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Acute and chronic management of posttraumatic headache in children: A systematic review

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Abstract

Objectives: The goal of this paper is to provide a compilation of the evidence for the treatment of posttraumatic headache (PTH) in the pediatric population. Headache features and timing of therapy were considered.

Background: Headache is the most common symptom following mild traumatic brain injury (mTBI), affecting more than 80% of children and adolescents. It is unclear whether treatment for PTH should be tailored based on headache characteristics, particularly the presence of migraine features, and/or chronicity of the headache.

Methods: Systematic literature searches of PubMed, Embase, Scopus, and Cochrane databases (1985–2021, limited to English) were performed, and key characteristics of included studies were entered into RedCAP® (Prospero ID CRD42020198703). Articles and conference abstracts that described randomized controlled trials (RCTs), cohort studies, retrospective analyses, and case series were included. Participants included youth under 18 years of age with acute (<3 months) and persistent (≥3 months) PTH. Studies that commented on headache improvement in response to therapy were included.

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AUTHOR CONTRIBUTIONS
CPG was responsible for study conception, and design, designed and performed literature searches and organized data, was involved in abstract review, and article review and data input into RedCAP®, and wrote the manuscript. RH was involved in abstract review, article review and data input into RedCAP®, and reviewed the manuscript. SLI and KG provided critical feedback to study design, were involved in abstract review, and article review, and provided text and critical revisions to the manuscript. CLS was involved in study conception, study design, article review, and provided critical revisions to the manuscript. All authors read and approved the final manuscript.

Results: Twenty-seven unique studies met criteria for inclusion describing abortive pharmacologic therapies (9), preventative pharmacotherapies (5), neuromodulation (1), procedures (5), physical therapy and exercise (6), and behavioral therapy (2). Five RCTs were identified. Studies that focused on abortive pharmacotherapies were completed in the first 2 weeks post-mTBI, whereas other treatment modalities focused on outcomes 1 month to over 1-year post-injury. Few studies reported on migrainous features (7), personal history of migraine (7), or family history of migraine (3).

Conclusions: There is limited evidence on the timing and types of therapies that are effective for treating PTH in the pediatric population. Prospective studies that account for headache characteristics and thoughtfully address the timing of therapies and outcome measurement are needed.

Keywords

concussion; pediatric; posttraumatic headache; treatment

INTRODUCTION

Headache is the most common symptom following mild traumatic brain injury (mTBI). Posttraumatic headache (PTH) is reported by more than 80% percent of children and adolescents.[1] Eight percent of children who have had head trauma will have headache that persists beyond 3 months,[2] fulfilling International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria for persistent headache attributed to trauma or injury to the head and/or neck, here termed persistent PTH.[3] Migraine is the most common phenotype of PTH in children and is seen in up to 55% of cases.[4] Prior work in children suggests that PTH with migrainous features[5–9] or a personal or family history of migraine is associated with prolonged recovery.[5,6] The PTH “migraine phenotype” may represent a subset of patients who would benefit from more directed headache management.[9] This is of particular interest in the pediatric population due to the high incidence of migraine in the teenage years and early twenties.[10] In this age group, individuals prone to developing migraine may not have exhibited symptoms yet and mTBI may act as a triggering event for migraine.[11] Three reviews have focused on PTH treatment in the past decade.[12–14] Although informative, only one looked exclusively at children,[14] and none reported the presence of migrainous features.

The objective of this review was to identify randomized controlled trials (RCTs), cohort studies, retrospective analyses, and case series of youth (<18 years) with acute or persistent PTH that assessed the effect of pharmacologic, procedural, and nonpharmacologic treatments on headache improvement. Headache characteristics, including presence of migrainous features, and the timing of therapies were evaluated when available. This review identifies gaps in knowledge regarding the management of pediatric PTH to help guide future treatment trials.

METHODS

This systematic review preregistered protocol can be found on the Prospero database (ID CRD42020198703). PRISMA guidelines were followed,[15] except in the subgrouping of results to streamline integrating results within multiple treatment categories. Studies that met the following criteria were included: (1) at least 50% of subjects were younger than 18 years old, (2) acute (<3 months) and/or persistent (≥3 months) PTH of any phenotype was evaluated, (3) headache treatment response was reported, (4) sample size was >1, (5) written in English, and (6) published between 1985 and 2021. Headache features and duration were considered. We included peer-reviewed studies of a broad range of research designs given the limited research on the treatment of pediatric PTH. Papers that solely discussed diagnosis, evaluation tools, epidemiology, return to play or return to learn but not treatment were excluded. Review and opinion articles were also excluded, but one reviewer examined references to screen for additional articles that met inclusion criteria.

Our literature search strategy was designed to target four key concepts: (1) child and adolescent, (2) posttraumatic, (3) headache, and (4) treatment. Queries of PubMed, Embase, Scopus, and Cochrane review search engines were conducted on July 16, 2020 and May 3, 2021. Details of the search strategy can be found in the Appendix.

After duplicates were removed, two review authors independently screened the titles and abstracts of the search results for the inclusion and exclusion criteria. Information from the abstract search was saved in a Microsoft Excel® spreadsheet, and software generated in Matlab® was used to identify duplicates. Two authors independently extracted data from the selected studies and entered it into REDCap®, an electronic data management program, and each article was assessed for quality. We integrated the data as a descriptive synthesis rather than a meta-analysis due to the limited studies available. Study design type, as well as checklists provided by the National Institutes of Health (NIH) Quality Assessment Tools (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), which were specific to study type, were used to rank the data as "good," "fair," or "poor" based on prior reports that have used this tool[16] (Table 1).

Disagreements were reconciled by a third author. Data extraction included study information and characteristics, the therapeutic agent used, and outcomes assessed. Subject characteristics included headache features, family and personal history of migraine, details of treatment, and time from concussion to treatment were collected when available.

The main outcome measure was improvement of headache. This was intentionally broad to capture as many articles as possible that comment on change in PTH related to an intervention. This included subjective improvement in headache, change in headache severity and/or frequency, improvement in migrainous features (i.e., photophobia, phonophobia, and nausea), and headache-related disability.

RESULTS

Of the 3458 studies screened, 27 unique studies met criteria for final inclusion with a pooled sample size of 5036 participants (Figure 1). Seventeen of the studies (63%) included subjects that were 18 years old, with four of those (15%) including subjects older than 18. Therapeutic approaches were broadly characterized into abortive pharmacologic treatments, preventative pharmacologic treatments, procedures, neuromodulation, PT and exercise, and collaborative care and behavioral therapy (Table 2).

Abortive pharmacologic therapies

We identified six peer-reviewed articles and three conference abstracts that evaluated the use of abortive pharmacologic therapies for the treatment of PTH. This included two prospective RCTs. Abortive treatments were typically administered within the first 2 weeks following mTBI. Both oral and intravenous (IV) therapies were studied. Studies were generally limited by small sample size, lack of comparator group, and retrospective design.

Oral abortive therapies—The best evidence comes from a prospective randomized open-label study assessing scheduled acetaminophen, ibuprofen, or both compared to standard of care started within the first week of mTBI to treat PTH. Alternating ibuprofen and acetaminophen resulted in the fewest number of headache days and highest return-to-school rate, followed by ibuprofen alone, then acetaminophen alone.[17] Only median and range values were reported; no formal statistical significance testing was done.

In contrast, a large retrospective cohort study found no difference in the rate of persistent PTH at 3 months in those who used nonsteroidal anti-inflammatory drugs (NSAIDs) and/or triptans in the first 30 days compared to no treatment.[18] In fact, those who used triptans developed persistent PTH at higher rates.[18,19] A potential confounder is that subjects who used triptans may have had more significant headache and/or greater incidence of premorbid migraine, but this was not reported (NR). Additionally, medication doses and frequency were NR, and there was no metric for PTH severity at 3 months. Another study mentioned that triptans provided the most rapid relief for PTH, though more specific data were not included.[20]

A case series reported two subjects who had marked improvement in PTH following a 6-day oral methylprednisolone taper within the first month of sustaining an mTBI.[21] However, one subject required a more prolonged steroid taper due to headache recurrence, and many other co-agents were prescribed.

The potential risks of overusing abortive headache therapies following mTBI were highlighted by a retrospective analysis of adolescents presenting to a headache clinic with persistent PTH. Seventy percent of participants in this cohort met criteria for medication overuse headache (MOH); among those, 68.5% had improvement in headache when over-the-counter analgesics and NSAIDs were discontinued.[22] Notably, many of the subjects in this study were simultaneously receiving additional headache preventative pharmacologic treatments that may have impacted outcomes.

Intravenous abortive therapies—One small, RCT provided fair evidence that 3% hypertonic saline (HTS) was significantly more effective at decreasing headache severity than normal saline (NS) in youth with acute PTH immediately and 2–3 days after treatment.[23] This study benefited from a randomized design and a standardized pain scale, but it did not specify the acuity of the mTBI, the follow-up period was short, and the study was stopped early due to challenges with recruitment.

A subanalysis of a prospective cohort compared a single dose of IV metoclopramide given in the emergency department (ED) within 48 h of mTBI to no treatment. They found that IV metoclopramide did not reduce the risk of PTH at 1 and 4 weeks.[24] This study was unique because it looked at the impact ofabortive treatment on long-term headache outcome. However, dosing was NR, treatment was not randomized, and only a very small percentage (3%) were given metoclopramide; it is therefore possible that those with more severe headache at onset were treated.

A retrospective analysis of children ≤14 days of their mTBI who received IV fluids with either IV antiemetics (prochlorperazine or metoclopramide), IV ketorolac, or both found that most participants (80%–93%) experienced a >50% reduction in headache severity immediately following administration.[25] This study was limited by its retrospective design, unreported medication dosages, and lack of long-term outcomes.

Similarly, a retrospective chart review of an outpatient infusion center found that a single infusion of IV ketorolac, prochlorperazine, diphenhydramine, and NS improved headache in 85% of participants.[26] However, this study was limited by retrospective design, undefined mean mTBI duration and follow-up period, small sample size, and unreported dosages.

In summary, oral and IV abortive therapies administered within the first days following mTBI may offer immediate relief for PTH. Fair evidence supports alternating ibuprofen and acetaminophen in the first week,[17] as well as greater efficacy of HTS than NS in alleviating acute PTH.[23] Two studies provided poor evidence for acute benefit of IV medications commonly used to treat migraine.[25,26] In contrast, studies that looked at long-term (>1 week) effects did not find a benefit of NSAIDs, triptans,[18,19] or IV metoclopramide[24] for PTH. It is unclear whether abortive therapies can change the long-term trajectory of headaches following mTBI and whether MOH impacts likelihood of persistent PTH.[22]

Preventative pharmacologic therapies

Five studies have reported on the effectiveness of preventative migraine medications in children with PTH.[27] Quality of evidence was rated as poor for all studies.

One cohort study evaluated children with PTH who were prescribed different preventative medications for headache for a mean duration of 5.5 weeks. Full treatment response was defined as ≥50% reduction in headache frequency with functional improvement, which was met by 64% of the cohort across all medications; 45% reported headache resolution. Full response occurred in 13/18 prescribed amitriptyline, 1/11 prescribed nortriptyline, 5/8 prescribed flunarizine, 0/6 prescribed topiramate, 9/12 prescribed melatonin, and 2/2 prescribed indomethacin (both with stabbing headache). Limitations of this study include presence of active co-interventions and lack of clarity regarding timing of medication initiation and timing of assessment.

A second retrospective cohort study reported on children with persistent PTH treated with a preventative medication. Positive response to treatment was defined as ≥50% reduction in headache frequency, which was achieved by 10/20 patients overall. Positive response was reported by 4/11 of those prescribed amitriptyline, 3/6 prescribed propranolol, and 3/3 prescribed topiramate. Limitations of this study include unspecified time of initiation of medication and follow-up timing, as well as lack of specification of medication dosing.

Bramley et al. reported on the efficacy of amitriptyline in a subset of adolescents evaluated in a concussion clinic.[28] Participants with PTH ≥ 1 month were started on amitriptyline for headache prevention. Headache improvement was reported by 56/68 patients (82%) at a median of 4.4 months. Side effects were reported by 16/68 (23%). Females were more likely than males to report PTH (90% vs. 79%; $p = 0.004$) and were more likely to be prescribed amitriptyline (24% vs. 13%; $p = 0.004$).

Mackie and Kirkham[29] reported on PTH treatment in children presenting to a neurology clinic; 71% of patients had a migrainous phenotype. All patients received school accommodations, and 16 were treated with topiramate. Eighty-four percent of participants in the cohort overall reported headache improvement; of those treated with topiramate, 12/16 reported reduction in frequency and severity of migrainous headache. Limitations of this study include unspecified time of initiation of medication and timing of follow-up. Additionally, there were limited comparisons between those treated with topiramate compared with those treated with headache accommodations only.

One case series reported on six children who were diagnosed with pseudotumor cerebri following mTBI.[30,31] Initiation of acetazolamide resulted in resolution of headache in 5/6 patients; the one case that did not respond was found to have craniosynostosis. In three cases, acetazolamide was used in combination with topiramate when topiramate alone was not effective. Patients were initially treated with other medications including amitriptyline, propranolol, and cyproheptadine for presumed PTH with no or incomplete response. The study was limited because not all patients met diagnostic criteria for pseudotumor cererbri,[32] and it was difficult to ascertain whether pseudotumor cerebri was secondary to PTH given range of time to diagnosis.

In summary, data on preventative medication efficacy in PTH are limited by poor quality of evidence with reliance on retrospective data collection. The most evaluated medication was amitriptyline, with positive responses reported in 36%–82% of patients across three studies. Topiramate use was also described in three studies, but small numbers of patients resulted in variable efficacy outcomes, with response reported as 0%, 75%, and 100%. Notably, amitriptyline and topiramate were found to be ineffective as monotherapy in patients subsequently found to have intracranial hypertension following mTBI, highlighting the importance of identifying headache phenotype or underlying headache syndrome when treating PTH. While several studies reported on the presence of migrainous headache prior to or following mTBI, none evaluated its impact on treatment outcomes.

Neuromodulation

One retrospective study showed that transcranial direct current stimulation reduced headache frequency and severity in children with PTH. Over half reported headache resolution.[33] This study benefited from clearly defined metrics of headache improvement but was limited by the lack of comparison group, small sample size, and inconsistent number of treatment sessions used.

Procedures

Occipital nerve block—Three retrospective case series reported PTH improvement following occipital nerve blocks. All were limited by small sample size, concomitant therapies, variable number of nerve blocks administered, and lack of comparator group. One study found that nerve blocks were effective at treating youth with acute or persistent PTH, many of whom reported migrainous headache and a personal and/or family history of migraine. In this cohort, 71% of occipital nerve blocks resulted in headache resolution immediately, and 93% of subjects reported a good therapeutic effect defined as >24 h pain reduction or repeat nerve block request.[34] A smaller retrospective study also found benefit of greater occipital nerve blocks to treat adolescents with PTH; in this cohort, 6/15 patients had occipital neuralgia and 8/15 had occipital tenderness on exam. Nerve blocks were effective in reducing headache frequency with 9/15 participants reporting a ≥50% reduction,[35] although time to follow-up was not clear. Finally, a case series described three patients with posttraumatic occipital neuralgia who reported complete but temporary benefit (days) of occipital nerve blocks.[36]

Acupuncture—One case series reported on three youth with PTH who reported a reduction in headache severity following multiple acupuncture sessions.[37] The study is limited by the small case series design and concomitant use of other therapies for PTH in all three subjects.

In summary, there is consistent evidence that occipital nerve blocks may be helpful for treating PTH in youth, but evidence is limited by small sample sizes and lack of comparator groups. Very limited data suggest acupuncture may also be helpful.

Physical therapy and exercise

We identified six studies (three prospective,[38–40] three retrospective[41–43]) that evaluated PT and timing of increased activity on PTH in youth. Some reported headache improvement, whereas others found modest or no effect.

Physical therapy—A small prospective RCT of youth with postconcussion symptoms compared cervical spine and vestibular physical rehabilitation to standard of care. Both groups worked with a physiotherapist for 8 weeks or until medical clearance. Eleven of fifteen participants in the intervention group were medically cleared to return to sport versus 1/14 in the control group. None of the medically cleared patients reported persistent headache, although there was no significant difference in the reduction of headache symptom scores between those who were cleared or not cleared in either group.[38] Conclusions for this study are limited by small sample size, and most comparisons that were made were between those who were cleared or not cleared for sports, not intervention versus standard of care. Retrospective analysis of a large prospective cohort provided fair evidence that a 4-week active rehabilitation intervention improved headache and postconcussion symptom scores for youth with persistent symptoms at 4 weeks post-injury.[41] A small retrospective cohort study looking at the impact of PT, cardiovascular exercise, vestibular and oculomotor exercise, cervicothoracic manual therapy, and sports-specific training on postconcussion symptoms persisting beyond 3 weeks found a modest decrease in headache severity following intervention over 7 days to up to 6 months, though significance testing was not done. They did find a significant reduction in postconcussion symptoms overall (mean total symptom score pre-intervention 18.2 vs. post-intervention 9.1 $p < 0.01$).[42]

Exercise—A pilot, prospective RCT compared those who participated in a subsymptom threshold exercise program to a control group of youth who had sustained a concussion and were at least 4 weeks post-injury. Following intervention, both groups reported a higher percentage with mild or no headache. There was a significant effect in the intervention group when total postconcussion symptoms scores were evaluated, but significance testing comparing headache outcomes in the two groups was NR.[39] A prospective study found that completing diagnostic exertional testing did not significantly reduce headache symptom scores 24 h after testing. This study was limited by a high drop-out rate (31%).[40] One retrospective study looked at the impact of early physical activity (<3 weeks following mTBI) on the presence of PTH at the initial follow-up visit and found that those who did not report early physical activity were significantly more likely to report headache.[43] Interpretation of this study is limited by the possibility that those who did not report early physical activity may have been experiencing more significant and more debilitating postconcussion symptoms at onset.

In summary, there is poor to fair evidence to support physical and exercise therapy as a treatment for PTH, although not all studies reported a benefit. Notably, most studies were designed to look at postconcussion symptoms overall and not headache specifically.

Collaborative care, cognitive behavioral therapy, and biofeedback

A large prospective RCT reported that collaborative care including cognitive behavioral therapy (CBT), care management, and medication consultation as needed significantly improved patient satisfaction and postconcussion symptoms compared to standard of care. However, there was no significant improvement in PTH,[44] and details about medication used and for what purpose were not described.

Another retrospective analysis evaluated biofeedback as a treatment for PTH in youth. Forty-six percent of the cohort reported an improvement in PTH, with 35% reporting reduced frequency and 23% reporting reduced severity. Participants who reported a decrease in headache severity or frequency following biofeedback were less likely to be on antidepressant medications and more likely to have stayed in school compared to those who did not respond.[45] Sample size was NR and use of concomitant therapies limits interpretation.

In summary, collaborative care including CBT was shown to improve overall quality of life and postconcussion symptoms but did not specifically improve headache outcomes.[44] There is limited support for biofeedback improving PTH.

Headache risk factors and characteristics

Of 27 studies, 7 reported headache with migrainous features,[6,17,21,29,34,35,46] 7 reported on premorbid migraine history,[6,22,24,25,35,39,42] and 3 reported on migraine family history.[6,24,34] When reported, the frequency of headache was high, with 61%–87% of patients described as having daily or constant headache.[6,22,24,35,45] When considered as a confounding variable, presence of prior headache history appeared to impact treatment outcomes,[24,41] although this was not consistent across studies.[25]

Four retrospective studies (all poor data quality) reported targeted treatments to headache phenotype. One study evaluating the efficacy of topiramate as a preventative specifically commented on reduction of “migrainous” headaches.[29] Two patients with stabbing headache were effectively treated with indomethacin.[47] Case series that reported on posttraumatic occipital neuralgia[36] and posttraumatic pseudotumor cerebri[30,31] reported high response rates to targeted treatment.

Timing of therapies

Most abortive pharmacologic therapies were studied between 48 h and 14 days after mTBI, and their efficacy was measured immediately to days after treatment. All other treatment modalities were studied in youth with at least 3–4 weeks of persistent symptoms. In some cases, symptoms were persistent for >1 year. The duration of preventative pharmacologic treatment, when reported, ranged from 5.5 weeks to 4 months on average.

DISCUSSION

We did not identify any studies that provided good quality evidence for treatment of PTH in children and adolescents. This finding is unchanged from systematic reviews of pharmacologic and procedural PTH treatment in adults and children,[12,13] and from a review of postconcussive symptoms including headache.[14] We expanded on this work by focusing specifically on headache in the pediatric population, including a broader range of treatments, and assessing for the presence of migrainous headache features and/or family and personal history of migraine in the reviewed studies. Limitations of the study design include that the searches were limited to identifying articles in English that were published in 1985 or later.

Treatments that have been studied include abortive and preventative medications, procedures, neuromodulation, PT, exercise, collaborative care models, and behavioral therapies. There were two RCTs that supported the use of acetaminophen and ibuprofen[17] and IV HTS[23] in acute PTH. Overall evidence for preventative therapies was significantly limited by small sample sizes and lack of comparator groups. There was poor, but consistent evidence to support the use of occipital nerve blocks to treat acute and persistent PTH; however, sample sizes were small, and lacked appropriate comparator groups. The greatest number of prospective studies with comparator groups focused on nonpharmacologic strategies used to treat postconcussive symptoms including PT, exercise therapy, and collaborative care models. However, in most cases, headache was not the primary outcome, but rather one of multiple postconcussion symptoms being measured on an inventory. Further research is needed to assess the specific impact of these therapies on PTH.

Defining headache characteristics following mTBI

Although PTH is considered its own entity,[3] there has been an effort to identify features of other primary and secondary headache disorders in PTH. A predisposition to migraine appears to act as a catalyst for PTH development,[48] and some cases of PTH may be the abrupt onset of trauma-triggered migraine.[11] A recent prospective multi-center cohort study demonstrated that those reporting migrainous headache <8 weeks post-mTBI were more likely to have a prolonged recovery, and were more likely to be prescribed preventative migraine medication.[9] The authors proposed that migraine phenotype may represent a target for early intervention. We found that while many studies evaluated migraine-directed therapies, relatively few studies specifically reported on the presence of migrainous headache features and/or family or personal history of migraine. Studies that did target specific headache phenotypes reported high efficacy rates, although these were notably limited by small sample size and study design.

The severity and frequency of PTH may also impact the efficacy of treatments. Chan et al. found that subjects who had a head CT in the ED were more likely to not respond to a combination of IV abortive therapies,[25] with need for CT as a potential surrogate for symptom severity. While relatively few studies reported the presence of constant or daily PTH, this is a particularly critical group to focus efforts on due to high disease burden.

Acute versus persistent PTH

There was variability in the definition of persistent symptoms and the timing of preventative therapy initiation with 1 and 3 months being the most common cutoffs. This likely stems from different definitions of "persistent" in the mTBI literature, which range from 2 weeks up to 3 months.[49] ICHD-3 criteria define persistent PTH as >3 months.[3] Expert opinion has suggested that early treatment with preventative medications may be able to prevent the development of persistent PTH.[50] However, there is no clear evidence-based determination of when it is most appropriate to switch focus from abortive to preventative pharmacologic therapies based on the results of this current review.

Considerations for future clinical trial design

We propose the following recommendations based on our review:

1. There is a need to establish standardized and validated metrics to measure headache improvement in PTH. Although guidelines to determine the efficacy of abortive therapies in children with migraine have not been established, in adults, the International Headache Society (IHS) recommendation for measuring pain resolution at 2 h as a primary endpoint and change in 4-point severity scale as a secondary endpoint[51] would also be relevant for PTH. In children, the IHS recommends measuring the efficacy of preventative therapies as the change in total headache days/month.[52] Measuring the number of severe headache days/month in addition may more effectively capture improvement for individuals with continuous headache. The PedMIDAS[53] should be used as a metric of headache-related disability, which has been validated for time intervals as short as 1 month.[54]

2. Consensus is needed on what constitutes persistent symptoms for research studies and when to start preventative therapies. We propose defining persistent symptoms as 4 weeks or longer. Consensus is that symptoms persisting past the acute period (defined as 4 weeks for school-age children) usually do

not have a single etiology, but rather involve a complex interplay between multiple biopsychosocial factors leading to a more complicated recovery.[55] This definition diverges from the ICHD-3 criteria for persistent PTH[3] but would encourage early headache intervention to prevent the development of prolonged symptoms.[50]

3. Risk factors for prolonged recovery including family and personal history of migraine, and the presence of migrainous features with headache shortly after mTBI should be reported and taken into consideration in both research studies and clinical management of PTH.[5,6,9]

4. Headache characteristics, including the presence of MOH, should be considered when choosing the most appropriate treatment. ICHD-3 criteria[3] can be used to identify the characteristics and/or presence of other headache disorders following mTBI. Research is needed to understand whether mTBI can provoke other primary or secondary headache disorders and establish potential shared pathophysiologic mechanisms.

CONCLUSION

There is a paucity of evidence to guide clinicians on the timing and types of therapies that are effective for treating PTH. Well-designed prospective studies with appropriate sample size and comparator groups that include thoughtful approaches to headache features, and timing of therapies are needed.

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APPENDIX

SEARCH STRATEGY

Medline/PubMed:

("Child" [MeSH] OR "Adolescent" [MeSH] OR children OR pediatric OR teenager OR teenagers OR teen OR teens OR adolescents OR adolescence) AND ("Brain concussion" [MeSH] OR mild traumatic brain injury OR post-concussive OR concussion OR post-concussion OR post-traumatic OR post traumatic) AND ("Headache" [MeSH] OR "Post-traumatic headache" [MeSH] OR headaches) AND ("Therapeutics" [MeSH] OR "Treatment outcome" [MeSH] OR therapeutic OR therapy OR therapies OR treatment OR treatments OR intervention OR interventions OR management).

Embase:

("child"/de OR "adolescent"/de OR children OR pediatric OR teenager OR teenagers OR teen OR teens OR adolescents OR adolescence) AND ("brain concussion"/de OR mild traumatic brain injury OR post-concussive OR concussion OR post-concussion OR post-traumatic OR post traumatic) AND ("headache"/de OR "posttraumatic headache"/de OR headaches) AND ("treatment outcome"/de OR "therapy"/de OR therapeutic OR therapies OR treatment OR treatments OR intervention OR interventions OR management).

Scopus:

(child* OR adolescent* OR teen* OR pediatric) AND headache AND (concussion OR "mild traumatic brain injury") AND (therapy* OR treatment OR intervention OR management) AND PUBYEAR >1985 AND (LIMIT-TO (LANGUAGE, "English")).

Cochrane Library:

("Child" OR "Adolescent" OR children OR pediatric OR teenager OR teenagers OR teen OR teens OR adolescents OR adolescence) AND ("Brain concussion" OR mild traumatic brain injury OR post-concussive OR concussion OR post-concussion OR post-traumatic OR post traumatic) AND ("Headache" OR "Post-traumatic headache" OR headaches) AND ("Therapeutics" OR "Treatment outcome" OR therapeutic OR therapy OR therapies OR treatment OR treatments OR intervention OR interventions OR management).

Abbreviations:

HTS	hypertonic saline
ICHD-3	International Classification of Headache Disorders, 3rd edition
IV	intravenous
MOH	medication overuse headache
mTBI	mild traumatic brain injury
NIH	National Institutes of Health

NR	not reported
NS	normal saline
NSAID	nonsteroidal anti-inflammatory drug
PTH	posttraumatic headache
TBI	traumatic brain injury

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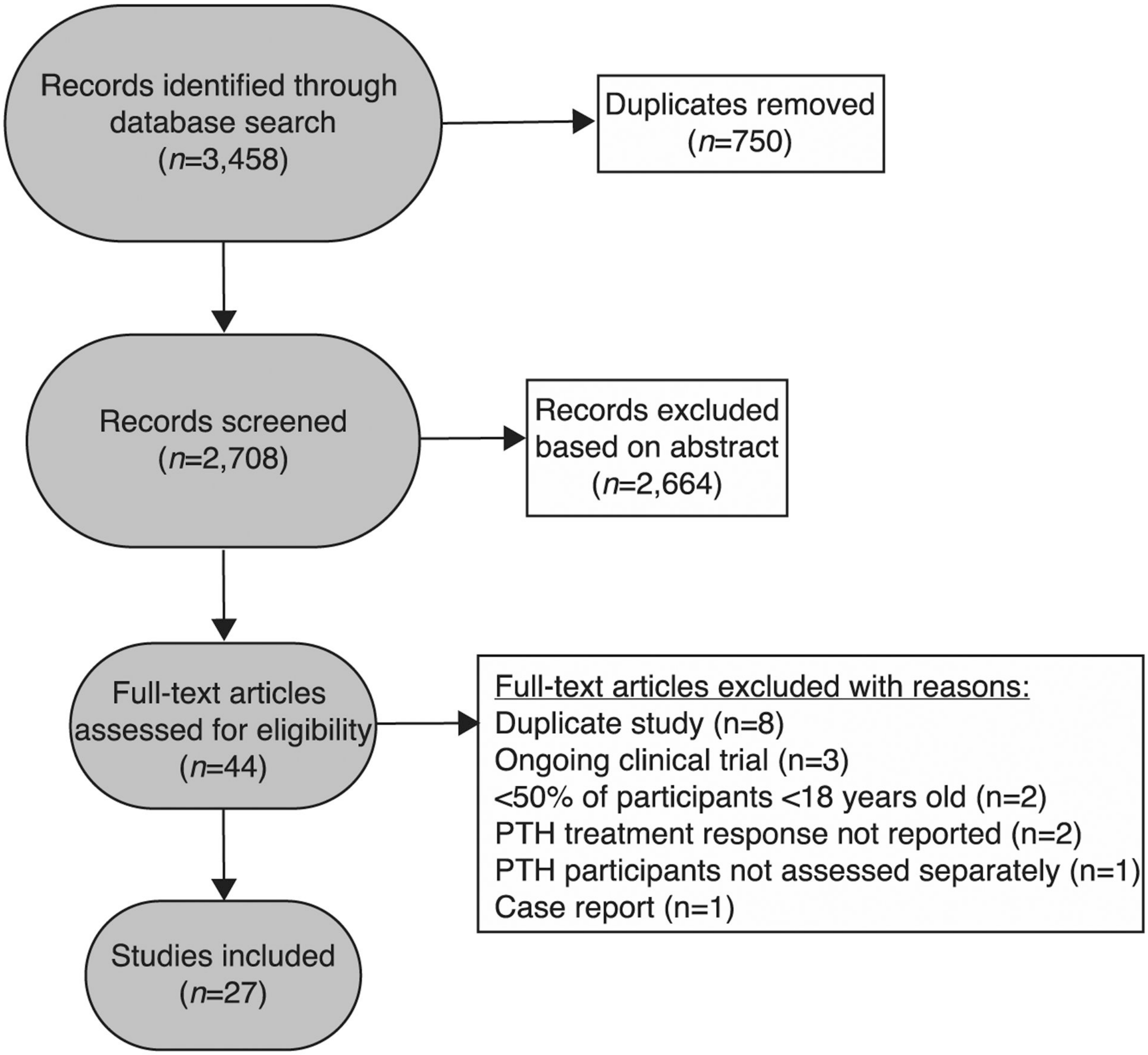

FIGURE 1.
Flow chart of article identification and selection

TABLE 1

Data quality assessment definitions

Data quality	Type of evidence
Good	• Well-designed, well-executed randomized controlled trials
Fair	• Randomized controlled trials with minor limitations including minor flaws in design or execution • Well-designed, well-executed nonrandomized controlled studies, or observational studies
Poor	• Randomized controlled trials with major limitations • Nonrandomized intervention or observational studies with major limitations • Uncontrolled clinical observations without comparison group (e.g., case series, case reports)

TABLE 2

Synopsis of findings from articles included in the systematic review

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
Abortive pharmacotherapies (oral)						
Petrelli et al. (2017)[17]	Prospective randomized open-label control trial	Participants presented to the emergency department within 48 h of mTBI Age range (mean): 8–18 years (12.9) n = 79 (50% female) **Included 18 years old	Migrainous headache: 39% Hx of migraine: NR FamHx of migraine: NR	Treatment with the following analgesic regimens for 1 week: **1** Ibuprofen 10 mg/kg q8 h ×72 h (n = 20) **2** Acetaminophen 10–15 mg/kg q4 h ×72 h (n = 20) **3** Alternating acetaminophen and ibuprofen ×72 h (n = 19) **4** Standard of care: no analgesic recommendations (n = 20)	Outcome measures: Number of headache days, number of headache episodes, headache intensity, and higher return to school rate over 1 week of treatment Outcome: • Patients in any of the treatment arms had fewer headache days, headache episodes, and lower headache intensity, and a greater percentage were back to school compared to the standard of care group. Subjects in the alternating group had the best response • Ibuprofen.: #headache days 5/7, back to school 61% • Acetaminophen: #headache days 7/7, back to school 33% • Both: #headache days 4/7, back to school 79% Standard of care: #headache days 7/7, back to school 21% • Mean (SD) headache episodes/patient/day and headache intensity for each of the 7 days in the trial were reported	Fair
Heyer et al. (2014)[22]	Retrospective cohort	Participants meeting criteria for medication overuse headache (MOH) who presented to a headache clinic >3 months following mTBI Age range (median): 13–17 years (15.2) n = 77 (63% female; 54/77 met criteria for MOH)	Migrainous headache: NR Hx of migraine: 37% FamHx of migraine: NR Note: 75.9% of participants with MOH had daily episodic or	Discontinuation of as-needed analgesics (ibuprofen, acetaminophen, naproxen, oxaprozin)	Outcome measure: Headache improvement or resolution within 2 months of discontinuing analgesics Outcome: • 68.5% of subjects with MOH reported headache improvement after discontinuing analgesics. No further statistical analysis was reported	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
			continuous headache			
Cohen and Conidi (2015)[20] (abstract)	Retrospective cohort	Participants were diagnosed with concussion/mTBI at a tertiary care center. Age range: 14–19 years $n = 19$ (randomly selected) **Included >18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Any reported therapies for PTH	Outcome measure: Headache relief Outcome: • Triptans and onabotulinumtoxinA reported as providing the most rapid headache relief. No statistical analysis was provided	Poor
Tejani et al. (2017, 2019)[18,19] (abstract)	Prospective cohort	Participants presented to a concussion clinic within 30 days of concussion/mTBI Age range: 6–18 years n 528 (45% female) **Included 18 years old	Migrainous headache: Hx of migraine: NR Hx of migraine: NR FamHx of migraine: NR	Effect of NSAID and triptan use within 30 days of concussion/mTBI **1** NSAIDs only (61% of participants) **2** Triptans only (1.1% of participants) **3** NSAIDs + triptans (5.3% of participants) **4** No treatment (32.6% if participants)	Outcome measure: Headache resolution, and headache severity at 3 months Outcome: • Reduction in number of subjects reporting headache from 75.4% to 18% regardless of treatment group with no significant difference between the NSAID group and no treatment group (81.4% → 18.6% vs. 86.6% → 13.4%, $p = 0.165$) • A higher proportion of subjects who used triptans reported greater headache severity compared to the NSAIDs group (5/5 triptans group vs. 10/28 NSAIDs + triptans group vs. 23/172 NSAID group, $p < 0.001$) • Subjects who used triptans reported greater headache severity than those who used NSAIDs (mean triptan only 1.6 95% CI: 1.0–2.4, mean triptan+NSAID 1.0 95% CI: 0.7–1.4, mean NSAID only 0.3 95% CI: 0.2–0.4, mean no med 0.2 95% CI: 0.1–0.3)	Poor
Bramley et al. (2012)[21]	Retrospective case series	Case series included a 10-year-old male and a 15-year-old female presenting with concussion/mTBI within the first month	Migrainous headache: 100% Hx of migraine: NR FamHx of migraine: NR	4 mg 6-day tapering Medrol dose pack in addition to other abortive and preventative therapies. Other medications included amitriptyline, melatonin, and gabapentin	Outcome measure: Descriptive, headache improvement Outcome: • Both subjects reported improvement with Medrol dose pack • One subject completed an additional 14-day taper because of symptom return following	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
					completion of the first taper. No significance testing was reported	
Abortive pharmacotherapies (intravenous)						
Lumba-Brown et al. (2014)[23]	Prospective randomized controlled trial	Participants were recruited acutely following concussion/mTBI in an emergency department (duration post-injury not specifically reported) Age range (mean): 7–16 years (12) n = 44 (37% female)	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Participants were randomized to receive a single dose of 10 ml/kg of one of the following given over 1 h: **1** 3% hypertonic saline (HTS, 52% of participants) **2** Normal saline (NS, 48% of participants)	Outcome measure: Wong-Baker face scale pain score before versus immediately after infusion, and 2–3 days later Outcome: • Participants who received HTS reported a greater reduction in pain scores compared to NS immediately (3.52 vs. 1.14-point decrease, mean difference between groups −2.38 95% CI: −0.3 to −1.4*, $p < 0.001$) and 2–3 days after infusion (4.61 vs. NS 3.00-point decrease, mean difference between groups −1.61 95% CI: −2.90 to −0.30, $p = 0.014$) • A multiple-regression model used to adjust for initial higher pain reports in the HTS group and other potential confounders still demonstrated a significantly greater reduction in pain in the HTS compared to NS group (mean difference between groups −1.86 95% CI: 0.92 to 2.79*)*95% CI intervals may contain an error, and sign conventions may also be reported in error	Fair
Bresee et al. (2018)[24]	Prospective cohort, planned subanalysis	Participants presented to the emergency department within 48 h of concussion/mTBI Age range: 8–17 years n = 2095 (41% female)	Migrainous headache: NR Hx of migraine: 13% FamHx of migraine: 47% Note: 75% reported constant headache	Participants received one of the following: **1** Single dose of IV metoclopramide (dosage not reported, 3% of participants) **2** No treatment (97% of participants)	Outcome measure: Persistent headache at 1 and 4 weeks Outcome: • IV metoclopramide was *not* associated with lower rate of persistent headaches at 1 week (unadjusted RR 1.0 95% CI: 0.8–1.3; adjusted multivariable logistic regression OR 0.6 95% CI: 0.4–1.1; adjustment with propensity score using 1:4 matching algorithm RR 0.8 95% CI: 0.6–1.2)	Fair

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
					• At 4 weeks (unadjusted RR 1.0 95% CI: 0.9–1.2; adjusted multivariable logistic regression OR 0.8 95% CI: 0.4–1.5; adjustment with propensity score using 1:4 matching algorithm RR 0.9 95% CI 0.8–1.1)	
Chan et al. (2015)[25]	Retrospective cross-sectional	Participants presented to the emergency department within 14 days of concussion/mTBI (mean 2 days) and received IV headache treatment Age range (mean): 8–21 years (13.8) n = 254 (51% female) **Included ≥18 years old	Migrainous headache: NR Hx of migraine: 21% FamHx of migraine: NR	Participants received IV NS bolus and the following IV medications (dosages not reported): **1** Ketorolac only (21% of participants) **2** Prochlorperazine, metoclopramide, chlorpromazine (12% of participants) **3** Ondansetron only (15% of participants) **4** Ketorolac + metoclopramide or prochlorperazine (52% of participants)(4)	Outcome measure: Treatment success defined as >50% reduction in headache severity score (0–10) after infusion. Headache resolution was also reported Outcome: • 86% (95% CI: 82.0%–90.4%) had treatment success overall • 80% in the ketorolac only group • 93% in the metoclopramide or prochlorperazine only group • 89% in the combined group • 79% in the ondansetron only group • 52.4% (95% CI: 46.3–58.5) reported headache resolution overall • Patients who got a head CT were less likely to have treatment success (80% vs. 91%, p = 0.008) • Patients who did not get a head CT were significantly more likely to have treatment success (multivariable analysis OR 2.95, 95% CI: 1.39–6.56)	Poor
Katz et al. (2018)[26] (abstract)	Retrospective cohort	Participants presented with concussion/mTBI to an outpatient infusion center Age: ≤18 years n = 27 **Included 18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Participants received a single dose of IV ketorolac, prochlorperazine, diphenhydramine, and 20 ml/kg NS IV fluid (medication dosages not reported)	Outcome measure: Headache improvement, headache severity scale (0–6) at follow-up after the infusion Outcome: • 23/27 (85%) reported headache improvement, 1/27 (4%) found no improvement, 3/27 (11%) were not asked	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
					• Mean headache score was reduced from a 4/6 to a 2/6. No significance testing was reported	
Preventative pharmacotherapies						
Kuczynski et al. (2013)[47]	Retrospective cohort	Participants presented with concussion/mTBI to a concussion clinic a median of 6.9 months (range 1–29 months) post-injury Age range (mean): ≤18 years (14.1) n = 44 (66% female) **Included 18 years old	Migrainous headache: 39% Hx of migraine: 14% FamHx of migraine: 52% Note: 61%experienced daily headache at the start of treatment	Participants were placed on the following medications for a mean duration of 5.5 weeks (SD 4.3 weeks): **1** Amitriptyline, up to maximum of 1 mg/kg/day based on response (n = 18, 41%) **2** Nortriptyline, dosage not given (n = 9, 20%) **3** Topiramate up to 1.5–2 mg/kg/day to a max 200 mg/day (n = 6, 14%) **4** Flunarizine, dosage not given (n = 8, 18%) **5** Melatonin, 3–10 mg nightly (n = 12, 23%) **6** Indomethacin, dosage not given (n = 2, 5%) 39% received more than one treatment	Outcome measure: Significant response defined as ≥50% reduction in headache frequency. Headache resolution was also reported Outcome: • 64% reported successful response to preventative migraine medications: • 13/18 (72%) on amitriptyline • 1/11 (11%) on nortriptyline • 0/6 (0%) on topiramate • 5/8 (63%) on flunarizine • 9/12 (75%) on melatonin • 2/2 (100%) on indomethacin (had stabbing headache) • 45% reported headache resolution • Length of time for follow-up was not a significant predictor of symptom resolution (χ^2 = 0.341, p = 0.559)	Poor
Bramley et al. (2015)[28]	Retrospective cohort	Participants presented to a concussion clinic, “majority within 1–3 weeks of concussion” Age range: 13–18 years n = 400 (38% female) **Included 18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Amitriptyline started in those with persistent headache at 1 month postconcussion (n = 68; 17% of participants) at 10–100 mg/day (median 25 mg/day) for a median duration of 4 months (range 2–7 months)	Outcome measure: Improvement in headache symptoms Outcome: • 82% (95% CI 70%-91%) reported improvement in headache symptoms • 33% (95% CI 12%-38%) of those on amitriptyline reported side effects • Females were more likely to be prescribed amitriptyline (24% vs. 13%, p = 0.004)	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
Markus et al. (2016)[46]	Retrospective case-control study	Participants with TBI (81% with concussion/mTBI) presented to a headache clinic a median of 12 months (range 2–120 months) after injury	Migrainous headache: 54%	20 participants were prescribed one of the following agents: **1** Amitriptyline ($n = 11$) **2** Propranolol ($n = 6$) **3** Topiramate ($n = 3$) (Dosages not reported)	Outcome measure: Positive response was defined as ≥50% reduction in number of headache days	Poor
		Age range (median): 2–17 years (9) $n = 74$ (43% female)	Hx of migraine: NR FamHx of migraine: NR		Outcome: • 10/20 (50%) of TBI participants prescribed preventative medication reported a positive response: • 36% improved on amitriptyline • 50% on propranolol • 100% on topiramate • No significance testing was reported	
Mackie and Kirkham (2017)[29] (abstract)	Retrospective cohort	Participants presented with concussion/mTBI to a nurse-led neurology clinic	Migrainous headache: 71%	All participants received school accommodations/decreasing cognitive load. In addition, 16 participants (42%) were treated with topiramate (median dose 2 mg/kg/day)	Outcome measure: Headache improvement, reported reduction in migraine frequency/migraine severity	Poor
		Age range (median): 3–16 years (13.8) $n = 38$ (45% female)	Hx of migraine: NR FamHx of migraine: NR		Outcome: • 84% reported headache improvement from the whole cohort • 12/16 participants (75%) prescribed topiramate reported reduction in frequency and severity of migrainous headaches • No significance testing was reported	
Sabo et al. (2017, 2018)[30,31]	Retrospective case series	Case series of children and adolescents diagnosed with pseudotumor cerebri following mTBI	Migrainous headache: NR	Acetazolamide 750–1000 mg BID (not all dosing reported) for a treatment interval 6 weeks-4 months	Outcome measure: Headache improvement	Poor
		Age range: 5–16 years $n = 6$ (66% female) Case series of children	Hx of migraine: NR FamHx of migraine: NR	Topiramate (dosing not reported)	Outcome: • 4/5 had improvement with acetazolamide, the nonresponder was found to have craniosynostosis	

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
		and adolescents diagnosed with pseudotumor cerebri following mTBI			• 1/1 had improvement with topiramate + acetazolamide • Two worsened on amitriptyline, and one worsened on propranolol, and one had only mild improvement on cyproheptadine prior to being diagnosed with pseudotumor cerebri • No significance testing was reported	
Neuromodulation						
Pinchuk et al. (2013)[33]	Retrospective cohort	Participants with diagnosis of chronic PTH based on ICHD-2 criteria, 6–9 months following concussion/mTBI	Migrainous headache: NR	Transcranial direct current stimulation (tDCS) for 30–45 min per session with 60–90 μA intensity (number of sessions not reported)	Outcome measure: Headache frequency (days/month), headache severity scale (0–10), % patients with ≥50% reduction in headache frequency, and % patients with headache resolution for ≥4.5 months post-tDCS	Poor
		Age range (median): 11–16 years (13.6) *n* = 44	Hx of migraine: NR FamHx of migraine: NR		Outcome: • 52% reported headache resolution, with an additional 29% reporting ≥50% reduction in headache frequency • Headache severity significantly improved (mean 5.4 SD 1.8 → mean 1.9 SD 1.2; $p < 0.001$) • Headache frequency significantly improved (mean 10.3 SD 6.5 → mean 4.1 SD 2.2; $p < 0.001$)	
Procedures						
Dubrovsky et al. (2014)[34]	Retrospective case series	Participants with mean of 70 days post-injury with a diagnosis of acute or persistent PTH based on ICHD-3	Migrainous headache: 83%	Greater occipital nerve block ±lesser occipital nerve block ± supraorbital nerve block with 2% lidocaine + epinephrine; participants received between 1 and 6 nerve blocks with median duration between repeated nerve blocks of 18.5 days. Many subjects received abortive therapies, preventative therapies, or both concomitant to their nerve block	Outcome measure: Good therapeutic effect was defined as decrease in pain for >24 h or requested repeat nerve block, headache pain severity immediately after nerve block (0–10 scale)	Poor
		Age range (mean): ≤18 years (14.6) *n* = 28 **Included 18 years old	Hx of migraine: NR FamHx of migraine: 77% Note: history of headache was reported to be 70%		Outcome: • 93% reported good therapeutic effect, and 71% of nerve blocks resulted in 0/10 headache pain • Headache intensity decreased pre-versus post-headache (mean = 5.6, SD = 1.6 vs. mean = 0.4, SD = 0.9); % reduction mean = 93%, SD = 13%	

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
Seeger et al. (2015)[35]	Retrospective case series	Participants treated in concussion and TBI clinic who received a nerve block for PTH, mean of 5.6 months post injury (range 1–12 months) Age range (mean): 13–17 years (15.5) *n* = 15 (14 presented for follow up), (67% female)	Migrainous headache: 40%. Hx of migraine: 6% FamHx of migraine: NR Note: 13/15 (87%) had daily headaches at time of procedure 6/15 (40%) met ICHD-3 criteria for occipital neuralgia	Greater occipital nerve block with 2% lidocaine + steroid (triamcinolone or methylprednisolone). Study did not comment on concomitant use of other therapies	Outcome measure: Full response was defined as >50% reduction in headache frequency, mean headache frequency (days/month) at follow-up was also reported. Routine follow up was via telephone 2–4 weeks after the procedure and 2–3 months for an in-person visit. Secondary outcomes included Rivermead Post-concussion Symptoms Questionnaire (RPSQ), and the Pediatric Quality of Life Inventory (PedsQL) Outcome: • 64% of children had full response • Headache frequency decreased from mean 26 SD 7 days/month to mean 18 SD 12 days/month ($p = 0.014$) • RPSQ scores significantly decreased following treatment (mean 33.67 SD 13.47 vs. 24.33 SD 18.54; $t(5) = 3.04$, $p = 0.029$) • PedsQL improved post-treatment (mean 52.04 SD 21.36 vs. 68.75 SD 27.50; $t(7) = -2.62$, $p = 0.035$)	Poor
Zaremski et al. (2015)[36]	Retrospective case series	Participants (16, 17, and 28 years old) presented with symptoms of occipital neuralgia following concussion/mTBI **Included ≥18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Variable: Greater and lesser occipital nerve block, trigger point injections, cervical medial branch block of C2 to C3, third occipital nerve blocks	Outcome measure: Headache improvement Outcome: • Both participants under 18 years old experienced complete but temporary relief from nerve blocks. No significance testing was reported	Poor
Lin and Tung (2016)[37]	Retrospective case series	Participants (8 yM, 15yF, and 18 yF) with PTH **Included 18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Acupuncture for 6 to >12 sessions initiated 4–6 weeks following concussion/mTBI for persistent headache	Outcome measure: Headache frequency, headache severity (10-point scale) Outcome: • All subjects reported reduction in headache frequency and a 3–7 point reduction in headache severity. No significance testing was reported	Poor
Physical therapy and exercise						

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
Schneider et al. (2014)[38]	Prospective randomized controlled trial	Participants with persistent postconcussion symptoms a mean of 50 days (range 8–276) following concussion/mTBI Age range (median): 12–30 years (15) *n* = 31 (42% female; 2 withdrew) **Included ≥18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Participants were randomized into the following groups: **1** Intervention group (*n* = 15): cervical spine and vestibular rehabilitation **2** Standard of care (*n* = 14) Both groups worked with a physiotherapist ×8 weeks or until medical clearance (mean number of sessions for each group = 6) Both groups received postural education, range of motion exercises, cognitive and physical rest until asymptomatic followed by graded exertion	Outcome measure: Numeric pain rating scale for headache (010) compared between those who were cleared to return to sport vs. those who were not cleared in the treatment and control groups. Primary outcome measure was return to sport within 8 weeks of treatment Outcome: • There was no significant difference in reduction of headache severity between cleared and not cleared subjects in the treatment or the control groups. Change in severity score (post - pre-treatment): • *Control group*: Cleared: −7 (*n* = 1); Not cleared: −2.5 (range −7 to 1, *n* = 12[a] one participant in this group did not complete the follow-up questionnaire), *p* > 0.05 • *Intervention group*: Cleared: −3 (−8 to 0, *n* = 11); Not cleared: −2.5 (range −4 to 1, *n* = 4), *p* > 0.05 • Treatment group was 10.27 times more likely to be medically cleared to return to sport within 8 weeks ($\chi^2 = 13.08$, $p < 0.001$)	Fair
Gauvin-Leplage et al. (2019)[41]	Retrospective analysis of a prospective cohort	Participants reported ongoing symptoms at 4 weeks following concussion/mTBI Age range (mean): 8–17 years (14.3) *n* = 355 (53%. female)	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Exercise based active rehabilitation intervention ×4 weeks	Outcome measure: Post-concussion symptom scale (PCSS) headache symptom score (0–6) compared from baseline to 2 and 4-weeks f/u. Primary outcome was total PCSS score at these visits Outcome: • PCSS headache scores decreased over the 4 weeks of treatment. PCSS headache score: Girls 2.5 at baseline, 2.1 at 2-weeks f/u, 1.5 at 4-weeks f/u; Boys 1.9 at baseline, 1.3 at 2-weeks f/u, 1.1 at 4-weeks f/u; ANOVA, *p* < 0.001 for headache score change over time • More girls reported headache, and had higher PCSS toral scores at baseline, and experienced a faster recovery compared to boys. Repeated-measures ANOVA, sex-specific difference for headache (*p* = 0.046). Generalized mixed regression model total PCSS by gender: Boys visit OR (95% CI): Visit 1: −8.81 (−12.37 to	Fair

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
					−5.26); Visit 2: −7.37 (−9.6- to −5.14); Visit 3: −11.40 (−14.33 to −8.48)	
De Matteo et al. (2015)[40]	Prospective cross-sectional study	Participants presented to a concussion clinic a median of 4.1 months (range 0.7–35) post-injury Age range (mean): 8–18 years (14.8) n = 54 (41% female; 69% completed follow-up) **Included 18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR	Exertional testing ×1 session	Outcome measure: Reduction in headache symptom score (0–6) at 5-min, 30-min, and 24-h post-exertional testing, headache improvement. Primary outcome was total decrease in symptom scores Outcome: • There was no significant difference in headache scores before vs. after exertional testing. Headaches worsened for 5 subjects and improved for 9 subjects. Mean headache symptom score decreased from 0.97 pre-exertion to 0.78 at 24 h post-exertion (Z = −1.10, p = 0.27), 30-min after exertion was also not significant (p = 0.39, Friedman test) • Overall, the total number of symptoms and symptom severity significantly decreased. There was a significant total decrease in symptoms at 30 min and 24 h post-exertion testing (30 min: severity χ^2 = 14.00, p = 0.001; number χ^2 = 8.7, p = 0.01; 24 h: severity Z = −3.47, p < 0.01)	Poor
Grabowski et al. (2017)[42]	Retrospective cohort	Participants were youth athletes with concussion symptoms persisting beyond 3 weeks (80% reported headache at initial visit) Age range (mean): 12–20 years (15) n = 25 (56% female) **Included >18 years old	Migrainous headache: NR Hx of migraine: 20% (also included chronic tension-type headache) FamHx of migraine: NR	PT, cardiovascular exercise, vestibular/ oculomotor exercise, cervicothoracic manual therapy and exercise, and sports specific training. Mean therapy duration was 84 days (range 7–266)	Outcome measure: Headache score of how bothersome headaches were from post-concussion symptom scale (PCSS, 0–6). Primary outcome measure was change in total PCSS Outcome: • Patients reported significantly decreased PCSS score post-PT. Total PCSS scores: Pre-PT mean 18.2 (SD = 14.2); Post-PT mean 9.1 (SD = 10.8); p < 0.01 • Significance testing was not done on the difference in headache scores pre-versus post-PT. Headache score: Pre-PT median 2 (range 0–5); Post-PT median 1 (range 0–5) • Athletes with a history of chronic migraine or tension-type headache had a mean 10.22 point	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
					higher post-PT score compared to athletes with no headache history ($p = 0.05$)	
Bailey et al. (2019)[39]	Pilot, prospective randomized controlled trial	Participants with concussion at least 4 weeks post-injury (mean 56 days) Age range (mean): 14–18 years (15.75) $n = 16$ (44% female; 1 withdrew due to repeat injury) **Included 18 years old	Migrainous headache: NR Hx of migraine: 37% FamHx of migraine: NR	Participants were randomized into the following groups: **1** Sub-threshold exercise program ($n = 7$): targeted 80% of heart rate that correlated with symptom exacerbation with physiotherapist ×6 weeks **2** Control group ($n = 8$): instructed on daily stretching activities at home ×3 weeks, then daily walking ×3 weeks	Outcome measure: % of participants with mild or no headaches defined as a Post-concussion Scale-Revised (PCS-R) headache score of ≤ 2 (0–6 scale). Primary outcome measure was change in total PCS-R score Outcome: • Total PCS-R scores decreased more in the intervention than in the control group when depression was accounted for (PCS-R % change: intervention group mean = −63.3%, SD = 17.4; control group mean = −56.8%, SD = −27.8; $F_{2,13} = 5.20$, $p < 0.05$, partial $\eta^2 = 0.32$) ANOVA (depression was a covariate). *1 subject from the intervention group was removed prior to analysis due to worsening PCS-R score and high baseline depression score • % with mild or no headache was compared between baseline and post-treatment (intervention group 33% → 67%; control group 33% → 63%). Significance testing was not done	Poor
Wilson et al. (2020)[43]	Retrospective cohort	Participants seen by a concussion specialist within 21 days of concussion stratified by early physical activity (PA) Median days post-injury was 8 for the early PA group and 12 for the no PA group ($p < 0.001$) Age range (mean): 8–18 years (14.8) $n = 575$ (34% female) **Included 18 years old	Migrainous headache: NR Hx of migraine: NR FamHx of migraine: NR Note: History of pre-existing headache was reported (28% across the cohort, no significant difference between groups)	Participants were stratified based on reports of early physical activity (prior to initial evaluation): **1** PA group ($n = 69$): Reported early physical activity **2** No PA group ($n = 506$): Reported that they did not have early physical activity	Outcome measure: Reporting persistent headache at the initial visit. Primary outcome was symptom resolution times Outcome: • The no PA group had significantly longer recovery times than the PA group (median 16 IQR 8–24 vs. 10.5 IQR 4–17, $p = 0.02$) • Subjects in the PA group were significantly less likely to report persistent headache at their initial visit when adjusting for pre-existing headache history (adjusted OR = 0.14, 95% CI: 0.07–0.26)	Poor

First author (date)	Study type	Participant characteristics		Treatment	Outcome	Data quality
Collaborative care, cognitive-behavioral therapy, and biofeedback						
McCarty et al. (2021)[44]	Prospective randomized controlled trial	Participants presented to a concussion clinic within 9 months of concussion/mTBI with ≥3 persistent symptoms at least 1 month after concussion	Migrainous headache: NR	Treatment: Cognitive behavioral therapy and care management with enhanced medication consultation if warranted ×6 months	Outcome measure: Traumatic Brain Injury-Quality of Life Headache Pain (13-item Likert-based scale). Primary outcome measure was improvement in postconcussive symptoms	Fair
		Age range (median): 11–18 years (14.7) *n* = 200 (62% female) **Included 18 years old	Hx of migraine: NR FamHx of migraine: NR Note: 25% reported a history of chronic headaches	Standard of care: Standard management by subspecialty clinics ×6 months	Outcome: • There was a significant difference between postconcussive symptom outcomes between the collaborative care group and standard of care group (net difference from baseline between groups mean 3 months −3.4 95% CI: −6.6 to −0.1; mean 6 months −3.0 95% CI: −6.4 to 0.3; mean at 12 months −4.1 95% CI: −7.7 to −0.4; effect size Cohen d at 3 months 0.26 and 12 months 0.32) • No difference in headache outcomes between collaborative care group and standard of care group (net difference from baseline between groups mean 3 months 0.2 95% CI: −1.9 to 2.3; mean 6 months −0.4 95% CI: −2.6 to 1.8; mean at 12 months −1.6 95% CI: −3.9 to 0.7)	
Schwarz et al. (2017)[45] (abstract)	Retrospective cohort	Participants received PTH treatment and were evaluated a median of 5.7 months following mTBI	Migrainous headache: NR	≥2 biofeedback sessions for treatment of PTH. Compared responders and non-responders	Outcome measure: % reporting reduced headache frequency, % reporting reduced headache severity	Poor
		Age range (mean): 8–18 years (15.5) *n* = NR (77% female) **Included 18 years old	Hx of migraine: NR FamHx of migraine: NR Note: 66% had daily headaches		Outcome: • 46% of participants responded to therapy, with 35% reporting reduced headache frequency and 23% reporting reduced severity • Responders were significantly more likely to have stayed in school (χ^2: 5.52, $p = 0.02$) • Responders were significantly less likely to be on serotonin reuptake inhibitors or tricyclic anti-depressants (χ^2: 3.86, $p = 0.05$)	

[a]Data quality measures were based on the National Institutes of Health (NIH) Quality Assessment Tools. Details can be found at https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.