Prazosin for Posttraumatic Headaches - Randomized Controlled Trial in Veterans and Active Duty Service Members

MIRECC PRESENTS

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Outline

- Background
  - Posttraumatic headaches (PTH) – context
  - Why prazosin?
    - Prior observations
    - Theoretical mechanism(s) of action
- Prazosin for PTH Randomized Controlled Trial (RCT)
  - Methods
  - Results of planned interim analysis
  - PTH participant case
- 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
- Other postconcussive symptoms - sleep disturbances, cognitive issues, photophobia, autonomic dysfunction, dizziness, personality changes (especially irritability), anxiety, depression, PTSD symptoms

Tyler G et al 1980
Theeler B et al 2013

Posttraumatic Headaches

- Phenotypically similar to primary headaches, most commonly (when persistent) migraine
- 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

- Rescue medications – interrupt onset or treat pain or other symptoms:
  - Nonspecific pain relievers - acetominophen, aspirin, NSAIDs, combination medications, e.g., Excedrin migraine, opioids
  - Medications specific to migraines – serotinergic agonists (ditans, triptans, dihydroergotamine [DHE]); CGRP inhibitors (CGRP receptor antagonists, CGRP monoclonal antibodies)
  - Medications to treat symptoms, including nausea, vertigo, muscle spasms
  - "Cocktail" – multiple medications from different classes taken at once
  - ER treatment – usually iv fluids, iv medications that might include DHE, sodium valproate, dilaudid, ketorolac, lidocaine, dopamine receptor blocker, dexamethasone

Posttraumatic Headaches

- Prophylactic medications – prevent headache onset:
  - Antihypertensives (beta blockers, calcium channel blockers)
  - Antiepileptics (neuronal stabilizing agents)
  - Antidepressants (tricyclics, SSRIs, SNRIs)
  - CGRP inhibitors
  - Botulinum toxin
  - Nerve block injections
  - Supplements (riboflavin, CoQ, butterbur, feverfew, magnesium)
  - Nonmedication treatments (neuromodulation, biobehavioral therapies)
- FDA-approved for chronic migraine prophylaxis:
  - Propranolol, timolol
  - Topiramate, valproic acid
  - Botulinum toxin

Posttraumatic Headaches

- Overlapping symptoms raises the question of whether PTH has a unique pathophysiology or if head trauma triggers migraines in a susceptible person

- Recent evidence suggests PTH and migraine have different clinical and imaging features

- Brain imaging findings include
  - Differences in regional volumes, cortical thickness, surface area
  - Iron accumulation in multiple brain regions correlated with HA frequency and number of lifetime mTBIs
  - Changes in fiber tracts that play a role in pain processing and integration
  - Changes in static and dynamic functional MRI connectivity

Schwedt, T et al 2017

Nikolova S et al 2021

Chong C et al 2021

Dumkrieger G et al 2019

Acute vs Persistent Posttraumatic Headaches

- Acute (<3 mo from injury) –
  - Tend to be tension-type or have less well-defined features, which may reflect acute brain injury effects
  - Usually resolve, but if continue are termed

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

Episodic vs Chronic Headaches

- Both tension-type and migraine headaches can transform from episodic to chronic
- Chronic tension-type:
  - ≥15 headache days/month lasting hours to days or unremitting; may have mild nausea
- Chronic migraine:
  - ≥15 headache days/month which on ≥8 days/mo have migraine features – i.e., not every day is a migraine
- 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 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

- Amplification of pain signaling and perception
- May be due to
  - Plasticity of the somatosensory nervous system in response to neural injury, inflammation
  - Alteration of endogenous pain inhibition pathways
- Net effect –
  - Uncoupling and centralization of pain sensation from noxious peripheral stimuli
  - Previously subthreshold inputs generate increased response (facilitation; potentiation) resulting in sensory hypersensitivity

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

Central Sensitization

- Features of central sensitization:
  - Allodynia – heightened sensitivity to normally painless stimuli, for example wearing glasses, earrings, hats, combing hair
  - Hyperalgesia – heightened sensitivity to pain
- Common in chronic migraine, fibromyalgia, temporomandibular joint dysfunction, neuropathy, and other chronic pain syndromes

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

Pathophysiology of PTH

- Emotional and affective responses to chronic pain are common
- For chronic migraine, one potential response is anticipatory anxiety, which can lead to taking medications pre-emptively to avoid having headaches
- This can result in “medication over-use” headaches that are indistinguishable from the original headaches
- Occurs in up to 40% of patients with PTH

Medication Over-use

- Regular overuse for >3 months of one or more headache “rescue” medications:
  - Simple analgesics (acetaminophen, aspirin, or other NSAID) on ≥15 days/month
  - Triptans, ergotamines, opioids, combination formulations, or use of multiple drug classes on ≥10 days/month

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 afferent signaling

Pathophysiology of PTH

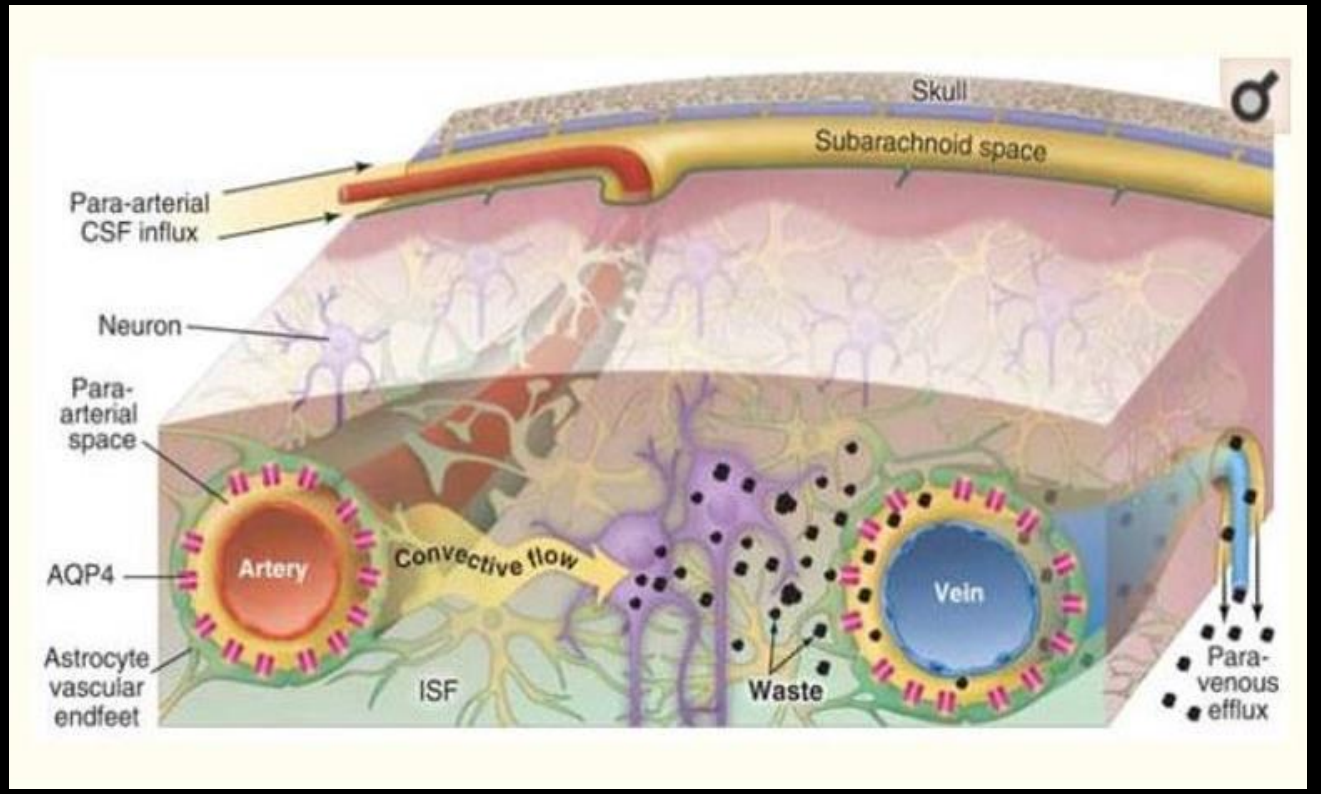
- Neurometabolic changes
- Disrupted neural networks
- Changes in excitation thresholds (e.g., cortical spreading depression)
- Release of pain mediators (e.g., calcitonin gene-related peptide - CGRP - and others)
- Impaired descending pain modulation
- Altered astrocyte function
- Glymphatic dysfunction

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

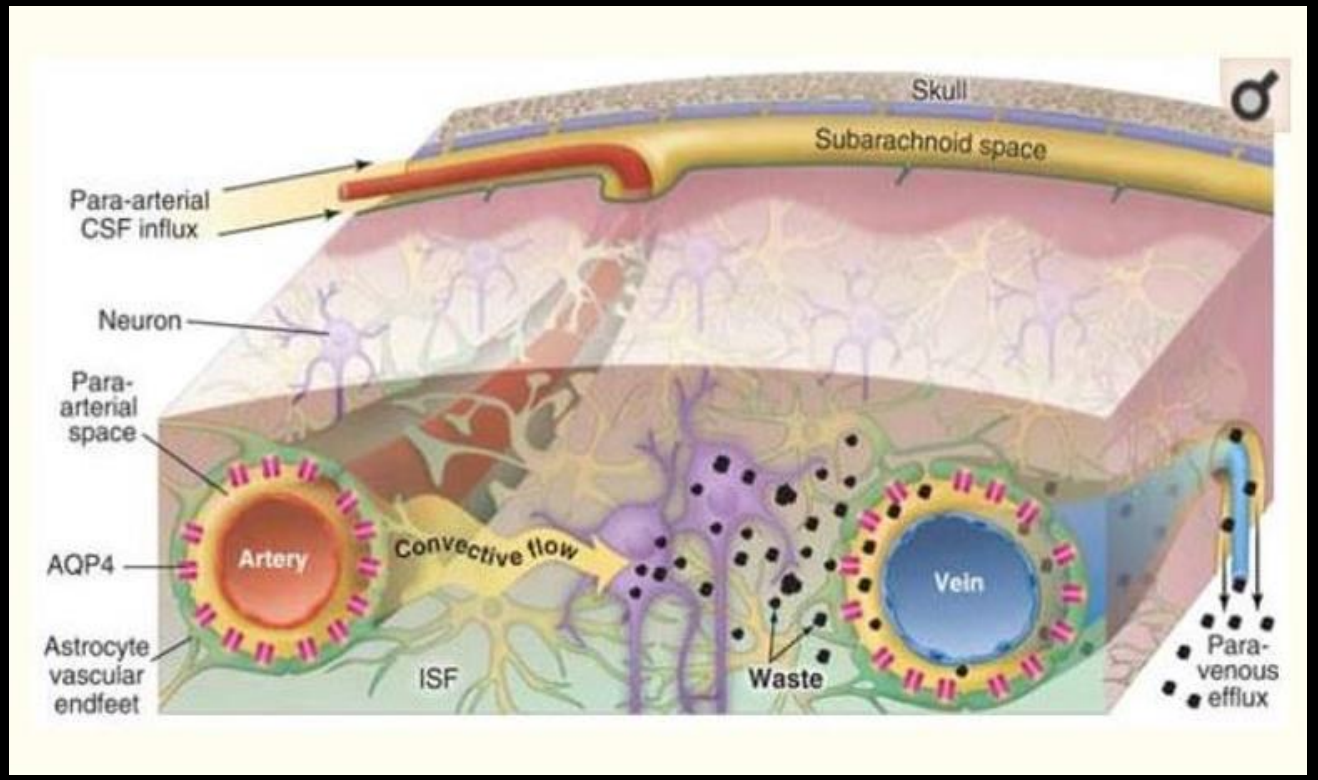
- Functions to clear toxic metabolites from the CNS via convective exchange of CSF and interstitial fluid (ISF)
- CSF influx along arteries; ISF efflux along veins. Function depends on perivascular channels formed by astroglial end-feet, which express AQP-4 water channels
- During sleep, interstitial 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 restorative function of sleep may result from enhanced removal of neurotoxic waste products that accumulate during wakefulness
- Wakefulness is driven in large part by LC–derived NA signaling
- AR antagonists, including prazosin, increase interstitial volume in awake mice to levels similar to sleep/anesthesia
- Adrenergic signaling may be important in modulating both cortical neuronal activity and interstitial space volume



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

- A neurologist with migraines who was started on terazosin for hypertension had resolution of his longstanding headaches
- Inspired by this experience, 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 1997

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 1997

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 74 OEF/OIF Veterans with blast mTBI, sleep disturbances, and PTH (71 with PTSD)
- Prazosin was titrated over 5 weeks to a maximum dose of 7 mg at bedtime

Ruff et al 2009

Comparison of effect of intervention between veterans who did or did not complete dosing of prazosin. We calculated *p*-values based on mixed-model analysis of variance (ANOVA).

Performance of Veterans ($N = 74$)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Completed Prazosin ($n = 62$)				
Baseline (mean ± SE)	16.10 ± 0.33	24.10 ± 0.26	7.18 ± 0.18	13.40 ± 1.07
After Intervention (mean ± SE)	6.37 ± 0.26	28.90 ± 0.15	3.58 ± 0.13	4.26 ± 0.35
p-Value by ANOVA *F*-Test	<0.001	<0.001	<0.001	<0.001
Did Not Complete Prazosin ($n = 12$)				
Baseline (mean ± SE)	15.90 ± 0.42	24.70 ± 0.53	6.50 ± 0.45	7.17 ± 0.66
After Intervention (mean ± SE)	12.00 ± 0.55	24.20 ± 0.53	6.67 ± 0.48	7.42 ± 0.72
p-Value by ANOVA *F*-Test	<0.001	NS	NS	NS

ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, NS = not significant, SE = standard error of the mean.

Table 3.

Comparison done at end of 6-month follow-up period of performance of veterans who were or were not taking prazosin. We calculated *p*-values based on mixed-model analysis of variance (ANOVA).

Performance of Veterans ($N = 74$)	ESS Score (0–24)	MOCA Score (0–30)	Headache Pain Intensity (0–10)	Headache Frequency (No./Month)
Taking Prazosin ($n = 64$, mean ± SE)	3.97 ± 0.18	29.00 ± 0.13	2.39 ± 0.12	1.88 ± 0.14
Not Taking Prazosin ($n = 10$, mean ± SE)	10.50 ± 0.58	24.80 ± 0.51	5.80 ± 0.29	7.00 ± 0.54
p-Value by ANOVA *F*-Test	<0.001	<0.001	<0.001	<0.001
All Veterans	4.85 ± 0.31	28.40 ± 0.21	2.85 ± 0.17	2.57 ± 0.25

ESS = Epworth Sleepiness Scale, MOCA = Montreal Cognitive Assessment, SE = standard error of the mean.

Ruff et al 2009

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

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

Raskind et al, 2013

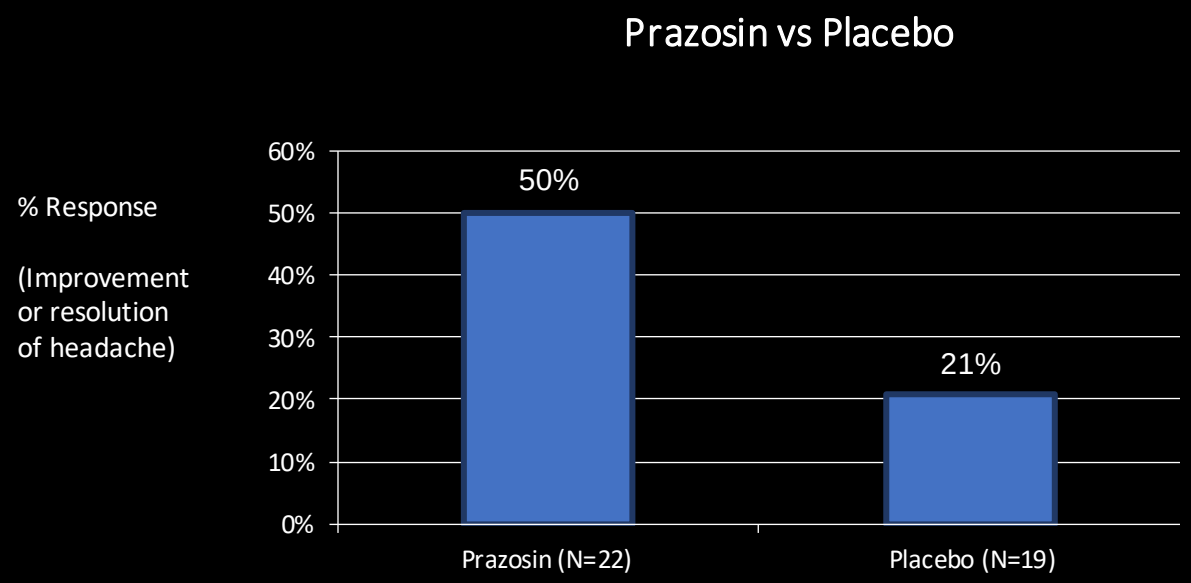
Prazosin for PTSD Study Participants with Headaches at Baseline

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, 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, 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 2008

Prazosin for Posttraumatic Headaches Study – Planned Interim Analysis Results

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

- Secondary outcome measures:
  - Change from baseline, prazosin vs placebo
    - % participants having ≥50% reduction in headache frequency
    - 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

PTH Study Participant Characteristics

	Prazosin	Placebo
Age at time of PTH-inciting injury		
Range	20 - 43	19 - 39
Mean ± SD	29 (±7.83)	25 (±5.55)
Duration of PTH, onset to study entry (years)		
Range	2-48	1-42
Mean ± SD	14 (±10.94)	14 (±13.83)
Mechanism of injury of PTH-inciting mTBI		
Blast	3	1
Impact	12	9
Blast + impact	6	2
Neck (including whiplash)	1	-
Blast + neck	1	-
Impact + neck	2	1
Blast + impact + neck	2	-
Any history of blast exposure with mTBI	15	3
Lifetime no. of mTBIs with and without LOC		
Range	1-49	1-36
Mean ± SD	8.7 (±9.63)	9.2 (±10.02)

PTH Study Participant Characteristics

Number of current + past prophylactic and rescue medications		
Range	2 - 23	0 - 11
Mean ± SD	6.5 (±5.34)	5.3 (±2.70)
Median	4	5
0-2	6 (22.2%)	1 (7.7%)
3-6	13 (48.2%)	8 (61.5%)
>6	8 (29.6%)	4 (30.8%)
Number non-medical treatments current, past, rescue, prophylactic*		
Range	0 - 9	0 - 5
0-2	20 (74.1%)	9 (69.2%)
3-6	6 (22.2%)	4 (30.8%)
>6	1 (3.7%)	0 (0%)

*Treatments specifically for the purpose of alleviating headaches, including acupuncture, chiropractic, nerve injections other than botulinum toxin, neuromodulation, yoga, meditation, cannabis products, caffeine

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

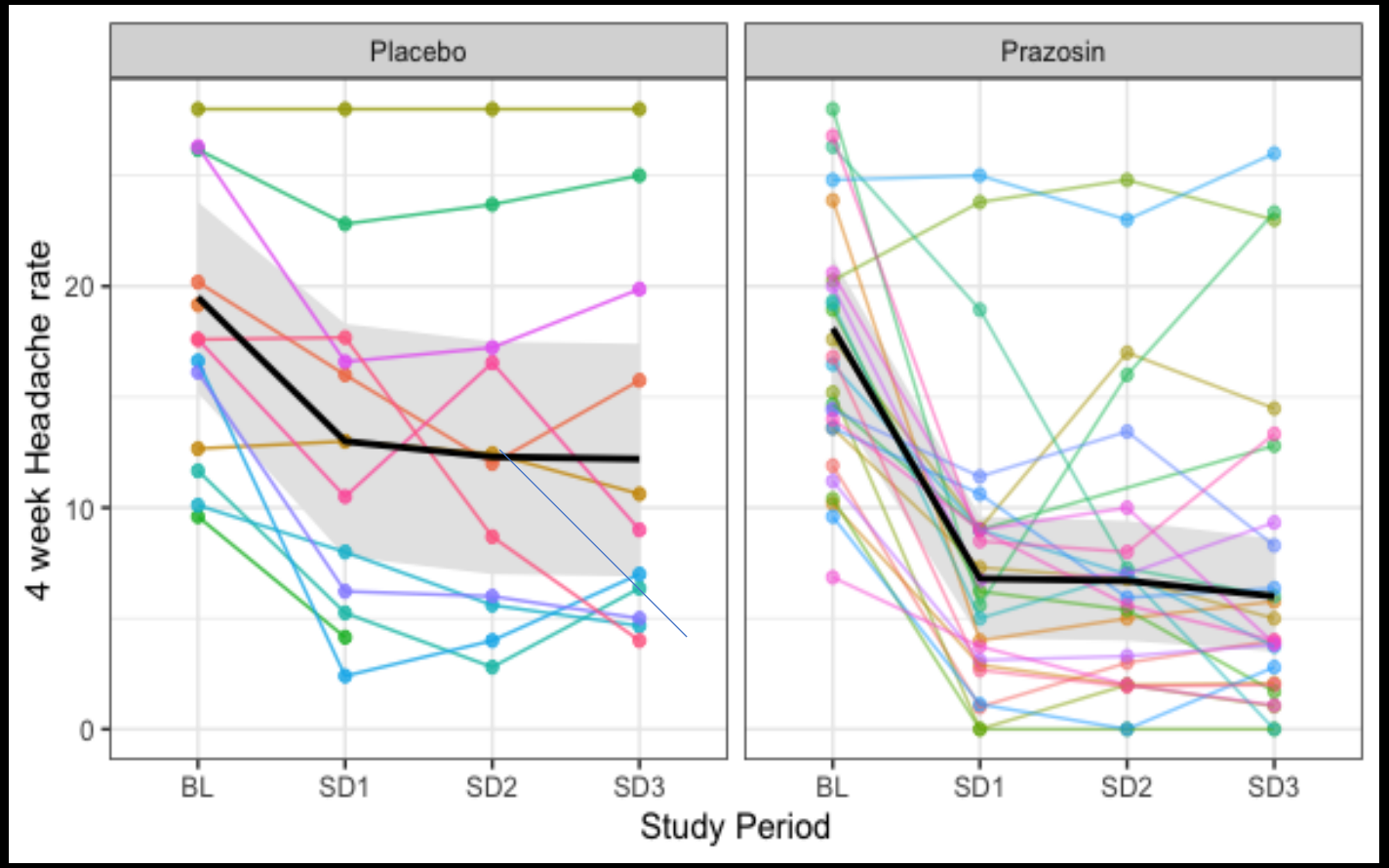
Primary Outcome Measure

	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

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.

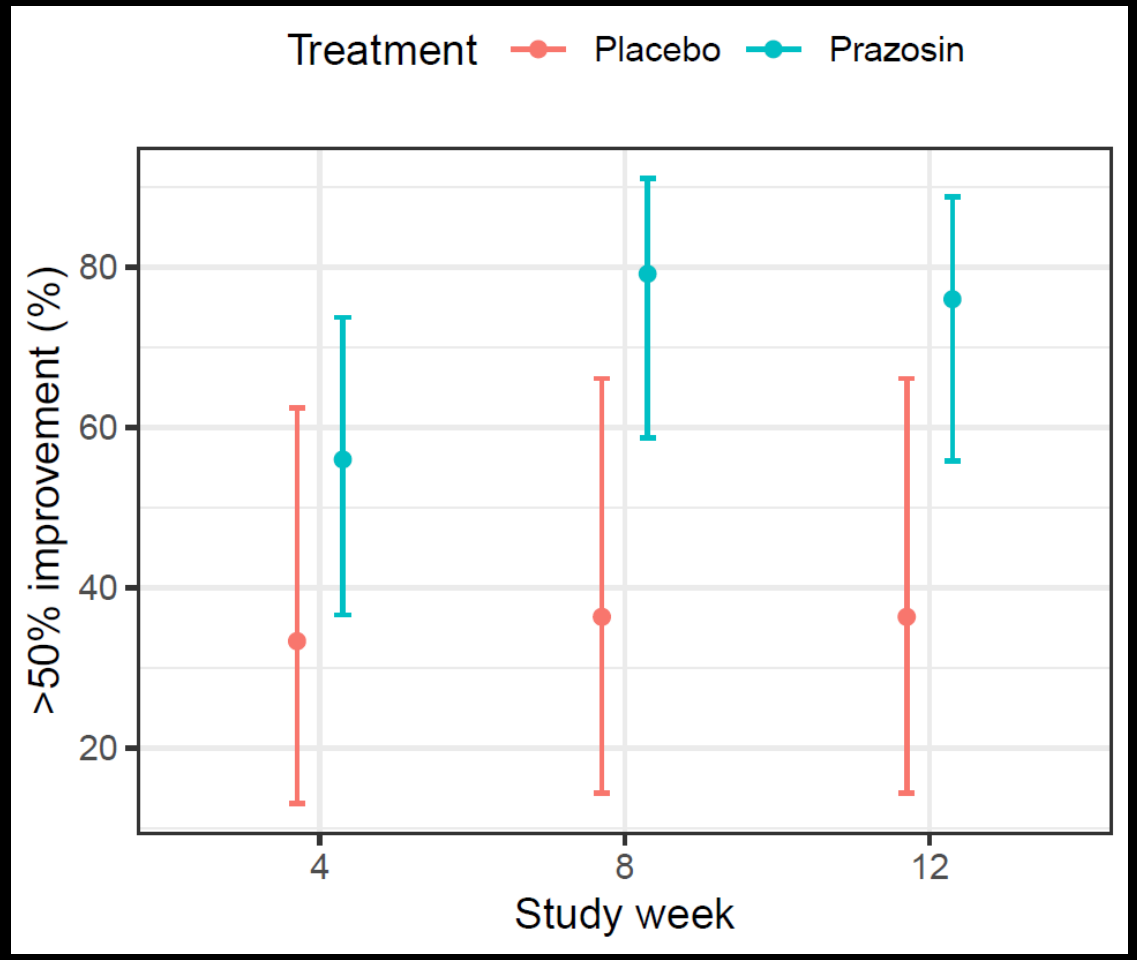
Change in 4-week headache frequency by study period and treatment group



Results for ≥50% Reduction in Headache 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

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



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

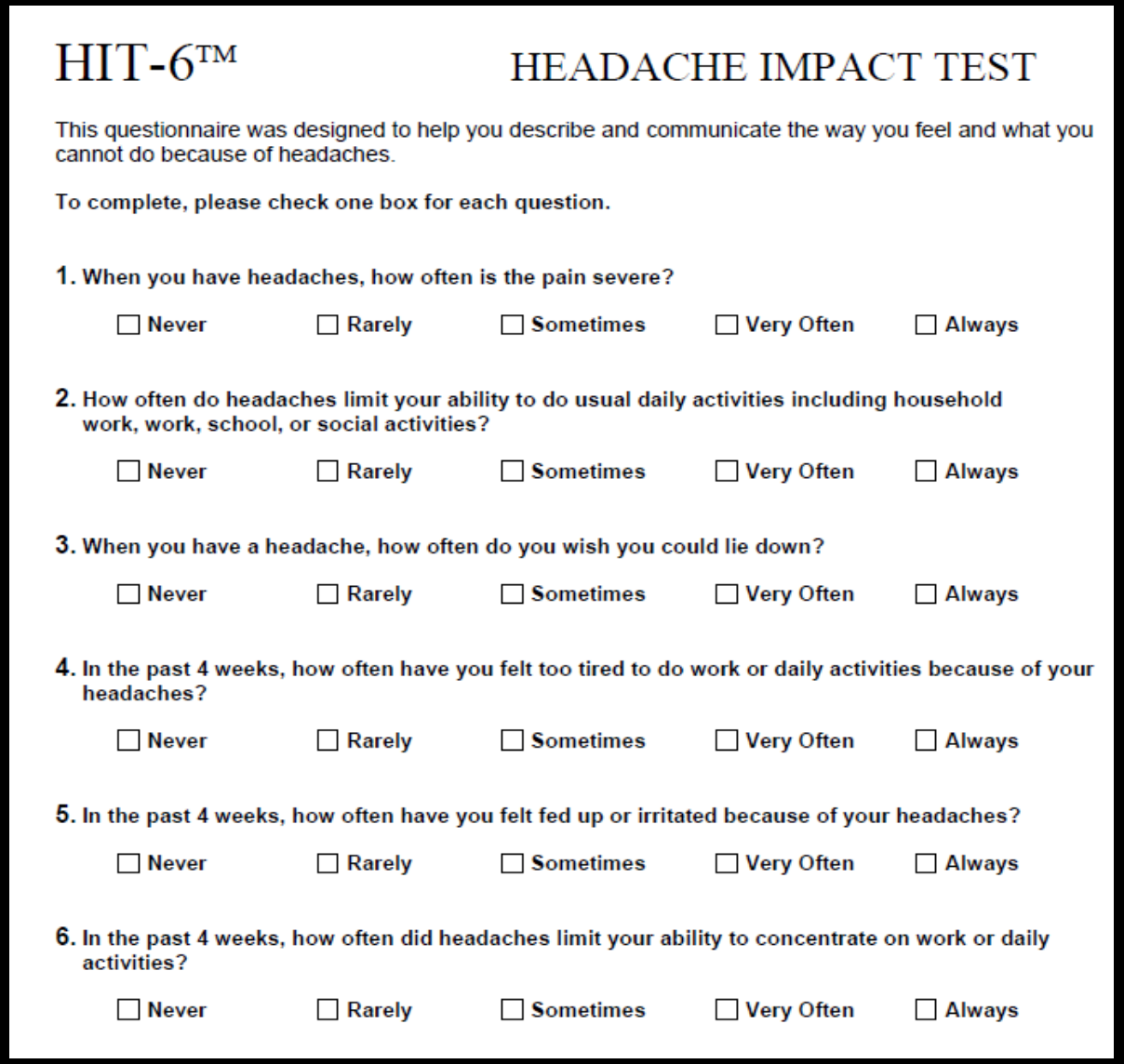
PTH Study Participant Headache Features

	Prazosin	Placebo	Total
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 chronic daily headaches (CDH) – 73% at baseline
- A prospective cross-matched study in a deployed population, PTH vs non-TBI deployed controls, showed a prevalence of CDH in 44% of PTH group vs 7% of controls
- Our study population is also enriched in medication over-use at baseline (68%)

Couch JR, Stewart KE, 2016

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:

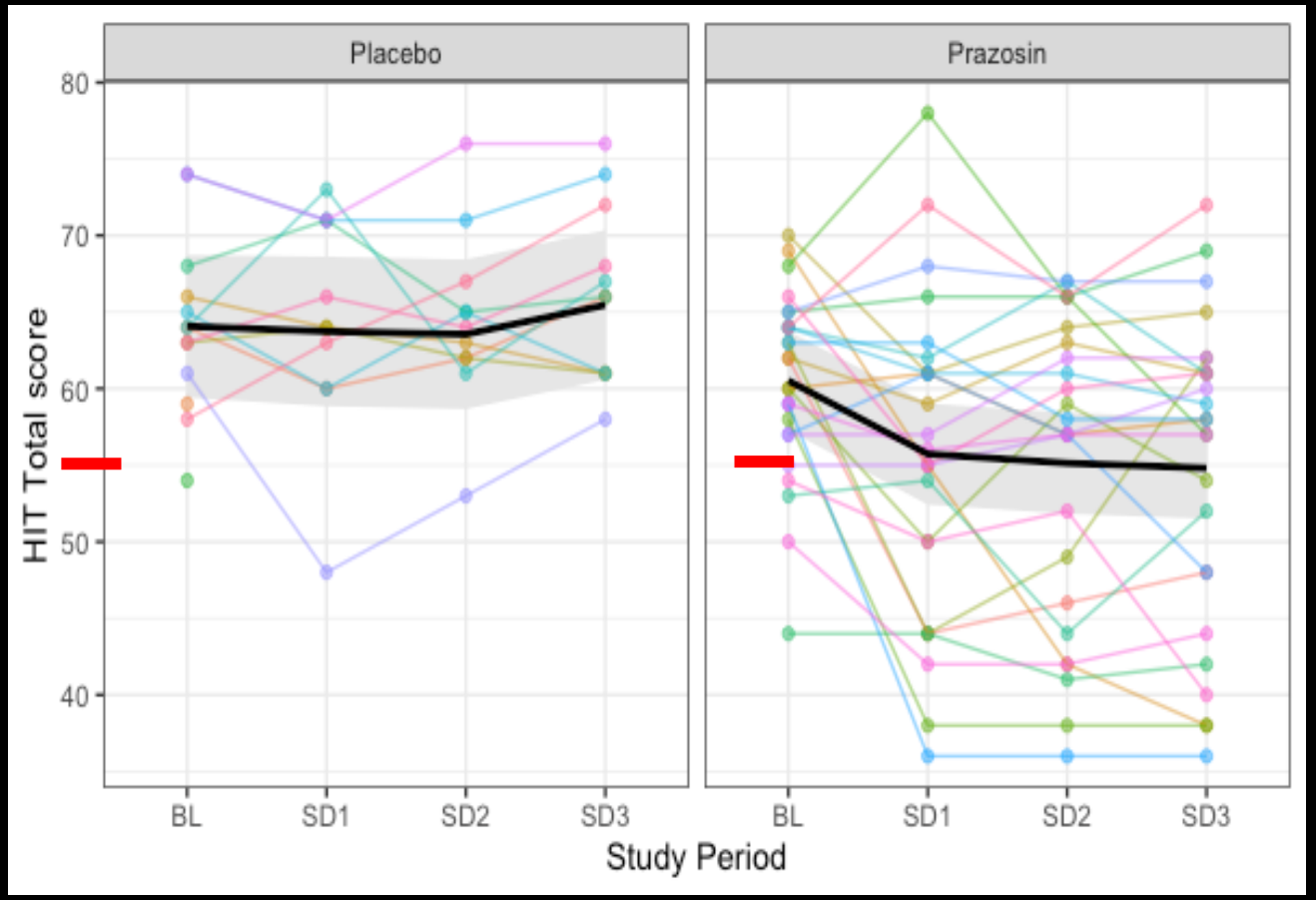
≤49	Little or no impact
50-55	Some impact
❖ 56-59	Substantial impact
❖ 60-78	Severe impact

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 4	63.7 ± 2.4	55.7 ± 1.7	-8 ± 3
Week 8	63.6 ± 2.4	55.1 ± 1.7	-8.4 ± 3
Week 12	65.5 ± 2.4	54.8 ± 1.7	-10.7 ± 3
Mean difference from baseline ± SE, (95% CI)			
Week 4 - 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 8 - 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 12 - 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

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.



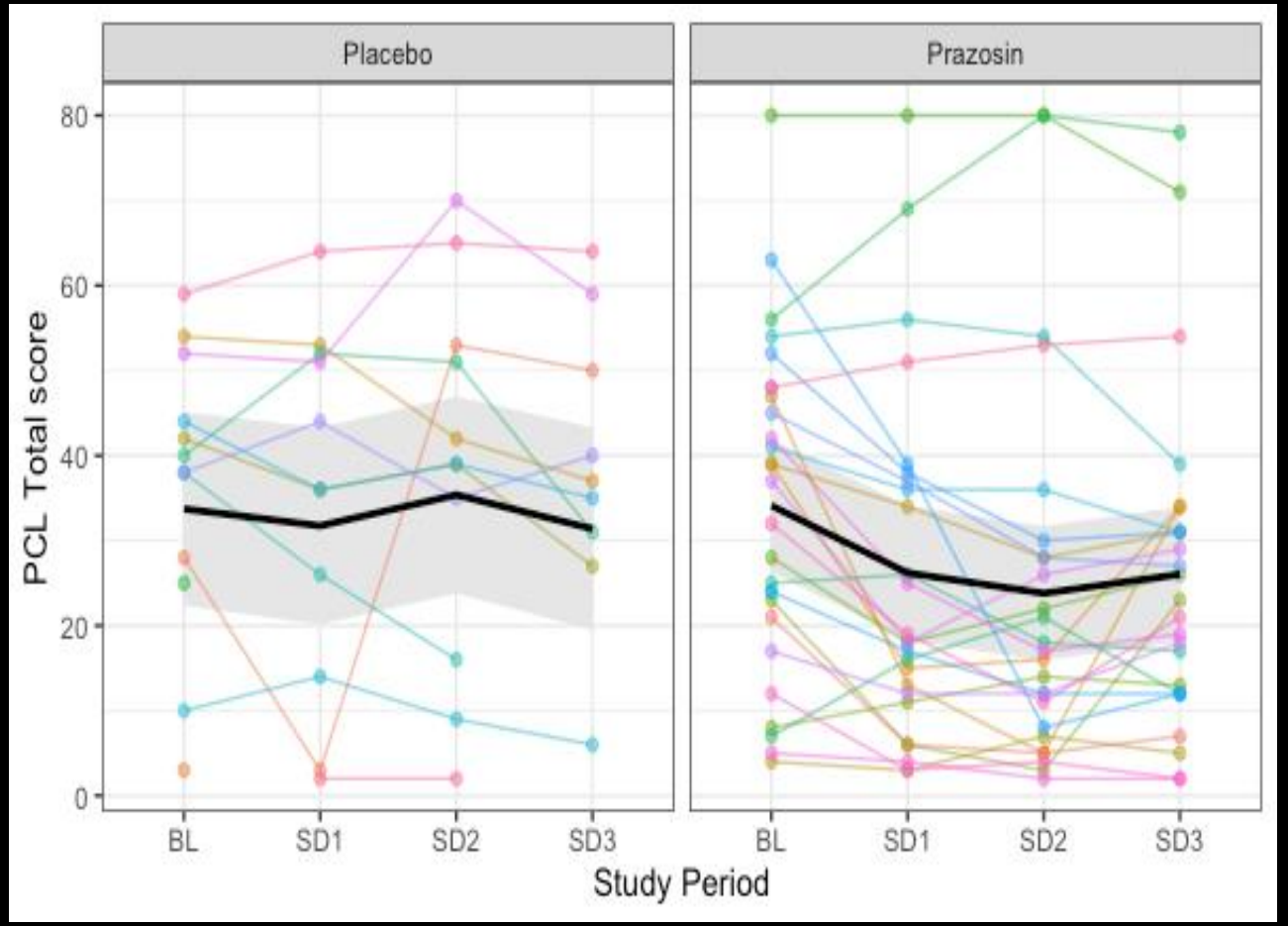
The mean scores in the prazosin group dropped to the “some impact” range from the “severe impact” range, and for some people to the “little or no impact” range

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 4	31.7 ± 5.8	26.2 ± 3.9	-5.5 ± 7
Week 8	35.4 ± 5.8	23.8 ± 3.9	-11.6 ± 7
Week 12	31.4 ± 6	26 ± 3.9	-5.3 ± 7.1
Mean difference from baseline ± SE, (95% CI)			
Week 4 - 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 8 - Baseline	1.6 ± 3.9, (-7.7, 10.9)	-10.3 ± 2.5, (-16.3, -4.3)	-12 ± 4.6, (-23, -0.9)
Week 12 - 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

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 PCL score on study period by treatment group interaction with study participant as a random effect.



PCL total score by study period and treatment group

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

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Madigan Study Team

- Dr. Paul Savage, Site PI
- Dr. Eileen Poupore, clinician
- Ameryth Hargrove, Site Study Coordinator
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