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Post-traumatic Headache: Pharmacologic Management and Targeting CGRP Signaling

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Abstract

Purpose of Review Post-traumatic headache is a common sequela of injury to the head and/or neck. Here, we review the current approach to pharmacologic management of post-traumatic headache and explore the therapeutic promise of targeting calcitonin gene–related peptide signaling to address unmet treatment needs.

Recent Findings The scarcity of data from controlled trials has left clinicians to rely on mainly expert opinion for the pharmacologic management of post-traumatic headache. The current view is that a phenotype-guided approach should be used, in which patients are treated according to the primary headache phenotype that their clinical features resemble the most (e.g. migraine, tension-type headache). Moreover, incremental advances are being made in the field that aim to identify possible cellular and molecular drivers of headache persistence. Calcitonin gene–related peptide has emerged as a key drug target which, in turn, has prompted novel insights on the potential importance of early initiation of pharmacologic treatment following the onset of post-traumatic headache. This, in turn, might prevent subsequent persistence and chronification of headache.

Keywords Treatment · Traumatic brain injury · Concussion · Secondary headache disorders

Introduction

Post-traumatic headache (PTH) is a disabling neurologic disorder that afflicts millions of people worldwide and can be attributed to either traumatic brain injury (TBI), whiplash injury, or craniotomy [1]. The diagnosis is based on largely clinical criteria outlined by the International Classification of Headache Disorders, 3rd edition (ICHD-3) [2]. Herein, PTH is characterized by 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. Headache of less than 3 months' duration is classified as acute PTH, whereas headache of more than 3 months' duration is classified as persistent PTH.

From a clinical standpoint, most patients who present with PTH complain of recurrent, if not daily, episodes of headache with features that resemble migraine and less often tension-type headache (TTH) [1, 3–9]. This merits emphasis because no medications have been approved for the treatment of PTH and current therapeutic approaches are therefore conceptually drawn from drug-based treatments demonstrated to be effective for migraine and TTH [1, 9]. The rationale is that tailoring therapeutics to specific headache phenotypes might provide more effective disease management although randomized clinical trials (RCTs) are needed to ascertain the value of a phenotype-guided approach [1]. Recent efforts have rather focused on possible cellular and molecular drivers of headache persistence and thereby identify drug targets that might prevent the persistence and chronification of cephalic pain [10, 11].

In this review, we outline the evidence for drug-based treatments of PTH. This is followed by a summary of treatment recommendations based on a headache phenotype-guided approach to disease management. We conclude with a glimpse at what the future holds in terms of addressing unmet needs with therapies targeting signaling molecule calcitonin gene-related peptide (CGRP) or its receptor.

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Pharmacotherapy

Management of PTH is mostly based on expert consensus rather than evidence from RCTs [1]. A 2019 systematic review concluded that there is minimal evidence to provide guidance on the pharmacologic treatment of acute and persistent PTH [12•]. Nonetheless, informed clinical decision-making should still comprise the right medication(s) at the lowest cost to the affected individual and society. Clinicians should also recognize that PTH is often difficult to treat [1], even when correctly diagnosed and appropriately managed. The failure of pharmacotherapies might, in part, be related to the heterogeneous nature of PTH in terms of frequency, duration, pain intensity, and evolution over time [1]. In addition, the presence of comorbid disorders tends to complicate effective disease management [1, 13]. A recent observational study found that symptoms suggestive of sleep disturbances, anxiety, depression, and mild cognitive impairment were frequently reported by patients with PTH [14]. Clinicians must therefore remember to screen for common comorbidities and tailor their treatment strategy according to the needs of the affected individual.

Pharmacologic treatment of PTH can be divided into two parts: the use of acute medications to provide pain relief for individual episodes with headache and the use of preventive medications to reduce the frequency, duration, or severity of headache [1]. Treatment will most often commence with simple analgesics that can be obtained over the counter, e.g., paracetamol/acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs). Some people with PTH can probably self-manage with these simple analgesics and are therefore unlikely to seek medical care. Others might experience headaches that become increasingly frequent or non-responsive to self-medication. Disease management should then be initiated and maintained by primary care practitioners. Referral to specialist care should be restricted to those who do not respond to initial treatment attempts, experience near-daily or daily headache, or present with comorbid disorders.

In practice, the current view is to apply a phenotype-guided strategy to pharmacologic management of PTH, as presented in Fig. 1 [1]. This approach entails that clinicians assign patients with a headache phenotype, most often a migraine-like or TTH-like phenotype [3–9]. All patients are then offered an oral NSAID with evidence-based effectiveness for the acute treatment of migraine and TTH, i.e., acetylsalicylic acid, diclofenac potassium, and ibuprofen [15–22]. If NSAIDs are poorly tolerated or contraindicated, paracetamol can be used as a substitute [23, 24]. Second-line treatment includes the analgesic combination of acetylsalicylic acid, paracetamol, and caffeine while those with a migraine-like phenotype might also benefit from a triptan or gepant [22, 25–30]. In addition, clinical experience suggests that antiemetics are a useful adjunct whenever headaches are accompanied by nausea [30], while intranasal or subcutaneous formulations of sumatriptan are helpful in those with headaches that peak rapidly [26]. An important advice for clinicians is also to recognize that at least three consecutive episodes of headache must be treated before the therapeutic response to a specific acute medication can be adequately assessed.

Considering the recurrent—and at times chronic—nature of PTH, effective disease management will often include preventive treatment. It is, however, difficult to give definitive guidance on when to initiate preventive treatment although there are a few rules to guide clinicians [1]. First, preventive treatment is usually needed when optimized acute medication therapy provides inadequate pain relief. Second, clinicians should consider initiation of preventive treatment when patients complain of headache on at least 8 days per month and are adversely affected. Lastly, preventive treatment is often necessary when patients report frequent use of acute medications and are at risk of developing medication overuse headache (MOH). In addition to initiation of preventive treatment, clinicians should encourage patients with MOH to discontinue the overused acute medication and switch to an alternative medication with limits (< 2 days per week) [31]. It should be mentioned that preclinical and clinical data suggest that the use of gepants, CGRP receptor antagonists, is not associated with the risk of developing MOH. A recent animal study reported that repeated administration of ubrogepant did not result in cutaneous allodynia or latent sensitization [32], both of which are surrogate markers of MOH in rodents [33]. Clinical data have also found that use of rimegepant every other day and atogepant every day over a 3-month period is effective for migraine prevention [34, 35]. However, restricted availability and high costs are likely to limit the broader use of ubrogepant and rimegepant in clinical practice.

Recommended preventive medications include amitriptyline, mirtazapine, and venlafaxine for patients with a TTH-like phenotype, while amitriptyline, candesartan, and certain beta blockers (e.g., propranolol, metoprolol) can be considered for those with a migraine-like phenotype [21, 22, 27, 30]. In addition, patients with a migraine-like phenotype might benefit from treatment with onabotulinumtoxinA and medications that target CGRP signaling, e.g., rimegepant, atogepant, and monoclonal antibodies (mAbs) against CGRP or its receptor (i.e., eptinezumab, erenumab, fremanezumab, and galcanezumab) [1, 27, 30]. In choosing the preventive medication, clinicians should consider side effect profiles and remember to account for the presence of comorbid disorders. Another important aspect is to inform patients that potential therapeutic effects are typically apparent after at least 2 months of treatment

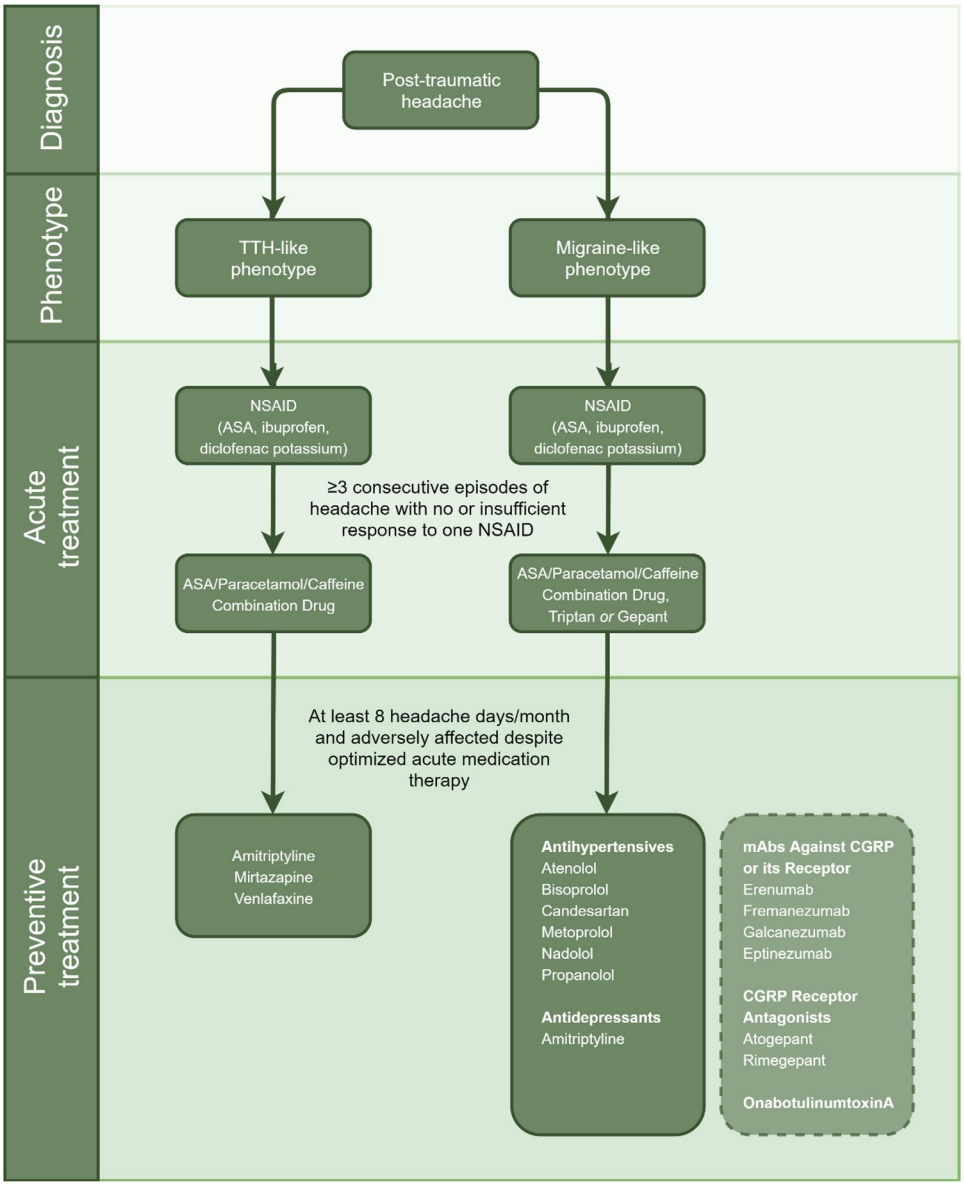

Fig. 1 Proposed algorithm for pharmacologic treatment of post-traumatic headache. Modified from Ashina et al., 2021, Lancet Neurol [1]. Recommended doses have been published elsewhere [1]

[30]. This might, in turn, provide the needed reassurances to reduce nonadherence and unnecessary treatment discontinuation. Active follow-up is also a key aspect to facilitate effective disease management and treatment adherence. In this context, clinicians should encourage patients to record their headache days and use of acute medications in a headache calendar. This will provide valuable information that can be used to evaluate the treatment response by review of therapeutic effectiveness, adverse events, and adherence. Further research is needed to identify strategies and methods for increasing adherence and treatment satisfaction.

Targeting CGRP Signaling

The trigeminovascular system is the anatomical and physiological substrate underlying the genesis of cephalic pain [21, 36–38]. Within this framework, nociceptive information is projected from first-order neurons in the

trigeminal ganglion to second-order neurons in the brain stem, before reaching third-order thalamic neurons [10, 21]. From the thalamus, nociceptive transmission is then conveyed to various areas of the cerebral cortex, including the somatosensory cortex [10, 21]. These processes are ultimately responsible for the perception of cephalic pain. It is, however, less clear by what mechanisms nociceptive impulses are initially evoked [10, 21]. Nonetheless, compelling evidence have implicated the release of various signaling molecules from primary afferents of neurons in the trigeminal ganglion that innervate pain-sensitive intracranial structures, including the dura mater and its blood vessels [10, 39, 40]. These signaling molecules include CGRP which, upon release from primary afferents, promotes vasodilation and modulates nociceptive transmission [10, 39, 41]. The binding of CGRP to its G protein-coupled receptor on vascular smooth muscle cells elevates intracellular levels of the second messenger cyclic adenosine monophosphate (cAMP), [36, 42]. This results in the opening of potassium channels that cause hyperpolarization of the vascular smooth muscle cell and thereby vasodilation [43–45]. The outflow of positively charged potassium and dilation of intracranial arteries is then hypothesized to activate and sensitize the perivascular nociceptors which, in turn, is responsible for the initial transmission of nociceptive impulses to the cerebral cortex, as described above [21].

The involvement of CGRP in PTH has been confirmed by several lines of evidence. First, CGRP has been implicated in the modulation of nociceptive transmission in rodent models of concussion [46, 47••, 48–50]. Second, there is robust evidence from a randomized, double-blind, placebo-controlled, two-way crossover study that intravenous infusion of CGRP induces headache with migraine-like features in patients with persistent PTH who reported no history of pre-existing migraine [51••]. The same study also found that headache intensity scores were significantly higher following CGRP infusion compared with placebo. Third, open-label trial data suggest that patients with persistent PTH might benefit from preventive treatment with a mAb against the CGRP receptor, erenumab [52••]. The authors reported that the mean number of headache days of moderate-to-severe intensity was 15.7 days at baseline; by week 9 through 12, the number was reduced by 2.8 days. Lastly, one small RCT found that preventive treatment with botulinum toxin type A was superior to placebo in patients with persistent PTH [53•]. The latter finding is interesting because preclinical studies have found that botulinum toxin type A can inhibit the release of CGRP from primary afferents [54]. Taken together, it seems plausible that therapies targeting CGRP signaling might, in part, address unmet treatment needs of people afflicted by persistent PTH. However, cautious enthusiasm is encouraged since fremanezumab (mAB against CGRP) did not prove superior to placebo for prevention of PTH in a recently published RCT [55]. The RCT was, nonetheless, underpowered and did not meet the pre-defined target enrollment. Further studies are therefore needed to ascertain the benefits of therapies targeting CGRP signaling.

An important consideration for the management of PTH is whether early treatment initiation can prevent the persistence and chronification of PTH [10]. The neurobiological rationale is that recurrent or continuous transmission of nociceptive information from primary afferents facilitates central sensitization of second- and third-order neurons [10, 56]. As soon as central sensitization (surrogate marker of headache chronification) is established, its maintained only partly by peripheral nociceptive input [56]. At this stage, it becomes difficult to treat the cephalic pain with medications whose site of action is predominantly outside of the central nervous system. This line of reasoning suggests that the highest therapeutic benefit is achieved when appropriate treatment is initiated before central sensitization (i.e., headache chronification) has been established. Early initiation of treatment with therapies targeting CGRP signaling might therefore reduce the transmission of nociceptive information to the central nervous system and prevent the persistence and chronification of cephalic pain. Indeed, animal data support the notion that early and continuous targeting of CGRP signaling prevents the development of immediate and delayed cephalic and extracephalic allodynia (suggestive of central sensitization) in concussed rodents [47••].

Conclusions

Advances in the pharmacologic management of PTH are long overdue. The scarcity of data from controlled trials limit clinicians to use a phenotype-guided approach based on expert opinion, in which PTH is treated according to the primary headache phenotype that its clinical features resemble the most. New therapeutics are therefore urgently needed and should target signaling pathways related to the persistence and chronification of PTH. Given the role of CGRP in the genesis of cephalic pain, it seems plausible that therapies targeting CGRP signaling hold promise for the future.

Declarations

Conflict of Interest David W. Dodick reports the following conflicts within the past 12 months: consulting: Amgen, Atria, Cerecin, Cooltech, Ctrl M, Allergan, Biohaven, GSK, Lundbeck, Eli Lilly, Novartis, Impel, Satsuma, Theranica, WL Gore, Nocira, Perfood, Praxis, AYYA Biosciences, Revance. Honoraria: Vector psychometric Group, Clinical Care Solutions, CME Outfitters, Curry Rockefeller Group, DeepBench, Global Access Meetings, KLJ Associates, Academy for Continued Healthcare Learning, Majallin LLC, Medlogix

Communications, MJH Lifesciences, Miller Medical Communications, WebMD Health/Medscape, Wolters Kluwer, Oxford University Press, Cambridge University Press. Research Support: Department of Defense, National Institutes of Health, Henry Jackson Foundation, Sperling Foundation, American Migraine Foundation, Patient Centered Outcomes Research Institute (PCORI). Stock Options/Shareholder/Patents/Board of Directors: Ctrl M (options), Aural analytics (options), ExSano (options), Palion (options), Healint (Options), Theranica (Options), Second Opinion/Mobile Health (Options), Epien (Options/Board), Nocira (options), Matterhorn (Shares/Board), Ontologics (Shares/Board), King-Devick Technologies (Options/Board), Precon Health (Options/Board), AYYA Biosciences (Options). Patent 17189376.1–1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis. Håkan Ashina reports no potential conflicts of interest.

Consent for Publication All authors have read the final version of the manuscript and approve its content for publication.

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• Of importance
•• Of major importance

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