (n=32)	Placebo (n=35)
Syncope	2	0
Dizziness	6	6
Drowsiness	1	2
Depressed mood	0	2
Headache*	1	7
Nasal congestion	5	2
Nausea	2	5
Palpitations	4	1

*more frequent in placebo condition, $p < 0.05$

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

Prazosin for Posttraumatic Headaches Study

- Funded by VA Career Development Award and DoD CDMRP
- RCT of prazosin vs placebo for prophylactic treatment of PTH
- 2:1 randomization to prazosin or placebo
- ~6-month trial, including
  - 5 weeks of pre-treatment headache log-keeping to confirm eligibility and for baseline data
  - 5-7 weeks of study drug dose titration
  - 12 weeks at steady dose
- Study design is based on consensus guidelines for RCTs for chronic migraine prophylaxis treatments

Silberstein S, etal Cephalalgia 2008; 28:484-95

Prazosin for Posttraumatic Headaches Study – Planned Interim Analysis Results

- Primary outcome measure:
  - Change from baseline, prazosin vs placebo, in 4-week headache frequency (headache diary)

- Secondary outcome measures:
  - Change from baseline, prazosin vs placebo
    - % participants having ≥50% reduction in headache frequency (headache diary)
    - Headache-related disability - Headache Impact Test-6 (HIT-6)
    - PTSD symptoms – PTSD Checklist (PCL)

PTH Study Demographics

	Prazosin	Placebo	Total
Randomized	27	13	40
VA Puget Sound (all Veteran)	13	6	19
Madigan			
Active Duty	9	5	14
Veteran	5	2	7
Men	24	12	36
Women	3	1	4
Age range	23-72	21-64	
Age, mean (std dev)	43 (±11.81)	40 (±11.91)	
Age, median	44	38	
Race/Hispanic ethnicity (H)			
White	17 (2H)	8	25
Black	5	3 (1H)	8
Other	2	2 (1H)	4
Native American	2 (1H)	-	2
Asian/Pacific Islander	1	-	1

Achieved Prazosin Dose

Achieved Dose	Prazosin	Placebo
0 mg	1[1]	
1 mg	1[2]	1[2]
1 mg am/4 mg hs	2	1[3]
2 mg am/6 mg hs	2	
5 mg am/10 mg hs	4	
5 mg am/15 mg hs	3	
5 mg am/20 mg hs	14	11
TOTAL	27	13

[1]Withdrawn after randomization but prior to starting study drug due to baseline orthostatic hypotension

[2] Unable to tolerate minimum dose; withdrawn from study

[3]Withdrew from study after SD1 for personal reasons

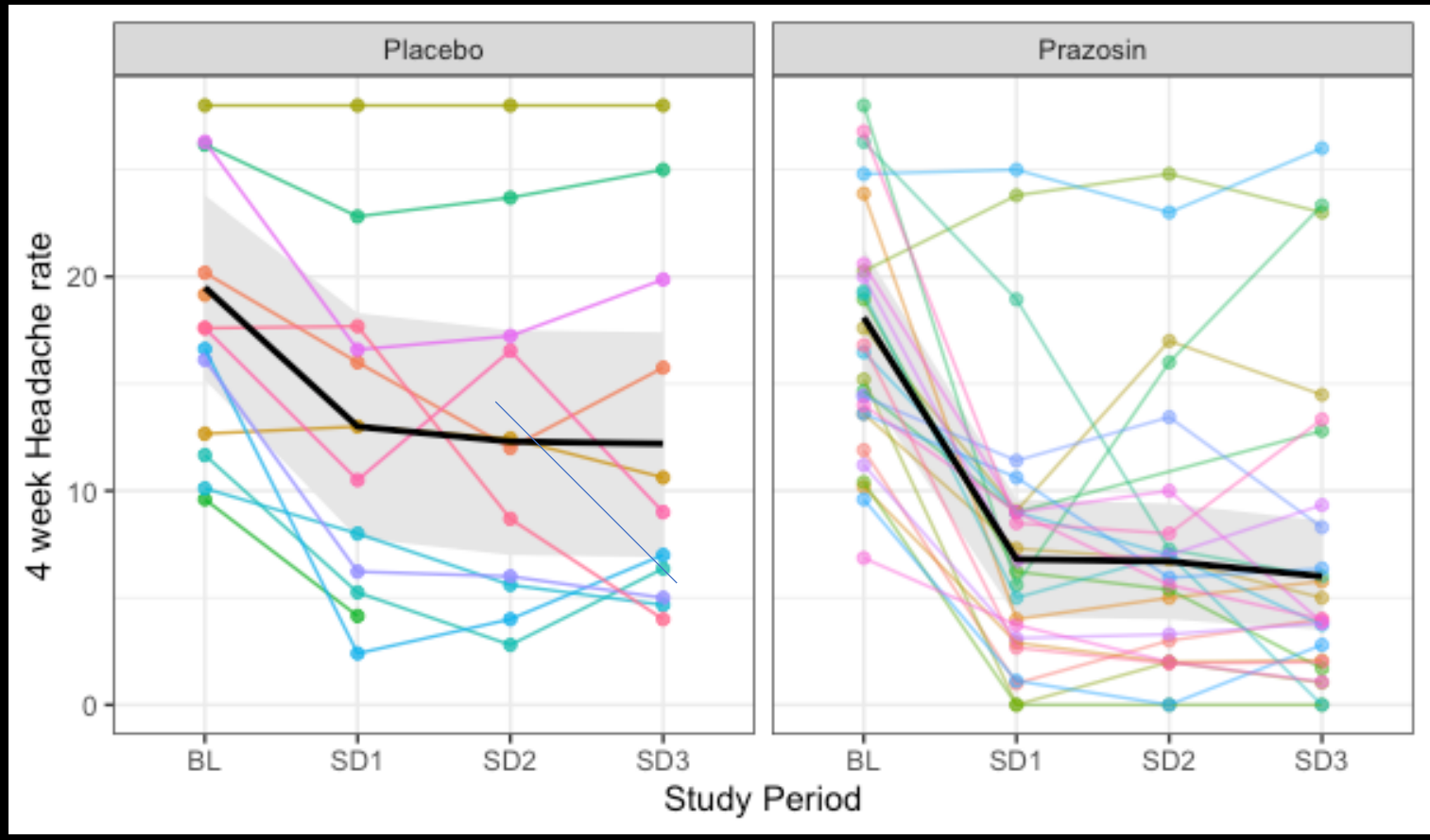
Change in 4-week Headache Frequency

	Placebo (n=13)	Prazosin (n=27)	Praz - Plac
Mean ± SE[1]			
Baseline	19.5 ± 2.2	18.1 ± 1.6	-1.4 ± 2.7
Week 4	13 ± 2.6	6.8 ± 1.4	-6.2 ± 3
Week 8	12.3 ± 2.7	6.7 ± 1.4	-5.6 ± 3
Week 12	12.2 ± 2.7	6 ± 1.3	-6.1 ± 3
Mean difference from baseline ± SE, (95% CI)			
Week 4 - Baseline	-6.5 ± 1.7, (-10.5, -2.4)	-11.3 ± 1.1, (-13.9, -8.7)	-4.8 ± 2, (-9.6, 0)
Week 8 - Baseline	-7.2 ± 1.8, (-11.4, -3)	-11.4 ± 1.1, (-14, -8.8)	-4.2 ± 2.1, (-9.1, 0.7)
Week 12- Baseline	-7.3 ± 1.8, (-11.6, -3.1)	-12.1 ± 1.1, (-14.7, -9.5)	-4.7 ± 2.1, (-9.7, 0.3)

[1] Estimates based on logistic mixed effects regression on study period and treatment interaction. Significance of study period by treatment interaction: p= 0.043

Table 1. Estimated mean 4-wk HA rate (± SE) by study period and treatment group and mean difference (95% CI) by treatment group from logistic mixed effects regression of presence of HA/day on study period by treatment group interaction with study participant as a random effect.

Figure 1. 4-week headache rate by study period and treatment group. Mean trajectory for each group estimated from a logistic mixed effects regression of presence of headache on study period by treatment group interaction.



Headache Features

	Prazosin	Placebo	Total
Randomized	27	13	40
Completed SD1	25	12	37
Completed SD3	25	11	36
Chronic daily headache at BL	19 (76%)	8 (67%)	27 (73%)
Chronic daily headache at SD1	3 (12%)	5 (42%)	8 (22%)
Medication over-use at BL	16 (64%)	9 (75%)	25 (68%)
CDH + MOU at baseline	12 (32%)	5 (42%)	17 (46%)

- Our study population is enriched in CDH. A prospective cross-matched study in a deployed population, PTH vs controls, showed a prevalence of 44% CDH
- Our study population is also enriched in medication over-use at baseline

Couch JR, Stewart KE Headache. 2016; 56(6):1004-1021

Results for ≥50% Reduction in HA Frequency

	Placebo (n=13)	Prazosin (n=27)	Praz/Plac	
	Mean Percent ± SE		Odds ratio (95% CI)	p (LR test)*
Week 4	33 ± 14	56 ± 10	2.5 (0.61, 10.7)	0.19
Week 8	36 ± 15	79 ± 8	6.6 (1.4, 32.1)	0.036
Week 12	36 ± 15	76 ± 9	5.5 (1.2, 25.7)	0.036

Table 2. Mean % of participants experiencing ≥50% improvement in HA frequency from baseline. *From logistic regression of HA% improvement on treatment for each month separately

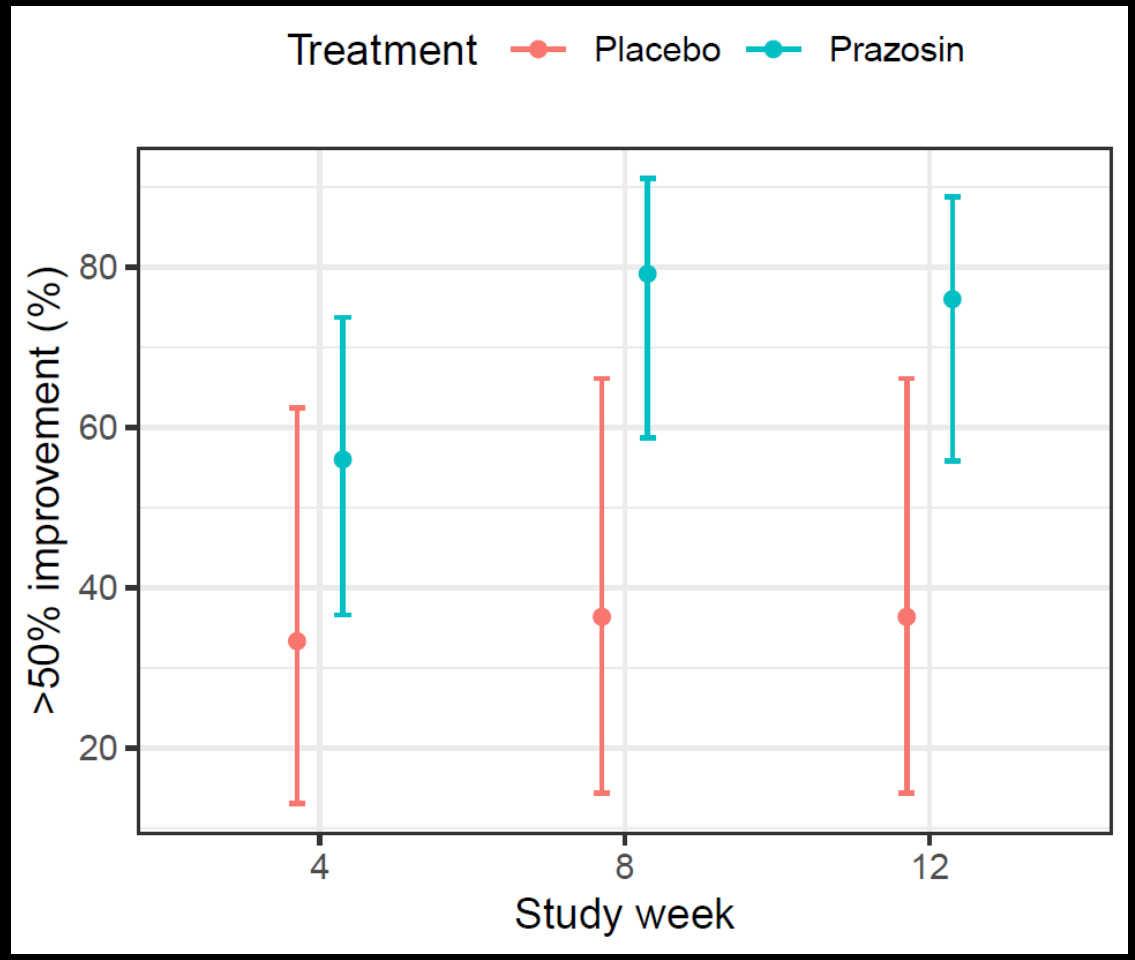


Figure 2: Percent of participants having ≥50% improvement in HA frequency from baseline (Mean, 95% CIs)

Headache Impact Test-6 (HIT-6)

HIT-6™ HEADACHE IMPACT TEST

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please check one box for each question.

1. When you have headaches, how often is the pain severe?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

3. When you have a headache, how often do you wish you could lie down?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

☐ Never ☐ Rarely ☐ Sometimes ☐ Very Often ☐ Always

- Self-reported measure of headache-related disability
- Scoring (points each item):

Never	6
Rarely	8
Sometimes	10
Very Often	11
Always	13

- Possible point range 36-78
- Four categories of impact severity:

≤49	Little or no impact
50-55	Some impact
56-59	Substantial impact
60-78	Severe impact

Change in HIT-6 Score with Treatment

	Placebo (n=13)	Prazosin (n=27)	Praz - Plac
Mean ± SE[1]			
Baseline	64.1 ± 2.3	60.5 ± 1.6	-3.6 ± 2.8
Week 1	63.7 ± 2.4	55.7 ± 1.7	-8 ± 3
Week 4	63.6 ± 2.4	55.1 ± 1.7	-8.4 ± 3
Week 8	65.5 ± 2.4	54.8 ± 1.7	-10.7 ± 3
Mean difference from baseline ± SE, (95% CI)			
Week 1 - Baseline	-0.3 ± 2.1, (-5.3, 4.6)	-4.8 ± 1.4, (-8.1, -1.5)	-4.4 ± 2.5, (-10.4, 1.5)
Week 4 - Baseline	-0.5 ± 2.1, (-5.5, 4.5)	-5.4 ± 1.4, (-8.7, -2.1)	-4.9 ± 2.5, (-10.8, 1.1)
Week 8 - Baseline	1.4 ± 2.1, (-3.6, 6.4)	-5.7 ± 1.4, (-9, -2.4)	-7.1 ± 2.5, (-13.1, -1.1)

[1] Estimates based on linear mixed effects regression on study period and treatment interaction. Significance of study period by treatment interaction: p=0.033

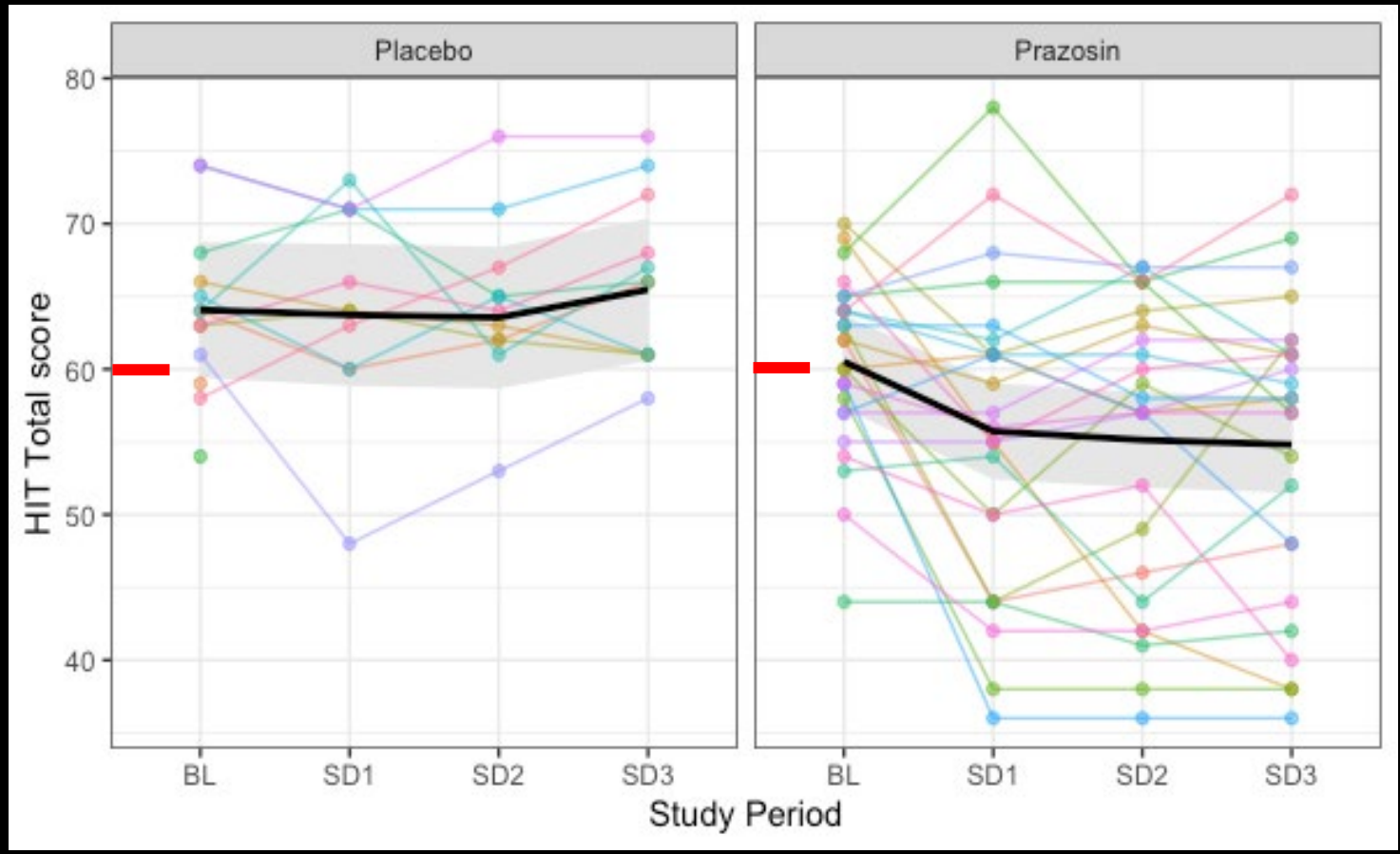


Table 3. Estimated mean 4-week HIT total scores (± SE) by study period and treatment group and mean difference (95% CI) by treatment group from linear mixed effects regression of HIT score on study period by treatment group interaction with study participant as a random effect.

56-59	Substantial impact
60-78	Severe impact

Results for PTSD Checklist (PCL) Scores

	Placebo (n=13)	Prazosin (n=27)	Praz - Plac
Mean ± SE[1]			
Baseline	33.7 ± 5.7	34.1 ± 3.9	0.4 ± 6.9
Week 1	31.7 ± 5.8	26.2 ± 3.9	-5.5 ± 7
Week 4	35.4 ± 5.8	23.8 ± 3.9	-11.6 ± 7
Week 8	31.4 ± 6	26 ± 3.9	-5.3 ± 7.1
Mean difference from baseline ± SE, (95% CI)			
Week 1 - Baseline	-2 ± 3.9, (-11.3, 7.3)	-7.9 ± 2.5, (-13.9, -1.9)	-5.9 ± 4.6, (-16.9, 5.1)
Week 4 - Baseline	1.6 ± 3.9, (-7.7, 10.9)	-10.3 ± 2.5, (-16.3, -4.3)	-12 ± 4.6, (-23, -0.9)
Week 8 - Baseline	-2.3 ± 4.1, (-12.1, 7.4)	-8.1 ± 2.5, (-14.1, -2.1)	-5.7 ± 4.8, (-17.1, 5.7)

[1] Estimates based on linear mixed effects regression on study period and treatment interaction. Significance of study period by treatment interaction: p=0.075

Table 5. Estimated mean 4-week PCL total scores (± SE) by study period and treatment group and mean difference (95% CI) by treatment group from logistic mixed effects regression of HIT score on study period by treatment group interaction with study participant as a random effect.

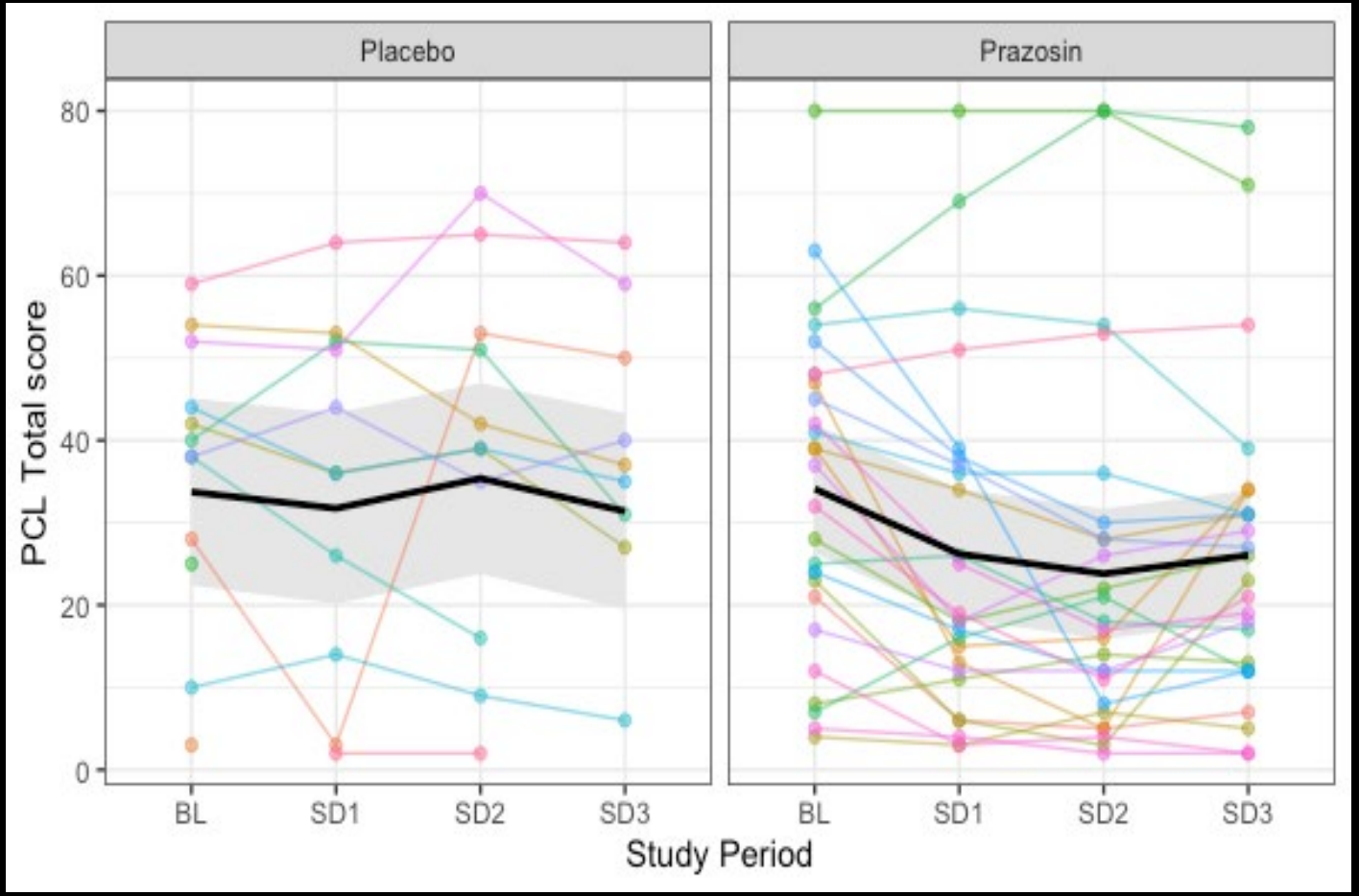


Figure 4. PCL total score by study period and treatment group. Mean trajectory for each group estimated from a logistic mixed effects regression of PCL score on study period by treatment group interaction.

PTH and Sleep

- Analysis of sleep self-report measures and actigraphy data is underway
- Analysis complicated by poor/sporadic correlation between the sleep diaries and actigraphy results – as also reported for other studies
- Our group has developed a method for reconciling discrepancies

Comparison of Prazosin for PTH Data with Other Studies

	N	Baseline 4-wk HA frequency, mean number mod-sev	Mean change in 4-wk freq mod-sev HA, BL to wk 12 (SD)	% having ≥50% decrease in mean mod-sev HA days, BL to wk 12	Mean HIT-6 score at BL (SD)	Mean change in HIT-6 score, BL to wk 12 (SD)
Prazosin for Posttraumatic Headaches due to Mild TBI (RCT)						
Prazosin	27	18.1 (1.6)	-12.1 (1.1)	76% ± 9	60.5 (1.6)	-5.7 (1.4)
Placebo	13	19.5 (2.2)	-7.3 (1.8)	36% ± 15	64.1 (2.4)	1.4 (2.1)
Praz-plac		-1.4 (2.7)	-4.7 (2.1)	40%	-3.6 (2.8)	-7.1 (2.5)
Erenumab for Posttraumatic Headaches due to Mild TBI (open label) (Ashina H et al. J of Headache and Pain. 2020; 21:62)						
Erenumab open label	89	15.7 (9.6)	-2.8 (6.8)	28%	61.6 (5.2)	-4.6 (7.3)
Topiramate for Chronic Migraine (RCT) (Silberstein SD et al. Headache. 2007; 47:170-180; Silberstein et al. Headache. 2009;49(8):1153-62.)						
Topiramate	153	17.1 (5.8)	-6.4 (5.8)	37.3%	Not available	Not available
Placebo	153	17.0 (5.0)	-4.7 (6.1)	28.8%	Not available	Not available
Top-plac		0.1	-1.7	8.5%	Not available	Not available

One Prazosin Study Participant – "Don"

- Mid-50s male Marines, Navy, multiple combat deployments
- Headache onset within 1 day of close-range IED blast in 2006
- Frequent severe headaches unresponsive to multiple medications and other treatments
- 5 types of headaches – migraine, tension-type, cervicogenic, mixed

One Prazosin Study Participant – "Don"

- Failed prior multiple treatments: topiramate, gabapentin, atenolol, verapamil, butterbur, acupuncture, massage, TENS unit, Cefaly
- Current prophylaxis: Botulinum toxin, amitriptyline, magnesium, riboflavin, Coenzyme Q
- Current rescue medications: "cocktail" consisting of tizanidine, diclofenac, cyproheptadine, rizatriptan +/- Vicodin when especially severe

Don's Response to Treatment with Study Drug

4-week	Pre-Treatment	Post-Treatment
HA frequency (days)	12	4
Rescue med use (days)	11	4

"If I'm on placebo, I want to stay on it"

Research Directions

- Relationship of PTH to glymphatic function
- Identify characteristics of prazosin responders with the goal of personalizing treatment of PTH and comorbid conditions
- Biomarker analysis, including serum, pupillometry

Thanks to:

VA MIRECC Study Team

- Elaine Peskind, CDA Mentor
- Clinicians who have assisted with study visits
- Investigators analyzing sleep data
- Conner Engle, Study Coordinator
- Soleil Groh, Research Assistant
- Jane Shofer, biostatistician
- Carol Xiang and data team
- Administrative assistants Hollie Holmes, Molly Chinn, Daniel Murray, Kimberly Harms

Madigan Study Team

- Dr. Paul Savage, Site PI
- Dr. Eileen Poupore, clinician
- Ameryth Hargrove, Site Study Coordinator
- Tammy Williams, Social Worker Clinician