CONCUSSION AND HEAD INJURY (A KAYE, SECTION EDITOR)



Treatment Options for Posttraumatic Headache: A Current Review of the Literature

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Accepted: 4 December 2023 / Published online: 22 December 2023 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2023

Abstract

Purpose of Review We evaluate evidence-based treatments for posttraumatic headache (PTH), a secondary headache disorder resulting from traumatic brain injury (TBI), comprising nearly 4% of all symptomatic headache disorders. Utilizing recent publications, we aim to inform clinicians of current treatment methods.

Recent Findings There is limited research on PTH treatment. A randomized controlled trial (RCT) of metoclopramide with diphenhydramine for acute PTH found that the treatment group (N=81) experienced more significant pain improvement than placebo by 1.4 points. For persistent PTH, an open-label study of erenumab (N=89) found that 28% of participants reported \geq 50% reduction in moderate-to-severe headache days, but an RCT of fremanezumab showed a non-significant reduction in moderate-to-severe headache days. A randomized crossover study of 40 patients with persistent PTH found that onabotulinum toxin-A decreased cumulative number of headaches/week by 43.3% in the treatment group and increased by 35.1% among placebos. In a study of military veterans with severe posttraumatic stress disorder and persistent/delayed onset PTH (N=193), patients who received Cognitive Behavioral Therapy reported significant improvements in headache-related disability compared to usual care (aggregate mean HIT-6, -3.4). A transcranial magnetic stimulation (N=24) study found that 58% of participants with mild TBI-related headache experienced a 50% reduction in headache frequency.

Summary New studies indicate promise in improving clinically important outcomes of PTH. However, more research is necessary to determine the optimal treatment and whether combining pharmacologic and nonpharmacologic treatment versus a single modality is more effective.

Keywords Posttraumatic headache · Traumatic brain injury · Pharmacological treatment · Nonpharmacologic treatment

Background

Posttraumatic headache (PTH) is one of the most common headache disorders globally, accounting for nearly 4% of all symptomatic headache disorders [1]. In ascertaining acute versus persistent PTH, the International Classification of Headache Disorders (ICHD)-3 identifies acute PTH as occurring within three months of traumatic brain injury

Mia T. Minen minenmd@gmail.com (TBI); persistent PTH is diagnosed if the headache continues after three months post-TBI [2].

Treatment for PTH is often determined based on phenotype [2, 3]. PTH most commonly presents as a migraine-like or tension-type phenotype [3, 4]. Given the prevalent and disabling nature of PTH, physicians must be knowledgeable on current pharmacological and nonpharmacological treatment options. As no treatment guidelines exist for PTH [5, 6], we review the existing research to help providers identify potential treatments. Notably, there are no Food and Drug Administration-approved treatments for PTH [6]; therefore, all treatments discussed below are considered off-label. We begin by discussing pharmacological treatment, such as behavioral therapies and neuromodulation.

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Pharmacological Treatment

Medications to Stop or Reduce Symptoms

Even though PTH is the most common complaint resulting from the ~ 1.7 million TBI-related adult emergency department (ED) visits in the United States [7], there is limited research on evidence-based treatments for patients with PTH [3]. In a study of 160 patients presenting to the ED with acute PTH, researchers aimed to identify the effectiveness of metoclopramide with diphenhydramine on patient symptoms [8]. They found that 20 mg of metoclopramide with diphenhydramine (25 mg) was more effective for associated headache pain relief than the placebo within one hour after administration (5.2 vs. 3.8, mean improvement using a 0-10 pain scale) [8]. In addition to headache-related symptom reduction, patients who received the intervention reported fewer post-concussive symptoms in the ED and within one week after discharge than those who received the placebo (in the ED, 16 vs. 25; one week after discharge, 14 vs. 21) [8]. One week after discharge from the ED, headache outcomes did not differ between the intervention and placebo groups, and most patients did not achieve sustained headache pain relief [8]. Despite the initial effectiveness of metoclopramide with diphenhydramine in reducing acute PTH symptoms [8], additional research is necessary to determine treatment duration and optimal dose. Moreover, the efficacy of metoclopramide with diphenhydramine is yet to be determined for patients with persistent PTH.

Literature on oral medications for PTH in outpatient settings supports over-the-counter non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin or ibuprofen [3, 6]. In a study of 100 adults with persistent PTH, researchers found that non-opioid analgesics had the highest reported usage of acute medications, including current and previous use (94%) [3]. However, 53% of subjects who used nonopioid analgesics reported a lack of efficacy for pain relief [3]. Despite these inconsistencies in efficacy, NSAIDs are commonly the first recommended treatment for PTH [3, 6]. Additionally, since PTH often presents as migraine-like, triptans, a common migraine medication, are frequently used to treat PTH [6, 9]. However, evidence on the effectiveness of triptans for PTH treatment is scarce. In the same study, almost half of the subjects who used triptans reported a lack of efficacy for pain relief (19/39) [3]. A potential benefit of triptans is the availability of different formulations, including orally dissolving tablets, nasal sprays, and injectable medication, which can be helpful for patients with nausea and/or vomiting, a common symptom of PTH [9].

Medications to Prevent Symptoms

Oral Medications

Clinicians have anecdotally found that anticonvulsants (e.g., gabapentin) and tricyclic antidepressants (TCAs) (e.g., amitriptyline) are effective for preventative treatment of persistent PTH (11). In a cohort study on the effects of gabapentin and TCAs (amitriptyline and nortriptyline), 277 patients with persistent PTH followed varying treatment plans (gabapentin, n=60; TCAs=94; no medication=123) [10]. The mixed-effects analysis indicated a slight overall decrease in symptom severity among patients regardless of treatment plan [10]. Symptom severity significantly decreased over time after the first physician visit (B=0.08, P<0.001) but not as a result of treatment [10]. Meanwhile, the piecewise regression analysis showed that patients treated with TCAs reported significantly lower symptom severity at the first follow-up visit than the prior visit (i.e., when the medication was prescribed) (P=0.005) [10]. However, whether TCAs caused this decrease cannot be determined due to the study design. Symptom severity also decreased among patients treated with gabapentin, although the decrease was not statistically significant (P=0.27) [10]. This analysis also indicated that TCAs improve symptom burden for more extended periods than gabapentin [10]. Overall, gabapentin and TCAs may improve symptom burden short-term for patients with persistent PTH [10]. Further research on the effectiveness of these medications for acute and persistent PTH is needed to establish the overall efficacy as a treatment method.

Topiramate (i.e., Topamax), another anticonvulsant, has been studied to assess its preventative effects on PTH [11]. A 2011 retrospective cohort study of 100 soldiers with persistent PTH found a 23% decrease in headache frequency among patients who received topiramate after 3 months (-4.5 headache days, P=0.02) [11]. Almost half of patients reported $a \ge 50\%$ reduction in headache frequency [11]. There is a lack of current research on the effectiveness of topiramate. Future research should focus on its efficacy for acute and persistent PTH and include non-military populations.

The authors believe that antihypertensive drugs, like lisinopril and candesartan, may also be prescribed for offlabel use to treat PTH. This is because they may be helpful for migraine prevention based on the Canadian Headache Society guidelines [12]. In addition, evidence suggests that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are helpful, specifically for mood disorders, by alleviating depression and preventing depression relapse [13]. Given the high rates of comorbidity for mood disorders with PTH [14], ACE inhibitors and ARBs may be an effective treatment option. One study found that probable or high risk of depression was significantly higher in patients with persistent PTH (n = 100) compared to healthy controls (n = 100) (42% vs. 2%, P < 0.01) [14].

Prazosin, an alpha-1 adrenergic receptor antagonist (i.e., alpha-blocker), has shown promise in preventing PTH; however, additional research is necessary to determine its efficacy [15]. In a pilot randomized controlled trial of 48 military service members with persistent headache attributed to mild TBI, researchers found a significant reduction in headache frequency from baseline to week 4 among those who received prazosin compared to those who received the placebo based on the intent-to-treat analysis (mean change, -10.8 ± 1.0 vs. -6.3 ± 1.5 , P < 0.001) [15]. Additionally, researchers measured headache burden using the Headache Impact Test (HIT-6) [15]. From baseline to week 12, mean HIT-6 scores significantly declined among those who received prazosin, a change from severe to moderate impact (P < 0.001) [15]. There were no statistically significant changes in mean HIT-6 scores among the placebo group, which remained a severe impact for the duration of the study [15]. As of August 2023, there are two active clinical trials on prazosin among military populations with headache attributed to mild TBI [16, 17].

Injectable Medications

Calcitonin gene-related peptide (CGRP) receptor antagonists have emerged as an evidence-based preventative treatment for migraine [18, 19] and show potential for PTH treatment. Current research indicates a correlation between intravenous infusions of CGRP and migraine-like headaches in patients with persistent PTH [19, 20]. Hence, CGRP receptor antagonists have been studied for PTH prevention. In an open-label study of 89 patients with persistent PTH, three doses of 140 mg erenumab, an anti-CGRP monoclonal antibody, were given to patients via subcutaneous injection over 8 weeks [18]. Patients reported a mean reduction in monthly moderate-to-severe headache days from baseline to week 9 through 12 $(2.8 \pm 6.8 \text{ days})$ [18]. Researchers found that 28% of patients reported a \geq 50% reduction in moderate-tosevere headache days [18]. Yet, in the phase 2 double-blind, randomized controlled trial of fremanezumab, the reduction in moderate-to-severe headache days among those who received the medication compared to placebo was not statistically significant (P=0.1876), nor were any secondary measures [21].

In addition to CGRP medications, onabotulinum toxin A has been approved to treat chronic migraine [22]. Few studies have examined whether onabotulinum toxin A is effective in PTH prevention. In a study of 40 military veterans diagnosed with persistent PTH, researchers found that headache frequency and severity clinically and significantly improved among those who received onabotulinum toxin A compared to those who received the placebo [23]. The overall number of headaches decreased significantly among the onabotulinum toxin A group (0.14 per week; P < 0.001), while those in the placebo group experienced a significant increase (0.08 per week; P=0.02) [23]. Cumulatively, the number of headaches per week decreased by 43.3% among the onabotulinum toxin A group and increased by 35.1% among the placebo group [23]. The mean pain severity was also significantly reduced in the onabotulinum toxin A group (0.06 per week; P=0.02) [23]. These results indicate that onabotulinum toxin A may be an effective preventative treatment for PTH in a clinical setting. However, further research is necessary to determine its long-term impact.

PTH and Vestibular Dysfunction

The vestibular system is a sensorimotor system intertwined for detecting self-motion, head and body positioning, motor responses, and multi-sensory integration with the sole effect of gaze stability and balance [24]. This includes peripheral structures of the inner ear and vestibular nerves and central structures, including cerebellar tracts, brainstem, and supratentorial regions [25]. The cause of post-concussion vestibular symptoms often indicates a central origin; others suggest a peripheral cause [26], and recently, a combination of both vestibular lesions was suggested [27]. Treatment with vestibular PT for purely peripheral posttraumatic vertigo can be effective. Yet when a patient presents with a posttraumatic vestibular etiology and migraine, or phenotypically close to vestibular migraine (VM), often vertigo can precede the migraine attack but can also occur during or after the headache [28]. The use of prophylactic medications for the treatment of posttraumatic VM is mainly intended to reduce attack frequency, duration, and severity of central vertigo and migraine [28].

Among the medications prescribed for migraine prevention, valproic acid, venlafaxine, and flunarizine are the most utilized [29]. Venlafaxine, a serotonin–norepinephrine reuptake inhibitor, is a clinically effective and safe medication that is widely used to treat depression; its mood-stabilizing effects likely help the concurrent mood symptoms seen in PTH [30]. 5-HT levels affect the onset of vestibular symptoms similarly to migraine [31]. Venlafaxine decreases 5-HT levels and, subsequently, vertigo attack frequency and can also reduce the levels of specific inflammatory cytokines that play a role in episodic vertigo [32].

A 2017 study comparing the above agents used a Dizziness Handicap Inventory (DHI) and a Vertigo Severity Score (VSS). Decreased total DHI scores were observed following treatment with all three medications (p < 0.05) [29]. Although valproic acid had no noticeable effect on VSS (p=0.27), decreased vertigo attack frequency was observed in the valproic acid group (p=0) [29]. Venlafaxine affected vertigo attack frequency (p=0), but flunarizine had no apparent effect (p=0.06) [29]. Venlafaxine and valproic acid were also preferable to flunarizine in decreasing the number of vertiginous attacks. Still, valproic acid was shown to be less effective than venlafaxine and flunarizine to reduce vertigo severity [29]. These agents give us options when treating PTH patients with vestibular symptoms until more targeted studies in this specific population can be done.

Non-Pharmacological Treatment

Behavioral Intervention

While behavioral interventions such as Cognitive Behavioral Therapy (CBT), Biofeedback, and Relaxation have been identified as Grade-A evidence-based preventative treatments for patients with migraine [33], limited evidence is available on the effectiveness of these evidence-based treatments for patients with PTH. Some research has shown that behavioral interventions for patients with PTH improve headache-related symptoms [33] while also targeting common psychiatric comorbidities, such as posttraumatic stress disorder (PTSD) [34].

In a randomized clinical trial of 193 military veterans with severe PTSD and comorbid PTH, participants who received CBT reported significant improvements in headache-related disability compared to the control (usual care) within 6 months (aggregate mean HIT-6 scores, -3.4; P = < 0.001 [34]. However, there were no statistically significant improvements in the severity of PTSD symptoms or headache frequency among participants who received CBT compared to the control (aggregate mean PCL-5 scores, -6.5, P=0.04; aggregate headache frequency, -2.9, P=0.07) [34]. Meanwhile, participants who received cognitive processing therapy (CPT) reported insignificant improvements in headache-related disability and significant improvements in PTSD symptom severity (-1.4, P=0.21; -8.9, P=0.01) [34]. Findings on the effectiveness of CBT for PTH are scarce, but treatment may be worthwhile if patients have psychiatric comorbidities often treated using CBT.

Neuromodulation

Transcranial Magnetic Stimulation (TMS) is one of the most common forms of neuromodulation and has promising potential for reducing headache-related symptoms in patients with PTH [35, 36]. Recent data suggest that repetitive TMS (rTMS) may reduce the severity of headache-related pain associated with PTH [37–39].

In a pilot clinical trial of rTMS for 20 patients with persistent PTH, headache severity decreased in those treated with rTMS compared to the sham group [37]. Additionally, quality of life in the rTMS group was reflected by 60% of participants being able to return to work after completion of 10 sessions versus only 10% of participants in the sham group [37]. In a study of 29 patients with mild TBI-related headache, participants treated with rTMS showed significant decreases in headache intensity (baseline to week 4 post-treatment, 23.0 + 17.7%; P < 0.01) and debilitating headache (week 4 post-treatment, 58.4% + 24.5%; P < 0.001) [38]. Additionally, 57% of patients who received rTMS reported no longer having persistent headaches four weeks post-treatment [38]. In a study of 24 military veterans with mild TBI-related headache, 58% of participants treated with rTMS saw a 50% reduction in headache frequency [39]. This reduction was maintained at the one-month follow-up time point [39]. Results from research on the effect of rTMS on PTH are varied but promising in improving headache frequency and severity in patient populations.

Conclusion

There is limited evidence on how to treat PTH. Numerous studies involve military veteran populations, which may not be generalizable. In addition to varied evidence, significant challenges in establishing treatment methodology arise due to the fluctuating standardized clinical diagnostic criteria. Many patients with PTH have been shown to improve independently, leading to difficulties with patient populations in randomized clinical or controlled trials. Future work should examine personalized medicine for PTH. Promising evidence on using oral and injectable medications should be further investigated to establish a more standardized treatment for patients with PTH. In addition, non-pharmacological treatment options for PTH should be explored as they have significant efficacy in migraine-based populations.

Author Contributions All authors contributed equally to the preparation of this manuscript.

Data Availability No datasets were generated or analyzed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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