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HEADACHE (RB HALKER, SECTION EDITOR)

Post-Concussive Syndrome: a Focus on Post-Traumatic Headache and Related Cognitive, Psychiatric, and Sleep Issues

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Abstract
Purpose of Review Post-traumatic headache (PTH) is a secondary headache disorder following traumatic brain injury. We sought to examine the recent literature on PTH and associated cognitive, psychiatric, and sleep conditions to understand the latest findings about the associated conditions and available screening tools, and to understand the available treatment options for PTH.
Recent Findings Up to one third of PTH patients may have depression and about one quarter may have insomnia. Anxiety and cognitive issues are also common. While there are few studies examining abortive medications for PTH, recent studies of preventive medications examine the efficacy of topiramate, and topiramate may be better than other oral preventive medications. Other currently investigated treatments include nerve blocks, onabotulinum toxin A, transmagnetic stimulation, and behavioral therapy (biofeedback).
Summary Due to an expanded focus on and knowledge of concussion and PTH, comorbid psychiatric, cognitive, and sleep issues have become more widely acknowledged and studied. However, more high-quality studies must be conducted to examine the underlying pathophysiology of PTH and associated symptoms and to determine the most effective abortive and preventive treatment options.

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Introduction

Approximately 2.5 million traumatic brain injury (TBI) cases are reported in the USA annually [1]. The vast majority of TBI cases (70–90 %) are considered mild [2, 3]. TBI may result in neurological changes such as headache, loss of consciousness, and post-traumatic amnesia as a result of contusion, axonal shearing, edema, and ischemia. Headache is the most prevalent and enduring of all of these symptoms, no matter whether the TBI was mild, mild repetitive, or moderate to severe, and this is independent of the degree of post-concussive syndrome and post-traumatic stress disorder (PTSD) [4]. Post-traumatic headache (PTH) has been defined by the International Classification of Headache Disorders (ICHD) 3 beta as a secondary headache disorder. This article will focus on the diagnostic criteria of PTH and its various phenotypes as well as associated comorbidities (depression, anxiety, cognitive complaints, and sleep issues), useful screening tools for the clinician, and a discussion of the recent advances in the management of PTH.

Post-Traumatic Headache

Acute and chronic post-traumatic headaches have been defined in the International Classification of Headache Disorder (ICHD) 3 beta edition. Table 1 describes the diagnostic criteria of the acute form, and the chronic form is similar but the duration of headache is over 3 months. A

Table 1 Acute post-traumatic headache as defined by the International Classification of Headache Disorders (ICHD)-3 Beta

Headache <3 months duration caused by traumatic injury to the head

Headache developed within 7 days after one of the following:

1. The injury to the head
2. Regaining of consciousness following the injury to the head
3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head

Either of the following:

1. Headache resolved within 3 months after the injury to the head
2. Headache has not yet resolved but 3 months have not yet passed since the injury to the head

Headache with Injury to the head fulfilling both of the following:

1. Associated with none of the following:
   a) Loss of consciousness for >30 min
   b) Glasgow Coma Scale (GCS) score <13
   c) Post-traumatic amnesia lasting >24 h
   d) Altered level of awareness for >24 h
   e) Imaging evidence of a traumatic head injury, ie., hemorrhage
2. Associated right after the head injury with 1+ of the following symptoms and/or signs:
   a) Transient confusion, disorientation or impaired consciousness
   b) Loss of memory for events just before/after head injury
   c) 2+ other symptoms suggestive of mild TBI: n/v, visual disturbance(s), dizziness +/− vertigo, impaired memory and/or concentration

Not better accounted for by another ICHD-3 diagnosis

Note 1: Headache must be reported to have developed within 7 days. This duration is somewhat arbitrary and was decided upon to yield higher specificity. There are Appendix criteria: "Delayed-onset persistent headache attributed to moderate or severe traumatic injury to the head" and "Delayed-onset persistent headache attributed to mild traumatic injury to the head." These diagnoses may be used when the interval between injury and HA onset >7 days.

Note 2: There is also "Chronic Post-Traumatic Headache" defined like "Acute Post-Traumatic Headache" but the headache has not resolved after three months.

somewhat controversial point is the requirement that the headache begins within 7 days of injury or of regaining of consciousness following the injury to the head or of discontinuing medication(s) that impair the ability to sense or report headache following the injury to the head.

While PTH has been defined as one disorder, its presentation can reflect different primary headache phenotypes [5]. The most commonly reported phenotype is migraine. For example, a prospective study based in a US trauma center evaluated 212 patients within 1 week of mild traumatic brain injury (mTBI) for the prevalence and characterization of PTH. Patients were followed by telephone at 3, 6, and 12 months post-TBI. There was a 91 % cumulative incidence of PTH at 1 year. About half (54 %) of the patients reported worsened or de novo headache immediately following the TBI. About half (49 %) of the PTHs were classified as migraine type or probable migraine phenotype. Two fifths (40 %) of the patients experienced a tension-type phenotype headache [6••]. In a retrospective cohort study, one third (34 %) of the civilian population PTH had a tension-type phenotype and 29 % had a migrainous phenotype. This is in comparison to active military personnel who were found to have predominantly migraine phenotype in 58 % of the population [7]. However, PTH can also present as other much less common phenotypes, including cluster headache [8, 9], hemicranias [8, 10, 11], short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [12], and nummular headache and primary stabbing headache [8].

The prevalence of headache after TBI ranges from 30 to 90 %, and the headache lasts for more than 1 year in 18–33 % of patients [13]. PTH can be disabling; a recent retrospective cohort study of TBI clinic patients found that soldiers with continuous, post-traumatic headaches are four times more likely to be discharged or retired from duty than those without such headache [14].

Numerous studies have been done to examine the natural progression of PTH [6••, 15–21]. Risk factors for the development of PTH include a prior history of headache and an age less than 60 [6••, 15, 17, 19, 20]. Emotional dysregulation producing psychiatric symptoms is also associated with increased risk of developing PTH [18, 22•, 23•, 24•, 25, 26•, 27].

PTH-Associated Symptoms

Both migrainous and tension phenotypes are often accompanied by psychologic symptoms (mood and anxiety), cognitive changes, and sleep disturbances [4]. Some associated symptoms, i.e., somatic symptoms, at least in athletes, are a predictor of recovery in concussion [28, 29]. Insomnia and other sleep disturbances are predictors of prolonged PTH recovery [30].

Depression

Approximately 30–46 % of veterans with mTBI are diagnosed with depression [23•, 31]. Depression is 43 times more likely if the patient was previously diagnosed with PTSD, since patients with mood disorders experience higher frequencies of post-concussive syndrome symptoms, including headache [32]. For example, in a prospective cohort study of 177 patients, pre-injury depressive or PTSD symptoms resulted in heightened severity of cognitive impairment and lower quality of life 3 months post-injury [33]. In adolescents, a history of concussion led to a 3.3-fold increased risk for depression diagnosis compared to those without prior concussion [34].

Depression occurs in 29.7–33.3 % of patients with PTH and is a strong predictor of post-traumatic headaches [18,

25, 22•, 23•, 24•, 26•, 27]. For instance, a recent prospective cohort study analyzed Patient Health Questionnaire (PHQ)-9 scores in TBI patients and found significantly higher scores in those suffering from PTH compared to those without PTH [24•]. Another retrospective cohort study found higher Self-rating Depression Scale (SDS) scores in patients with PTH compared to those without PTH who sustained a mTBI [18]. Wilk et al. demonstrated that post-concussive symptoms, including headache, were more closely associated with depression and PTSD than mTBIs [27].

Anxiety

Anxiety disorder is reported in approximately 24–27 % of adult TBI patients [23•, 32, 35]. A retrospective cohort of veterans found that 61 % of patients experienced one or more anxiety disorder episodes within 2 years of TBI [32]. Anxiety is strongly associated with decreased information processing speed [35]. Also, higher severity of cognitive impairment and depression following TBI were predictive of greater levels of social anxiety [36].

In terms of headache, heightened anxiety was reported in patients with mild to moderate TBI and PTH [18, 22•, 23•, 24•]. A retrospective cohort found higher Self-rating Anxiety Scale (SAS) scores in patients with relevant anxiety. The sum of post-traumatic symptoms, including headache, increased with higher SAS scores. Affective disorders enhance pain severity and increase attention to pain, and then pain triggers anxiety, which is associated with PTH [18].

Cognitive Changes

Significant research has been done investigating the cognitive changes that can occur with a mild TBI. A longitudinal study revealed that 33 % of ED mTBI patients were functionally impaired 3 months post-injury, and 22.4 % of mTBI patients were still functionally impaired 12 months post-injury. [37] Retrospective cohort studies revealed significant reductions in executive function and information processing speed [38–40]. For example, blast-induced mTBI patients demonstrated decreased ability to integrate visual sensory input [38]. This aligns with previous studies wherein greater than 66 % of veterans suffered visual deficits following blast-related mTBI [41, 42].

It has long been known that pain itself can cause cognitive issues. [43] Yet, there have also been some unexpected findings reported in the mTBI literature. In one study of pain in TBI patients, pain severity did not negatively impact neuropsychological test performance. In this study, though, the pain level was assessed based on the level of pain during the 2 weeks leading up to the testing, and thus, the level of pain at the time of the testing is unknown. [44] Research related to cognitive changes in PTH can be challenging, as it can be difficult to discern whether it is the pain or the underlying changes in the brain from the trauma causing these complaints. Research dedicated to assessing cognitive changes is underway [45], but more work is needed.

Sleep

Thirty percent to 70 % of adults report sleep problems and fatigue following TBI [46]. This number rises to 77 % when reporting subjective sleep disturbance, falls to 29–33 % when reporting insomnia, and falls to 9 % when reporting post-traumatic hypersomnia [47–49]. A retrospective cohort study reported that, compared to healthy controls, 49 % of TBI patients had significantly poorer sleep quality and 24 % had higher levels of daytime sleepiness [49, 50]. If patients have preexisting sleep problems, cognitive impairment and headaches may be more severe following concussion [51]. A recent retrospective cohort study found a significant relationship between headache, sadness, anxiety, irritability, and sleep problems (including fatigue, drowsiness, and difficulty falling asleep) [46]. Headache, anxiety, and depression were higher risk factors of insomnia than the severity of TBI in veterans, and insomnia was reported as a predictor of headache persistence in TBI patients [23•, 48]. A retrospective cohort study reported that 50 % of 25 % of mTBI patients who were diagnosed with a headache disorder were also diagnosed with insomnia, which makes approximately 12 % of the total study population [48]. More severe psychiatric symptoms, such as anxiety, lead to more severe sleep problems [46, 49]. A recent retrospective cohort study demonstrated a significant relationship between severe psychiatric symptoms and severe sleep symptoms, which became more severe over 3 years [46]. In addition, increasing psychiatric comorbidities, including anxiety and depression, were found to be correlated with increased daytime sleepiness, poorer sleep quality, and greater average number of naps per day. Increased depressive symptoms were associated with longer napping periods and poorer sleep efficiency [49].

Similarly, a study of PTH patients found that 27.43 % of the patients suffered from insomnia [23•]. Studies indicate that adequate prevention or treatment of sleep disorders will lessen the risk of depression. Sleep disorders, as well as symptoms of fatigue, are predictors of PTH severity [22•, 49, 52].

Screens for PTH

A number of screening measures have been developed for assessment of post-concussion symptoms, with headache commonly found to be the most frequently reported symptoms [53, 54]. The most commonly used symptom checklist is included as part of the Sideline Concussion Assessment Tool (SCAT-3), a screening tool developed to assess acute

post-concussion symptoms in a sports setting [55]. This checklist is now gaining momentum for use as an effective means for measuring concussion symptoms in non-athletes.

No scale has been developed or validated for specific assessment of PTH symptoms. However, further information about headache severity can be obtained from use of standard pain inventories, such as a Visual Analog Scale (VAS) or the Brief Pain Inventory (BPI) [56]. Assessment of subjective disability associated with PTH can be assessed with an instrument tailored for use with headache, such as the Migraine Disability Assessment (MIDAS) [57]. Other screens that might be used include the Pain Disability Inventory (PDI) and/or the Modified Somatic Pain Questionnaire (MSPQ), as both instruments have been found to be effective for identifying psychological and motivational affecting reports of pain associated with headache and other conditions [58–60].

A number of measures are available for screening of comorbid conditions affecting reporting of PTH symptoms. The Beck Depression Inventory and Beck Anxiety Inventory are two measures commonly used for this purpose, with multiple studies showing their association with reported headache symptoms [61–63]. When assessing headache associated with mTBI, one must also pay careful attention to the possible influence of Post-Traumatic Stress Disorder (PTSD), with the PTSD Checklist for DSM-5 (PCL-5) demonstrated to be an effective means for screening for the presence of that condition [64]. The Patient Health Questionnaire (PHQ)-15 is an instrument that can be used to quickly determine the presence of a possible somatic symptom disorder and its effect on headache symptom reporting [65].

Screening for cognitive impairment following concussion can be accomplished effectively with use of the Sideline Assessment of Concussion (SAC), a 30-item instrument that is now included in the SCAT-3 [55, 66]. Positive findings on the SAC in patients with severe headache symptoms will often signal the need for more detailed neurocognitive testing. There has also been a recent study characterizing PTH using the SCAT-3 [45]. Several brief computerized test batteries (e.g., ImPACT) have been developed and marketed for this purpose, although questions are raised about their clinical utility, due to the typically short-lived nature of cognitive impairment resulting from concussion and questions about the statistical reliability of the instrument [67]. In most cases, a referral for neuropsychological assessment, with standardized batteries of cognitive tests and more comprehensive measures of psychological functioning (e.g., Minnesota Multiphasic Personality–Restructured Format–2 MMPI-2-RF) will provide the most effective means for identifying the relative roles that cognitive and psychological factors are playing in reporting of post-concussion symptoms including complaints associated with PTH [68, 69].

Potential Explanations for PTH

Research suggests that PTH may have similar pathophysiology as migraine with activation of the trigeminovascular system [7]. It may be this neuropathic pathway that contributes to chronic PTH when the headache lingers past 3 months [70]. Though most of these changes resolve within 3 months they can become chronic without timely treatment [71].

Brain network activation (BNA) analysis is an innovative approach to understanding temporal-spatial brain activation in patients with and without PTH. A prospective, repeated measures study to assess post-injury BNA, cognitive functioning, and concussive symptoms, including headache, demonstrated decreased BNA and deviation from usual brain network activity in PTH patients compared to non-PTH patients and controls. BNA analysis of brain activity please change “can” to “may” be used as a tool to measure neurophysiological changes in the brain and supplement cognitive and symptom-based assays in post-traumatic migraine patients following concussion [72••].

Treatment

There have been many studies conducted examining how to best treat the various symptoms of post-concussive syndrome. However, given that the focus of this review is on PTH and associated symptoms (mood, sleep, and cognitive issues), we focus this review on the recent treatments studied for PTH. We also make brief mention of treatments of the associated symptoms, but this section is limited given that they were generally not investigated in the context of PTH.

Post-Traumatic Headache Treatments

Table 2 demonstrates the various treatments studied over the past 5 years, including medications, injections, brain stimulation, and behavioral treatment. All of the medications are considered “off-label.”

Oral Medications

Abortive Medications Several review articles cite triptans as the medication of choice for treating moderate to severe PTH attacks. While expert opinion recommends triptan usage in this population, there is limited data to support this. An observational study by Erickson et al. of soldiers found that triptans were prescribed to 73 out of 100 PTH patients. There was a 66 % response rate in patients with blast PTH and an 86 % response rate in patients with non-blast PTH [7]. The study did not specify which type of triptans were used. More research needs to be done to determine the most effective abortive treatments for PTH patients.

Table 2 Oral, procedural, and behavioral treatments and treatment devices studied for post-traumatic headache

Treatment type	Intervention (dose in mg/day)	Year	Author	Type of study	Number	Subject category	Brief finding
Oral	Amitriptyline: 10–100 mg (median: 25 mg)	2015	Bramley, H. [73]	Retrospective	400	Pediatric	Females were more likely to report a post-traumatic headache than males, and amitriptyline was the most effective pharmacological treatment. Patients described their headaches as most similar to tension-type or migraine-type; however, frequency, intensity, and disability varied widely.
	Amitriptyline: 5–1 mg//kg Topiramate: 12.5–1.5–2 mg/kg Melatonin: 3–10 mg	2013	Kuczynski, A. [17]	Prospective cohort	634 total; 44 in treatment cohort	Pediatric ED	Study had a pediatric ED cohort to study PTH and a separate treatment cohort. Medications were selected by a specialized headache and brain injury neurologist on the basis of mTBI comorbidities. Melatonin and amitriptyline were prescribed in the presence of a sleep disorder, and 39 % of patients received more than one treatment. 61 % of PTH patients had daily headaches; 39 % had migraine-type headaches.64 % of treatment cohort patients successfully responded to medication and 50 % saw a decrease in headache frequency. 45 % saw a complete resolution of headaches. Melatonin most significantly improved headaches in 75 % of patients. 68 % of patients improved with amitriptyline. No patients had a full response on topiramate, yet 35 % improved headaches.
	Amitriptyline: 25–50 mg Topiramate: 100 mg divided Nortriptyline: 25–50 mg Propranolol: 80 mg divided Valproate: 500 mg extended release	2011	Erickson, J. [7]	Retrospective cohort	100 (99 % male)	US Army Soldiers (veterans and active duty)	Migraine-type post-traumatic headaches experienced 17.1 days per month at baseline with MIDAS scores averaging around 6.7. PTSD, poor sleep quality, depression, and memory loss were common associated comorbidities.
Procedures	Onabotulinum toxin A (Botox)	2015	Yerry, J. [77••]	Retrospective cohort	64 (98 % male)	Adult	Migraine-type post-traumatic headaches experienced more than 15 days per month with continuous pain. 42.6 % improved with OBA injections.
	Greater Occipital and Supraorbital Nerve Blocks: 2 % lidocaine with epinephrine; 0.5-in. 30-gauge needle filled with 1 cm^3 volume for occipital and 0.5 cm^3 for supraorbital	2014	Dubrovsky, A. [75]	Retrospective case series	28	Pediatric	Following nerve block treatment, mTBI patients saw a 93 % decrease in headache intensity, and 71 % had their headaches completely relieved. Patients with complete headache relief experienced this immediately following the nerve block.
	Occipital nerve blocks	2015	Seeger, T. [76]	Retrospective case series	15	Pediatric	Of 15 patients with PTHAs following mTBI, 9 had a full response to treatment (complete relief of headaches) and 1 had a partial response to treatment. This resulted in a decrease in post-concussive syndrome scores and an increase in the quality of life.
Devices	Repetitive transcranial magnetic stimulation (rTMS)	2013	Misra, U. [81]	RTC	100	Adult	In patients with >4 HA days/month, 3 sessions on alternate days were given and analyzed after one

Table 2 (continued)

Treatment type	Intervention (dose in mg/day)	Year	Author	Type of study	Number	Subject category	Brief finding
							month. Headache frequency and visual analog scale scores significantly improved.
	Repetitive transcranial magnetic stimulation (rTMS)	2015	Leung, A. [80]	Prospective Case Series	6 (100 % male)	Adult (specifically middle-aged)	In patients with constant headaches with an intensity >4 on the Numerical Rating Pain Scale (NRPS), treatment with rTMS decreased average NRPS scores (5.5–2.6) and average headache frequency (1.0–5.8 attacks per week). Patients underwent four sessions of rTMS treatment over 2 months.
	Near-infrared laser phototherapy	2015	Morries, L. [82]	Retrospective case series	10	Adult	In 100 % of chronic TBI patients with headache, after treatment all had a 50 % or more reduction in or resolution of headache frequency. Patients underwent a total of 18 sessions three times per week for 6 weeks.
Behavioral	CBT: group therapy	2014	Kjeldgaard, D. [85]	RTC	90	Adult	NS between treatment group and waitlist group in change in HA frequency or intensity from baseline assessment to endpoint (differences in the same measures between treatment cohort and waiting-list cohort (no treatment group) 26 weeks after baseline). Patients underwent CBT treatment weekly for 26 weeks. CBT treatment consisted of education to provide strategies that would enable then to focus on changing their cognitive assumptions to improve quality of life over time as well as Autogenic training relaxation techniques.
	Biofeedback: neurotherapy	2015	Nelson, D. [84]	Prospective study	9 (88 % male)	War veterans	Reduced headache intensity from moderate or severe to mild (3 subjects reported resolution of headache pain after the final treatment, while 1 subject did not experience any change in pain level). 88 % of patients also presented with comorbid PTSD. Patients underwent 2–3 sessions per week for 2 months or until totaling 20 sessions.
	Biofeedback: heart rate variability (HRV)	2015	Kim, S. [83]	Prospective Study	13	Adult	HRV biofeedback improved emotional control and attention in tandem with patient quality of life (life satisfaction and self-esteem). Additionally, HRV biofeedback can increase cardiovascular coherence and self-awareness in patients with severe brain injury. Patients underwent 10 weekly 1-h sessions.

Preventive Medications Few medications have been studied for the daily preventive treatment of PTH. Moreover, there is limited high quality data for the treatment of PTH as treatments have been studied in randomized controlled trials. One of the more commonly studied medications is amitriptyline, and it has been studied in both the pediatric and adult populations [7, 17, 73]. Studies as far back as the 1980s have demonstrated the efficacy of amitriptyline. For example, retrospective cohort studies reported 56–80 % of adult patients experienced reductions in headache frequency and intensity following amitriptyline treatment [5, 74]. Recent pediatric cohort studies have noted a 68–82 % improvement in PTH symptoms, with 50 % of patients reporting a decrease in headache frequency and 45 % reporting complete resolution of headaches following amitriptyline treatment [17, 73]. Topiramate has also recently been studied in PTH. A recent retrospective cohort study of veteran and active duty soldiers demonstrated that topiramate reduced PTH frequency by more than 23 % in patients and appeared to be more effective than tricyclic antidepressants (amitriptyline, nortriptyline) in mitigating PTH symptoms. In this study, there were no significant differences in the discontinuation rates between the various preventive medications (topiramate, amitriptyline, nortriptyline, propranolol, and valproate). Furthermore, despite the known cognitive side effects of topiramate, there were no significant differences in the discontinuation rates of subjects treated with and without topiramate. Among all PTH subjects, there was a 16 % reduction (decrease of 2.6 days/month) of headache. Among patients with non-blast PTH, headaches significantly decreased by 6.7 days per month or 41 %. However, headache frequency in patients with blast PTH was unchanged 3 months after starting preventive medication. Furthermore, only 29 % of blast PTH patients experienced a 50 % or greater decline in headache frequency compared to 57 % of non-blast PTH patients. The patients taking topiramate had better outcomes; headache frequency was significantly lessened by 4.5 headache days per month or 23 %, and 48 % of patients taking topiramate achieved a 50 % or greater reduction in headache frequency. This is in comparison to the tricyclic antidepressants where headache frequency was unchanged 3 months after starting a TCA. There was not enough power to detect a statistical difference in headache frequency for propranolol or valproate. Migraine Disability Assessment Scale (MIDAS) scores were significantly decreased by a mean of 57 % in PTH subjects 3 months after starting treatment, with blast and non-blast PTH patients having similar reductions in MIDAS scores [7]. There was also a pediatric ED prospective cohort study which reported that melatonin significantly improved headaches in 75 % of patients and amitriptyline improved headaches in 68.5 % of patients [17].

Nerve Blocks and Injections

Following greater occipital and supraorbital nerve block treatment, pediatric mTBI patients had a 93 % decrease in headache intensity, and 71 % had their headaches completely relieved. Those who experienced complete headache relief generally did so immediately following the nerve block procedure [75]. Occipital nerve block treatment was slightly less successful in children, with 60 % of patients having a full response and complete relief of headaches. This resulted in a decrease in post-concussive syndrome scores and an increase in the quality of life [76].

Onabotulinum toxin A has been studied for PTH prevention. Sixty-four percent of active duty military patients experiencing more than 15 headache days/month with continuous pain were treated with onabotulinum toxin A and reported improved PTH symptoms. Patients receiving these injections failed previous treatments of topiramate (up to 200 mg daily) with additional conjunction use of propranolol, and most were at risk of overusing triptans. In addition, the treatment improved rates of return to duty in soldiers with PTH and decreased the likelihood of oral treatment addiction [77••]. There is currently an ongoing prospective study of onabotulinum toxin A being conducted [78].

Brain Stimulation

Recent studies of repetitive transcranial magnetic stimulation (rTMS) indicate that it may be a promising treatment for decreasing headache pain, severity, and frequency in adults [79–81]. In a randomized controlled trial (RCT), patients with general PCS symptoms showed an overall decline in PTH frequency, which underscores the potential use of rTMS in patients with persistent post-concussive symptoms, a population that is notably difficult to treat. One month of rTMS treatment resulted in a 50 % reduction in headache frequency in 78.7 % of adult patients and significant improvements in headache severity [79]. In a small retrospective case series of chronic TBI patients, near-infrared laser phototherapy treatment reduced or resolved their headache frequency in all patients [82].

Behavioral Therapy

Heart rate variability (HRV) biofeedback treated emotional dysregulation following severe TBI in 100 % of patients through improved emotional control and attention in tandem with patient quality of life (measured by life satisfaction and self-esteem) [83]. A small prospective case series with

veterans ($N = 9$) reported reductions in headache intensity using Flexyx Neurotherapy System biofeedback. For example, three of the subjects reported complete resolution of pain after the final treatment, while one subject experienced no change in pain level. Eight patients also experienced diminished PTSD and perceived cognitive complaints [84]. A recent RTC demonstrated the unsuccessful nature of group therapy when no patients receiving the treatment saw a significant change in headache frequency or intensity over the course of the study [85].

Treatments for Mood Disturbances After TBI

Since patients with mood disturbances are at greater risk for poor recovery from TBI and associated post-traumatic symptoms, neuropsychological screening prior to treatment initiation is suggested to implement more precise interventions for this specific group of people and to address risk factors [86]. For this reason, it is recommended that physicians treating concussive patients have clinical expertise in mental health conditions to administer appropriate treatment to these patients [87]. A nonrandomized trial of 15 TBI patients found that 87 % of patients experienced decreased depressive symptoms after 8 weeks of treatment with sertraline [88]. A recent study also revealed that sertraline improved quality of life in depressed post-TBI adults [89]. An earlier cohort study demonstrated that 46.2 % of mild-moderate TBI patients showed decreased depressive symptoms following a 10-week treatment with citalopram [90]. Regardless of treatment, depressive TBI patients should be monitored for long-term suicidal ideation post-injury. A recent prospect study of 2296 ED TBI patients found that 6.3 % express suicidal ideation at 3 months post-injury and 8.2 % at 8 months [91].

Treatments for Cognitive Disturbances After TBI

Several pharmacological interventions have been used to treat cognitive disturbances following TBI. A recent retrospective study reported improvement in memory function and cognitive fatigue in pediatric TBI patients using amantadine; however, verbal memory and visual motor processing speed did not improve [92]. Amantadine has also been shown to decrease disability rating scores of moderate-severe TBI patients [93], and earlier studies have also found significant cognitive improvement in TBI patients treated with amantadine [94, 95]. Evidence supporting methylphenidate as a pharmacological treatment is contradictory. A 2016 randomized control trial with 11 mild-severe TBI patients found that methylphenidate does not improve processing speed or attention issues post-TBI, unlike a 2004 study which found the opposite in 34 adults with moderate-severe TBI [96, 97]. Meanwhile, another 2016 study of 30 patients with mild-moderate TBI found long-term efficacy (with 6 month post-injury treatment) of methylphenidate through improvement of mental fatigue and cognitive function (including processing speed, memory, and attention), as well as improvements in depression and anxiety [98]. An RTC found improvements in memory and attention in thirteen patients treated with lisdexamfetamine dimesylate (Vyvanse); however, clinical trials have yet to be completed on this drug [99]. An earlier RTC found that donepezil can also help with memory and cognition problems after TBI [100].

Treatments for Sleep Disturbances After TBI

Prior treatment of associated post-TBI symptoms, including anxiety, depression, PTH, and poor sleep hygiene, can cause relief from sleep disturbances [101]. Melatonin supplements have been found to improve sleep dysfunction in children following TBI [102]. Also, an earlier randomized controlled trial using a combination of low-dose amitriptyline and 5 mg of melatonin found improvements in sleep quality, duration, and latency in TBI patients with insomnia [103]. Recent findings for use of ramelteon showed increased total sleep time and total sleep onset latency compared in thirteen total mild-severe TBI patients compared to placebo [104]. Sleep latency was also improved in mild-moderate TBI patients using high doses (250 mg) of modafinil [105]. Additionally, treatment with prazosin can reduce daytime sleepiness after 6 months, as demonstrated by Ruff et al. in a prospective cohort study on veterans [106]. An RTC revealed reduction of sleep disorders in active duty post-deployment service members with mTBI using a telephone-based problem solving treatment (PST). Improvement in sleep quality due to PST subsequently relieved associated concussion symptoms, mood disorders (including depression, anxiety, and PTSD), and pain based on self-report [107].

Limitations in Conducting PTH Research and Ideas for Future Research

Research on PTH is challenging because it is hard to standardize or match patients for studies; patients have different mechanisms of injury and first present for medical attention at varying times. Some patients may initially consider headache a common occurrence after head injury and thus forego medical attention. Other patients may suffer from headaches at baseline and may consider their post-traumatic headache to be a form of their regular headache, which can also lead to deferral of seeking medical attention. Also, the typical trajectory is that patients improve with time, so it is hard to assess whether it is the medication or time that is responsible for the improvement in the symptoms.

Additional research is needed in abortive therapy and preventive therapy. RCTs need to be done to examine the best treatments for these patients.

Conclusions

With the increased attention on concussion and PTH, there is increasing awareness of the accompanying psychiatric, cognitive, and sleep issues. Additional research needs to be done to better understand the underlying brain network connectivity that relates the headaches to these symptoms. Furthermore, high-quality studies need to be conducted to examine appropriate abortive treatments for PTH as well as the most effective preventive medication and behavioral treatments.

Compliance with Ethical Standards

Conflict of Interest Mia Minen and Alexandra Boubour declare that they have no conflict of interests. Harjasleen Walia has a patent pending for Concussion Impact Sensor. William Barr was an expert witness consultation on medicolegal cases.

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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