Post-traumatic headache attributed to traumatic brain injury: classification, clinical characteristics, and treatment

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Post-traumatic headache is a common sequela of traumatic brain injury and is classified as a secondary headache disorder. In the past 10 years, considerable progress has been made to better understand the clinical features of this disorder, generating momentum to identify effective therapies. Post-traumatic headache is increasingly being recognised as a heterogeneous headache disorder, with patients often classified into subphenotypes that might be more responsive to specific therapies. Such considerations are not accounted for in three iterations of diagnostic criteria published by the International Headache Society. The scarcity of evidence-based approaches has left clinicians to choose therapies on the basis of the primary headache phenotype (eg, migraine and tension-type headache) and that are most compatible with the clinical picture. A concerted effort is needed to address these shortcomings and should include large prospective cohort studies as well as randomised controlled trials. This approach, in turn, will result in better disease characterisation and availability of evidence-based treatment options.

Introduction

Post-traumatic headache is a disabling secondary headache disorder, which is often attributed to traumatic brain injury and affects millions of individuals worldwide.[1,2] Population-based data have shown that the lifetime prevalence of this disorder is estimated to be 4·7% in men and 2·4% in women.[3] Progress in research has improved disease characterisation and shed light on the natural course of the disorder.[4–9] The clinical presentation of post-traumatic headache is characterised by recurrent episodes of headache that can vary considerably in terms of frequency, duration, and pain intensity.[4,5] Headache features are often reported to resemble those of primary headache disorders, such as migraine and tension-type headache.[4,5,10] For this reason, and due to the scarcity of controlled trials of post-traumatic headache, most clinicians tend to treat the disorder with therapeutics that are recommended for migraine and tension-type headache.[11–13] Despite these shortcomings, new developments have provided insights that could be used to effectively combat this disabling neurological disorder.

In this Review, we provide a comprehensive overview of the classification, clinical characteristics, and management of post-traumatic headache. Each section includes a concise overview of the available evidence and is followed by three to five key messages to guide current and future research efforts. Lastly, we propose a treatment algorithm to aid clinical decision making in the absence of robust data from controlled trials of post-traumatic headache.

Classification

Post-traumatic headache is classified as a secondary headache disorder in the International Classification of Headache Disorders (ICHD)-3.[14] Its diagnosis is based on clinical criteria and, thus, usually established on medical history and exclusion of differential diagnoses (panel 1).[14] According to the ICHD-3,[14] post-traumatic headache can be attributed to traumatic brain injury, whiplash injury, or craniotomy. The ICHD-3 requires that patients have onset of headache within 7 days of the injury or, alternatively, within 7 days of regaining consciousness or recovering the ability to sense and report pain.[14] This 7-day threshold is needed to establish the causal relationship between injury and subsequent onset of headache. Although this threshold is a diagnostic requirement, clinicians should be mindful that the 7-day threshold was established on the basis of expert opinion due to the scarcity of scientific evidence.[14] Some clinicians and researchers have argued that the threshold should be extended to 14 days, which was the original threshold defined in the ICHD-1.[15] In the absence of robust data, it largely becomes a discussion of specificity versus sensitivity. Prospective cohort studies are needed to ascertain whether the 7-day threshold should be changed. In the meantime, the ICHD has defined appendix criteria for delayed onset of acute post-traumatic headache between 7 days and 3 months after injury.[14] Another important issue relates to the diagnosis of post-traumatic headache in people with a pre-existing primary headache disorder (eg, migraine and tension-type headache). In such instances, a diagnosis of post-traumatic headache can only be assigned if the pre-existing headache clearly worsens in close temporal relation to the injury.[14] This worsening would usually entail at least a doubled headache frequency or severity, or both.[14] Clinicians should then assign both the initial primary headache diagnosis and a diagnosis of post-traumatic headache.[14]

Post-traumatic headache is initially stratified according to the type of injury, either traumatic brain injury, whiplash injury, or craniotomy.[14] The second stratification classifies post-traumatic headache as either acute or persistent.[14] Acute post-traumatic headache is defined by onset of headache within the 7-day threshold and remission within 3 months of onset.[14] If the headache persists beyond 3 months, it is classified as persistent post-traumatic headache.[14] A third stratification based on injury severity is also applied in the case of post-traumatic

headache after traumatic brain injury, which can be classified as post-traumatic headache attributed to either mild traumatic brain injury or moderate-to-severe traumatic brain injury.[14]

Limitations of the current ICHD-3 criteria are many,[14] but these limitations are largely due to the scarcity of data. First, broad clinical features suggestive of post-traumatic headache are not mentioned in the diagnostic criteria. Indeed, post-traumatic headache is described exclusively as "any headache".[14] Phenotyping of an individual patient's clinical features is useful, to better characterise the headache disorder and facilitate more informed clinical decision making. Second, persistent post-traumatic headache is not defined by any headache frequency threshold.[14] Clinicians can, in theory, assign the diagnosis of persistent post-traumatic headache to a patient with one monthly headache day of mild intensity, and to a patient with 30 monthly headache days of moderate-to-severe intensity. These limitations, along with the arbitrary 7-day threshold, are issues that warrant further investigation to improve the diagnostic criteria in future iterations of the ICHD (panel 1). Moreover, clinicians should note that there are multiple widely used definitions of mild traumatic brain injury and moderate-to-severe traumatic brain injury in the literature.[16–21] These differ somewhat from each other as well as from the definitions of traumatic brain injury severity that are provided in the ICHD-3.[14] Aside from traumatic brain injury severity, it is also problematic to compare populations with traumatic brain injury within and across studies if the mechanisms of injury differ. We would, therefore, encourage consistent use of traumatic brain injury stratification on the basis of the mechanism of injury. An initial stratification should differentiate between closed and open head injuries, with the open head injuries defined by penetration of the skull. Closed head injuries should be further stratified into imaging-positive and imaging-negative on the basis of whether there are any abnormal findings (eg, contusion), as determined by conventional CT or MRI. Taken together, more robust comparative assessments can be made if future studies clearly stratify patients with post-traumatic headache according to traumatic brain injury severity as well as mechanism of injury. If universally recognised traumatic brain injury criteria are published at some point, it would be important to revise the ICHD-3 criteria with regard to grading of traumatic brain injury severity accordingly.

***Panel 1*: Key messages on classification**

- Post-traumatic headache can be attributed to traumatic brain injury, whiplash injury, or craniotomy.
- The diagnosis of post-traumatic headache is based on clinical criteria, as defined in the International Classification of Headache Disorders (ICHD)-3.
- ICHD-3 defines acute post-traumatic headache as onset or considerable worsening of headache within 7 days of the head or neck trauma that remits within 3 months of onset.
- ICHD-3 defines persistent post-traumatic headache as onset or considerable worsening of headache within 7 days of the head or neck trauma that persists beyond 3 months of onset.
- More studies are needed to ascertain the proportion of individuals with traumatic brain injury who develop delayed onset of acute post-traumatic headache, defined as onset of headache between 7 days and 3 months after the traumatic brain injury.

Clinical characteristics

Natural course

An area of key clinical interest is the natural history of post-traumatic headache (panel 2). However, case definitions of post-traumatic headache and traumatic brain injury differ substantially between studies, and adherence to the ICHD-3 criteria for post-traumatic headache is low.[5,8,9,22–25] This inconsistency precludes drawing firm conclusions, although some lessons have been learned from the available data. A considerable proportion of patients with traumatic brain injury develop acute post-traumatic headache[5,26,27] that remits in some people and persists in others.[24] This finding also accords with population-based data that have shown an increased risk of reporting new-onset headache or exacerbation of pre-existing headache after admission to hospital due to head trauma.[28] A US-based cohort study showed that 114 (54%) of 210 patients admitted to hospital due to mild traumatic brain injury had acute post-traumatic headache within 7 days of the injury.[22] The corresponding figure was 66 (66%) of 100 patients in an Austrian cohort who had been admitted to the emergency department due to mild traumatic brain injury.[5] Another emergency department-based cohort study reported that acute post-traumatic headache was one of the most common complaints after mild traumatic brain injury.[29] Of 910 patients, 464 (51%) had acute post-traumatic headache within 2 weeks of the mild traumatic brain injury.[29] From a clinical standpoint, it seems that post-traumatic headache is more common after mild traumatic brain injury than after moderate-to-severe traumatic brain injury.[30,31] Some evidence favours this observation,[32] whereas other data show no such association.[8] Taken together, there is a need for large prospective cohort studies to ascertain whether there is any association between post-traumatic headache and traumatic brain injury severity.

The natural history of persistent post-traumatic headache has been studied in several prospective cohort studies.[9,27,33,34] A Scandinavian cohort study showed that 42 (42%) of 100 patients with mild traumatic brain injury complained of persistent post-traumatic headache at 3 months after injury,[33] whereas a Dutch cohort study reported the corresponding figure to be 95 (23%) of 409 patients.[27] In a large European and Israeli multicentre

***Panel 2*: Key messages on clinical characteristics**

Natural course

- Most individuals who sustain a mild traumatic brain injury or whiplash injury report acute post-traumatic headache within 7 days of the trauma.
- Post-traumatic headache remits within 3 months of onset in some people, but a substantial proportion of affected individuals continue to report persistence of headache beyond 3 months of onset.
- An international commitment to use definitions of post-traumatic headache provided by the International Classification of Headache Disorders is needed to acquire high-quality and comparative data on the natural course of the disorder. As a minimum, case definitions of post-traumatic headache and traumatic brain injury should be clearly described.
- The proportion of individuals who report onset of acute post-traumatic headache within 7 days of traumatic brain injury should be firmly established in large prospective cohorts. Corresponding figures for persistent post-traumatic headache at 3 months, 6 months, and 12 months or more after traumatic brain injury should also be established in large prospective cohort studies.

Headache features

- The clinical presentation of post-traumatic headache most often resembles a migraine-like phenotype followed by a tension-type headache-like phenotype, based on available clinic-based data.
- Atypical clinical presentation (eg, a trigeminal autonomic cephalalgia-like phenotype) should call for review of the diagnosis, although some patients with post-traumatic headache might experience a trigeminal autonomic cephalalgia-like phenotype.
- Large prospective studies are needed to ascertain common headache features and create more awareness among clinicians on post-traumatic headache symptomatology.
- Clinical use of diagnostic headache diaries with daily entries is encouraged to determine the headache features of an individual patient.

Other clinical features

- Individuals with post-traumatic headache often report symptoms suggestive of comorbid disorders, such as sleep disturbances, anxiety, depression, and post-traumatic stress disorder.
- Clinicians should recognise and screen patients with post-traumatic headache for comorbid conditions that are commonly reported sequelae of traumatic brain injury—eg, sleep disturbances, anxiety, depression, cognitive dysfunction, vestibular symptoms, and post-traumatic stress disorder.
- Management of medication overuse headache might be useful in patients with post-traumatic headache, considering that some data suggest withdrawal of overused acute medications is accompanied by a reduction in headache frequency.
- Future iterations of the International Classification of Headache Disorders should clarify whether individuals with post-traumatic headache can be assigned with a secondary diagnosis of medication overuse headache. If so, the term pre-existing primary headache should be changed to pre-existing headache, omitting the word primary.

cohort study,[9] about 30% of patients with mild traumatic brain injury reported persistent post-traumatic headache at 3 months and 6 months after injury. The corresponding figures were 286 (58%) of 496 patients at 3 months after injury and 219 (54%) of 406 patients at 6 months after injury in a Chinese cohort of patients with mild traumatic brain injury.[34] Moreover, in the Chinese cohort study, 164 (49%) of 332 patients continued to experience persistent post-traumatic headache at 12 months after injury.[34] Taken together, these findings underscore that persistent post-traumatic headache is a common sequela of mild traumatic brain injury. It also seems that prevalence of persistent post-traumatic headache is relatively high, at least within the first year after mild traumatic brain injury. This observation merits special emphasis and accords with a 2020 meta-analysis,[35] wherein prevalence of post-traumatic headache after whiplash injury was examined. In this meta-analysis, acute post-traumatic headache was reported by 60% of patients within 7 days of whiplash injury in non-population-based studies. This figure then became 23% at 3 months, 30% at 6 months, and 38% at 12 months after injury. The available data were, however, limited by methodological differences between studies.[35] Generally, it is difficult to compare prevalence of post-traumatic headache based on the type of injury since a wide array of case definitions and methods of assessment has been used in the literature. Furthermore, to the best of our knowledge, population-based data are only available from one Norwegian study, in which individuals aged 30–44 years were sampled to ascertain the 1-year period prevalence of secondary chronic headache disorders.[36] The 1-year period prevalence was estimated to be 0·21% after traumatic brain injury, whereas the corresponding figures were 0·17% after whiplash injury and 0·02% after craniotomy.

Headache features

Characterisation of clinical features is an important step towards better understanding of post-traumatic headache

(panel 2). However, the ICHD-3 criteria do not describe any typical clinical features of post-traumatic headache.[14] Nonetheless, much progress has been made, and clinic-based studies have begun to consistently document typical features in patients with post-traumatic headache.[4,5] Often, investigators assign a headache phenotype to patients on the basis of the primary headache disorder that their clinical features most resemble. The consensus seems to be that a migraine-like phenotype is the most typical clinical presentation, followed by a tension-type headache-like phenotype.[4,5,37] A 2020 clinic-based study reported that 91 (91%) of 100 patients with persistent post-traumatic headache and no pre-existing primary headache disorder (except infrequent episodic tension-type headache) had recurrent headache episodes with migraine-like features.[4] The remaining nine patients had a pure chronic tension-type headache-like phenotype. A key observation was that all headache days met the criteria for a migraine-like or tension-type headache-like phenotype. This finding also accords with a 28-day prospective diary study, in which 64 patients with persistent post-traumatic headache had to complete a headache diary with daily entries.[37] In that study, 56 (88%) of 64 patients with persistent post-traumatic headache had migraine-like features, whereas the remaining eight patients had a pure tension-type headache-like phenotype. Post-traumatic headache is, therefore, not necessarily a migraine that has been merely evoked by head trauma.

Typical pain features of post-traumatic headache have been documented in some clinic-based studies.[4,5] The relative frequency of each pain feature differs between studies and should be interpreted with caution. In 66 patients with acute post-traumatic headache, usual headache was reported to be bilateral in 37 (56%) and moderate-to-severe in 39 (59%).[5] The corresponding figures were 65 (65%) and 95 (95%) in another study that included 100 patients with persistent post-traumatic headache.[4] Moreover, among patients with migraine-like features (n=91), 87 (96%) reported migraine-like headache to be accompanied by photophobia and phonophobia, whereas 65 (71%) had accompanying nausea.[4] The most common self-perceived triggers of migraine-like headache were stress, poor quality of sleep, and bright lights.[4] Taken together, it can be posited that migraine and persistent post-traumatic headache with migraine-like features share similar underlying mechanisms.[1] Indeed, experimental data have shown that intravenous infusion of calcitonin gene-related peptide (human α-CGRP) induces migraine attacks in patients with migraine[38,39] and headache exacerbation with migraine-like features in patients with persistent post-traumatic headache.[40]

An important point of criticism of the available literature is that it is mainly based on data from clinic-based studies. These studies tend to include patients with post-traumatic headache who are more adversely affected by their headache and more often seek medical care compared with people with post-traumatic headache in the general population. Indeed, it should be noted that almost 50% of individuals with traumatic brain injury do not seek medical care, particularly those with a mild traumatic brain injury.[41] Therefore, it is reasonable to assume that clinic-based studies would find a higher proportion of individuals with a migraine-like phenotype, compared with estimates in the general population. Taken together, the distribution of headache phenotypes merits further investigation and should be ascertained in population-based studies. This finding does not negate that patients who need medical care will often have a migraine-like phenotype. Once the diagnosis of post-traumatic headache has been established, clinicians must always assess the clinical features to develop an appropriate treatment plan and exclude differential diagnoses. Atypical clinical presentation might call for review of the diagnosis. For example, only few reports of clinical features are suggestive of a trigeminal autonomic cephalalgia-like phenotype in patients with post-traumatic headache.[42] Such clinical presentation warrants further enquiry, although it cannot be excluded that head trauma, in rare instances, might result in post-traumatic headache with a trigeminal autonomic cephalalgia-like phenotype. In general, clinicians should encourage patients with post-traumatic headache to use diagnostic headache diaries with daily entries to support any assessment of headache features.[43] Headache diaries require little time consumption and patients can easily fill them out at home.[43] The use of electronic diaries has emerged in recent years and benefits from digital time stamps and push notifications to ensure entry of headache data in a timely manner. The acquired information is then used to better characterise an individual patient's clinical features and facilitate more informed clinical decision making. Compliance might be an issue for some patients with post-traumatic headache, although there are discordant data on the issue from two clinical trials that used headache diaries with daily entries.[37,44]

Other clinical features

Post-traumatic headache is often considered the most common sequela of mild traumatic brain injury. However, it should be emphasised that there are other mild traumatic brain injury-related sequelae, such as sleep disturbances, anxiety, depression, mild cognitive dysfunction, and vestibular symptoms (panel 2).[9,45–48] These traumatic brain injury-related sequelae, along with headache, are cardinal features of post-concussion syndrome.[18,49,50] An initial clinical assessment should, therefore, account for common sequelae of mild traumatic brain injury. Indeed, studies have reported that sleep disturbances, anxiety, and depression are common in individuals with post-traumatic headache.[27,51,52] Recognition and clinical management of these non-headache symptoms should, in turn, facilitate more informed clinical decision making. It is unclear whether psychiatric and cognitive comorbidities are independently associated with post-traumatic headache or are exclusively attributed to mild traumatic brain injury.

However, one prospective cohort study did report that patients with acute post-traumatic headache have more sequelae after mild traumatic brain injury than do patients without post-traumatic headache.[5] Further investigation is needed to ascertain the association between post-traumatic headache and other mild traumatic brain injury-related sequelae.

Another area that merits special emphasis is the occurrence of medication overuse headache in individuals with post-traumatic headache. The development of medication overuse headache is attributed to excessive use of acute medications (eg, simple analgesics, triptans, and opioids).[14,53] Two small clinic-based studies have reported that medication overuse headache is not uncommon in patients with post-traumatic headache,[54,55] and withdrawal of overused analgesics might provide therapeutic benefits in some patients.[55] In this context, it should be mentioned that patients with post-traumatic headache seemingly cannot be assigned with a secondary diagnosis of medication overuse headache according to the ICHD-3 description.[14] Medication overuse headache is defined as "headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more or 15 or more days/month, depending on the medication) for more than 3 months".[14] This description does not accord with the ICHD-3 criteria for medication overuse headache, in which the term "pre-existing headache disorder" is used instead of "pre-existing primary headache".[14] The latter interpretation ("primary headache") has been used in acclaimed reviews on medication overuse headache that have been published in recent years.[53,56] Taken together, the discrepant wording is problematic and should be addressed in future iterations of the ICHD (panel 2). For this purpose, it is essential to ascertain whether withdrawal of the overused medications is associated with less headache in people with post-traumatic headache. If so, there would be compelling evidence to change the current ICHD description for medication overuse headache.

Post-traumatic headache in specific populations

Post-traumatic headache in sports

Sporting events are a common setting in which mild traumatic brain injury can occur, and the term sport-related concussion is, therefore, often used. In a consensus statement by the Concussion in Sport Group,[20] sport-related concussion was defined broadly as "traumatic brain injury induced by biomechanical forces". This vague definition is somewhat problematic, as it differs from case definitions widely used to classify mild traumatic brain injury that is not necessarily related to sports.[18] Prevalence rates are highly sensitive to the definitions and methodology used. Hence, comparative assessments are challenging and uniformity in the methods applied are much needed. Despite these shortcomings, epidemiological investigations have been useful to quantify and better understand the widespread prevalence and associated disability of sport-related concussion.

In a self-administered questionnaire survey,[57] the Centers for Disease Control and Prevention assessed the prevalence of mild traumatic brain injury that had been sustained during sports or recreational activities in high school students based in the USA. 15% of students reported a history of at least one concussion (approximately 2·5 million students), whereas 6% reported having had two or more concussions. These figures are probably much higher considering that an estimated 50% of all sport-related concussions are not reported.[58] Much evidence suggests that many athletes intentionally under-report or hide symptoms suggestive of a sport-related concussion.[59] A meta-analysis has shown that the highest incidences of sport-related concussions were seen in contact and collision sports.[60] The highest incidences per 1000 athlete exposures were 4·18 in rugby, 1·20 in hockey, and 0·53 in American football; by contrast, the lowest estimated incidences were 0·06 in basketball and 0·03 in volleyball.[60]

Although post-traumatic headache is consistently reported to be a common complaint after sport-related concussion,[61] accurate prevalence estimates cannot be inferred. This finding is largely due to post-traumatic headache being reported as part of a composite measure that aims to ascertain the prevalence of post-concussion syndrome. As such, post-traumatic headache is rarely, if ever, defined in accordance with the ICHD-3 criteria. Nonetheless, a systematic review concluded that acute post-traumatic headache is associated with prolonged or poor recovery, or both, after sport-related concussion.[62] These findings could be important for the clinical management of sport-related concussion and merit confirmation in large prospective cohort studies that apply the ICHD-3 definition of post-traumatic headache. Taken together, clinical research into post-traumatic headache in sports is an area opportune for improvement and progress should be imminent (panel 3).

Post-traumatic headache in military personnel

Military personnel are widely considered a population at risk for traumatic brain injury due to combat-related training and activities (panel 3). About 430 720 US military service members have sustained a traumatic brain injury within the past 20 years.[63] Of these, 354 991 (82%) were listed as mild traumatic brain injury or concussion.[63] Increasing attention to sequelae of mild traumatic brain injury has provided important evidence to quantify the widespread prevalence of post-traumatic headache. Of 978 US military service members with a mild traumatic brain injury, 957 (98%) had episodes of headache within the final 3 months of deployment.[64] The same study also reported that 361 (38%) of 957 participants fulfilled the ICHD-3 criteria for acute post-traumatic headache. Of these 361 individuals, 27% had chronic daily headache,[64] which might explain, to some degree, reported low rates

of return to duty among military service members with post-traumatic headache.[65]

From a clinical standpoint, it is important to recognise the considerable disability associated with post-traumatic headache. In a 2020 study, post-traumatic headaches were more frequent and severe than were non-traumatic headaches in military service members who had recently returned from deployment and were undergoing routine post-deployment health assessments.[66] The authors also reported that 17 (9%) of 198 participants with post-traumatic headache had continuous headache, defined as daily headache that was unremitting. Higher figures of continuous headache have been reported in clinic-based studies of military personnel with post-traumatic headache.[65,67] This observation should be explored further, and in civilian populations. It seems reasonable to assume that patients with post-traumatic headache, who report continuous headache, are more difficult to treat and likely to need referral to specialist care. In general, clinical management of post-traumatic headache in military service members requires special attention. Headache features will most often resemble a migraine-like phenotype,[10] but any treatment plan should also account for known and possible unknown comorbidities. These comorbidities are prevalent in military service members and include sleep disturbances, vestibular symptoms, post-traumatic stress disorder, and non-cephalic pain or injuries.[68] Clinicians should note that not all comorbidities are necessarily attributed to post-traumatic headache or a consequence of traumatic brain injury. A review of medical history and screening for common comorbidities should, therefore, be part of the initial clinical assessment. Additionally, clinicians should make note of the cause of injury in military service members. It is possible that the natural course and clinical features of blast-related traumatic brain injuries differ from other causes of traumatic brain injury, with the other causes of traumatic brain injury probably being more comparable with those reported in civilians.

Clinical management

Management of post-traumatic headache depends on the severity of the disorder and its evolution over time (panel 4). Individuals with few monthly headache days of mild-to-moderate pain intensity can probably manage with simple analgesics obtained over the counter (eg, non-steroidal anti-inflammatory drugs and paracetamol). If self-medication is ineffective or headache episodes become increasingly frequent, clinical management is mainly by primary care providers, through whom preventive therapy can be initiated. A point that merits emphasis is the need for agreed realistic objectives. Any therapeutic approach aims to effectively manage post-traumatic headache and is not to be considered a cure. Patient education is key and necessary to achieve treatment adherence. Referral to specialist care should be considered if the patient is difficult to treat or if clinical management is complicated by comorbidities.

***Panel 3*: Key messages on post-traumatic headache in specific populations**

Post-traumatic headache in sports

- International consensus is needed on definitions of sports-related concussion and mild traumatic brain injury to avoid discordant findings related to post-traumatic headache due to methodological differences.
- Adherence to the International Classification of Headache Disorders-3 criteria is needed to provide robust data on the prevalence of post-traumatic headache following sports-related concussion.
- Future studies should investigate whether quick return to play is associated with persistence of post-traumatic headache at 3 months after trauma.

Post-traumatic headache in military personnel

- Mild traumatic brain injury and subsequent onset of post-traumatic headache is a public health challenge of vast proportions in military service members.
- Research is needed to uncover the natural course of post-traumatic headache among individuals who develop continuous and unremitting daily headache.
- Best clinical practices should be identified for military service members with post-traumatic headaches.

***Panel 4*: Key messages on clinical management**

- Randomised controlled trials are needed to establish evidence-based acute and preventive therapies for post-traumatic headache. For this purpose, guidelines for controlled trials should be developed to establish post-traumatic headache-specific outcomes and eligibility criteria.
- Headache diaries with daily entries are the best instrument to assess the effectiveness of candidate therapies for post-traumatic headache.
- In the absence of robust evidence from controlled trials, we propose a phenotype-guided treatment algorithm on the basis of expert opinion and available data from controlled trials in patients with migraine and tension-type headache.
- Medications to avoid include oral ergot alkaloids, opioids, and barbiturates.

As with other headache disorders, pharmacological agents are regarded as the mainstay of clinical management. These agents are divided into acute and preventive medications, which are currently used as off-label options for post-traumatic headache. The use of these medications as off-label treatments is due to the scarcity of literature on evidence-based therapies for post-traumatic headache and few available randomised controlled trials.[11,69–71] Choice of acute and preventive treatment is, therefore, usually based on individual patient-level headache features. If the

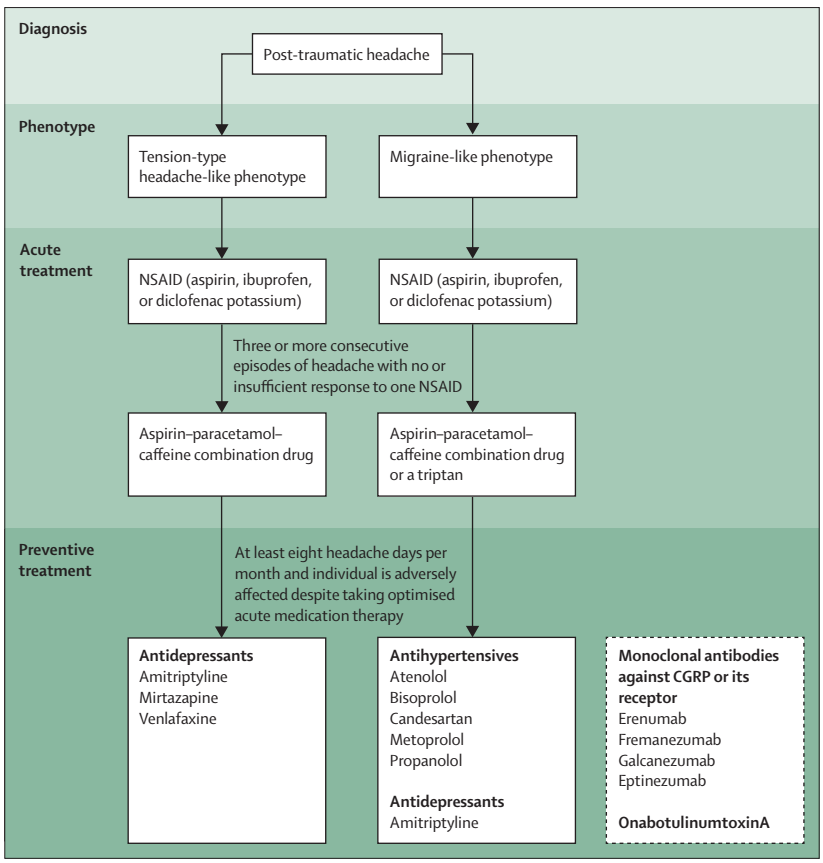

Figure: **Proposed algorithm for pharmacological treatment of post-traumatic headache attributed to traumatic brain injury**

Management of post-traumatic headache is largely based on expert opinion due to the scarcity of data from controlled trials. A phenotype-guided approach is typically applied in clinical practice and patients are most often stratified into a migraine-like or tension-type headache-like phenotype. A stepped-care treatment approach is recommended, and therapy should commence with the least resource-intensive treatment and work upwards in case of no or inadequate pain relief after treatment of three consecutive episodes of headache, or intolerance due to adverse events. For individuals with a tension-type headache-like phenotype, clinicians should initiate preventive treatment with amitriptyline. If ineffective or poorly tolerated, second-line preventive treatment options include mirtazapine and venlafaxine. For individuals with a migraine-like phenotype, clinicians are encouraged to initiate preventive treatment with β blockers, candesartan, and amitriptyline because these treatments are less expensive and widely available, compared with onabotulinumtoxinA and monoclonal antibodies against CGRP or its receptor. Recommended doses have been published elsewhere.[43] CGRP=calcitonin gene-related peptide. NSAID=non-steroidal anti-inflammatory drug.

post-traumatic headache mostly resembles a migraine-like phenotype, clinicians tend to recommend medications used for migraine, whereas a tension-type headache-like phenotype would be treated with medications used for tension-type headache. Clinic-based data have reported that frequently used acute medications for post-traumatic headache include simple analgesics and triptans.[4] The same study showed the most used preventive medications were antihypertensives (eg, propranolol and candesartan), antidepressants (eg, amitriptyline), and anticonvulsants (eg, topiramate and sodium valproate).[4] Notably, these are all considered evidence-based preventive medications for migraine.[72] A 12-week, open-label trial from 2020 has also reported evidence that erenumab, a monoclonal antibody targeting CGRP, might have therapeutic benefits for patients with post-traumatic headache.[73] A reduction of 50% or more in monthly headache days of moderate-to-severe intensity was observed in 25 (28%) of 89 participants by weeks 9–12.[73] Two randomised placebo-controlled trials (NCT04098250 and NCT03347188) are currently underway, in which the effectiveness of CGRP-targeted therapies in post-traumatic headache will be ascertained. On another note, it is unclear whether patients with post-traumatic headache might benefit from non-pharmacological treatment options, such as biobehavioural therapies, physical therapy, acupuncture, and neuromodulation devices. A multidisciplinary approach to clinical management should be explored, given that patients with post-traumatic headache often have symptoms suggestive of sleep disturbances, anxiety, and depression, as well as chronic neck pain.[4,27,51,52]

Proposed pharmacological treatment algorithm

Considering the scarcity of evidence from available controlled trials, it is reasonable to use a primary headache phenotype-guided approach to clinical management of post-traumatic headache (panel 4). Compelling evidence has underscored the shared biological foundations of post-traumatic headache with migraine and tension-type headache.[1] Intravenous infusion of the signalling molecule CGRP evokes migraine attacks in patients with migraine[38,39] and headache exacerbation with migraine-like features in patients with post-traumatic headache.[40] Future studies should ascertain whether a phenotype-guided approach holds merit, to avoid reliance on expert opinion exclusively. Until then, we propose use of a treatment strategy (figure) based on clinical experience and documented effectiveness of pharmacological agents from controlled trials in patients with migraine or tension-type headache, or both.[43,72,74,75] An important caveat that should be noted is the demographic differences (eg, age and sex) between patients with post-traumatic headache and patients with migraine or tension-type headache, particularly so for military populations with post-traumatic headache. We suggest that non-steroidal anti-inflammatory drugs are used as first-line acute medications and offered to all patients with post-traumatic headache. If contraindicated, paracetamol could be used as a substitute. Headaches that are accompanied by nausea can be treated with antiemetics (eg, metoclopramide and domperidone) as adjuncts. Treatment failure is defined as no or inadequate pain relief after treatment of three consecutive episodes of headache or intolerance due to adverse events. Second-line acute medications should be the analgesic combination of aspirin, paracetamol, and caffeine. In patients with a migraine-like phenotype, oral triptans (eg, sumatriptan, rizatriptan, and eletriptan) can also be offered after failure of a non-steroidal anti-inflammatory drug. If nausea precludes oral intake or the headache peaks rapidly, it might be helpful to administer sumatriptan by subcutaneous injection. Other options for headache that peaks rapidly are intranasal formulations of triptans (ie, sumatriptan

and zolmitriptan). Further research is needed to ascertain whether 5-HT_{1F} agonists (ditans) and small-molecule CGRP receptor antagonists (gepants) hold promise in the acute treatment of post-traumatic headache.

It is uncertain whether the ICHD-3 allows a secondary diagnosis of medication overuse headache to be assigned to patients with post-traumatic headache.[14] Nonetheless, clinical evaluation of acute medication use should always involve an assessment of the number of days with drug intake. Clinicians should address regular overuse of acute medications with withdrawal therapy combined with initiation of preventive treatment.[43,53] Moreover, some acute medications must be avoided altogether due to substantial adverse effects. These include oral ergot alkaloids, opioids, and barbiturates.[43,72]

The addition of preventive treatment is often needed in patients with post-traumatic headache. When to initiate this treatment is unclear, considering that there is no established headache frequency threshold. Therefore, this decision should be made on a case-by-case basis and in adherence with local practice guidelines. As a general principle, we recommend initiation of preventive treatment in patients who, despite optimised acute medication therapy, continue to be adversely affected by post-traumatic headaches and report at least eight monthly headache days. The figure sets out recommended preventive medications that should be considered on the basis of a primary headache phenotype-guided approach—ie, migraine-like and tension-type headache-like phenotype. Again, it should be emphasised that this approach is based entirely on expert opinion due to the scarcity of scientific evidence. In patients with a migraine-like phenotype, broader use of onabotulinumtoxinA and monoclonal antibodies against CGRP or its receptor is likely to be limited due to restricted availability and high costs. Choice of preventive therapy must be made on an individual basis and account for comorbid conditions. For example, added benefits might be provided by use of amitriptyline in patients with post-traumatic headache who have comorbid depression or insomnia. Moreover, the proposed treatment algorithm does not recommend use of anticonvulsants with evidence-based effectiveness in migraine prevention (ie, topiramate and sodium valproate) because of their tolerability profile. Common drug-related adverse reactions to topiramate and sodium valproate include cognitive difficulties, which are a priori, a common complaint in patients with traumatic brain injury, including those with mild traumatic brain injury.[46]

The general purpose of preventive therapy is to reduce the frequency, duration, or pain intensity of headaches, thereby mitigating the attributable burden of post-traumatic headache. Another possible benefit of preventive therapy might be prevention of persistent post-traumatic headache. Chronification and persistence of headache is often attributed to central sensitisation of neurons within the brainstem and thalamus.[76,77] Development of chronic migraine usually takes years, whereas patients with post-traumatic headache often develop chronic daily headache rapidly, sometimes within weeks or months. It could be speculated that early initiation of preventive therapy in patients who present within 4–6 weeks of the traumatic brain injury might prevent central sensitisation and thereby chronification and persistence of headache. Controlled trials should be implemented to assess this hypothesis and determine whether early initiation of preventive therapy prevents the development of persistent post-traumatic headache.

Search strategy and selection criteria

We searched MEDLINE (from database inception to March 15, 2020) using the search terms "headache", "traumatic brain injury", "concussion", "post-traumatic headache", "posttraumatic headache", and "head injury". We largely selected publications from the past 5–10 years, with no language restrictions, but we did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters were cited to provide readers with more details and more references than this article has room for. Whenever possible, we emphasised citing systematic reviews, evidence-based guidelines, and meta-analyses, followed by cohort studies and cross-sectional studies.

Conclusions

A shared interest among patient advocates, clinicians, and researchers has spurred much progress in the field of post-traumatic headache within the past 10 years. These efforts have led to a better understanding of common clinical features and comorbidities that characterise the disorder. However, essential questions remain to be answered regarding the natural course of post-traumatic headache, and any revision of the diagnostic criteria should be preceded by rigorous field testing of any proposed changes. Moreover, controlled trials are key to identify evidence-based therapies for the acute and preventive treatment of post-traumatic headache. Such efforts should also ascertain whether phenotype-guided approaches that are widely used in clinical practice hold merit and are associated with better responsiveness to therapy. Taken together, future advances should restrict reliance on expert opinion to instances in which scientific evidence is unavailable or scarce. This approach would, in turn, facilitate more informed clinical decision making and address unmet needs.

Contributors

HA and MA contributed to the conception and design of this Review. All authors contributed to the drafting and critical revision of this Review and approved the final version.

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on an advisory board for Allergan, currently receives research support from Eli Lilly, and is an associate editor for *Cephalalgia* and *Pain Medicine*. HWS has received speaking fees from Novartis and Teva. MJL reports grants and personal fees from Eli Lilly, personal fees from Sanofi-Aventis and YuYu Pharma, and grants from Novartis, Teva, Allergan, and Yuhan, outside of the submitted work. MA is a consultant, speaker, or scientific adviser for AbbVie, Allergan, Amgen, Alder, Biohaven, Eli Lilly, Lundbeck, Novartis, and Teva; primary investigator for Alder, Amgen, Allergan, Eli Lilly, Lundbeck, Novartis, and Teva trials; has no ownership interest and does not own stocks of any pharmaceutical company; serves as an associate editor of *Cephalalgia*, and associate editor of the *Journal of Headache and Pain*; and is president of the International Headache Society. All other authors declare no competing interests.

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