Emerging Novel Pharmacological Non-opioid Therapies in Headache Management: a Comprehensive Review

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Abstract

Purpose of Review Chronic headache is a significant worldwide problem despite advances in treatment options. Chronic headaches can have significant a detrimental impact on the activities of daily living.

Recent Findings Patients who do not obtain relief from chronic head and neck pain from conservative treatments are commonly being managed with interventional treatments. These interventional treatment options include botulinum toxin A, injections, local occipital nerve anesthetic and corticosteroid infiltration, occipital nerve subcutaneous stimulation and occipital nerve pulsed radiofrequency (PRF), sphenopalatine ganglion block, and radiofrequency techniques.

Summary Recently, evidence has emerged to support non-opioid-based drug and interventional approaches. Overall, more research is necessary to clarify the safety and efficacy of interventional treatments and to better understand the pathogenesis of chronic headache pain.

Keywords Non-opioid · Headache · Botox · Multimodal analgesia

Introduction

Headaches encompass a broad range of pain symptoms in the head and neck region. Migraine headaches, trigeminal autonomic cephalgias, tension headaches, postdural puncture headache, spontaneous intracranial hypotension, cervicogenic headache, occipital neuralgia, and cervical myofascial pain are all examples of headaches and headache-associated pain. Until recently, pain management has been largely addressed with opioids. Yet considering the worldwide opioid crisis, new models of pain management are being applied to pain disorders, including in the management of acute and chronic

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headache. Conservative treatment of headaches often involves lifestyle modification and antiinflammatory or baseline analgesics such as ibuprofen and acetaminophen. However, patients with chronic headache conditions or headache-associated pain may not obtain relief with these treatments.

Multimodal anesthesia is a technique that is becoming more common among physicians. It involves the use of two or more mediations from different classes to achieve pain relief and is now being used to treat headaches. Some commonly used agents include acetaminophen, non-steroidal antiinflammatory drugs (NSAIDs), magnesium, ketamine, dexmedetomidine, liposomal bupivacaine, and new neuraxial and peripheral regional techniques, as well as patient-controlled modalities. Novel interventional techniques are also being developed and refined to treat headaches. For example, injection of botulinum toxin is an interventional treatment that has been shown to decrease the frequency of headaches in patients with chronic headache disorders. Likewise, suboccipital steroid injections have been demonstrated as a successful cluster headache treatment option. Trigeminal autonomic cephalgias are a particularly difficult headache type to treat; however, occipital nerve stimulation (ONS) has been well described as a beneficial treatment option. More interventional pain procedures include radiofrequency lesioning, sphenopalatine ganglion block, and other methods of neurolysis. These procedures are continually evolving to become safer, more precise, and more readily available for clinicians to provide to their patients [1]. Additionally, acupuncture and transcutaneous electrical nerve stimulation can be used as adjuncts in MMA packages. Future treatments may include genetic testing, herbal remedies, and an extended role of acute pain services by health care providers. Unfortunately, there are gaps in evidence-based recommendations for these types of treatments and more research is necessary to determine best practice guidelines [2]. This investigation, therefore, reviews various categories of headaches, their pathophysiology, types of treatment currently available, and new models and methods of pain relief considering acute and chronic headache pain.

Headache Pathophysiology

The interpretation of pain comprises a complex sequence of pathways ranging from tactile peripheral nociceptive nerve receptors to neurochemical reactions within the central nervous system. "Headache" is the umbrella term for pain localized to one's head or neck and has etiologies ranging from simple contusions or lacerations to vasoactive peptide imbalances of the central nervous system [3]. With the continued advancements in neuroimaging and neurochemical monitoring, the pathophysiology for the development of various types of headaches has become better illuminated which has in turn aided in the development of more targeted and successful treatments.

Migraine Headaches

Migraine headaches are the most common form of headache affecting an estimated 10% of the global population [4]. Given the prevalence and morbidity associated, migraine neurophysiological processes have been the focus of decades of research. It is hypothesized that there are three phases the to a migraine headache: the premonitory phase, the asura, and the headache itself. The premonitory phase is reported to occur as many as 12 h to 3 days prior to the onset of the headache itself [4]. Both the symptoms (fatigue, mood changes, and food cravings) and neuroimaging of cerebral blood flow suggest the hypothalamus and limbic system play pivotal roles in this stage of the headache [4]. The aura phase which directly precedes the headache itself is where patients will frequently describe transient most commonly visual but sometimes sensory or motor disturbances. While these events are unique and hallmarks of the disease, they only occur in roughly one-third of patients [4]. First described in 1944, the aura stage of the headache involves the initiation and propagation of cortical spreading depression (CSD) [4]. Several hypotheses exist as to the exact mechanism of CSD, but what is understood is that there is a repeated wave of cellular depolarization resulting in the accumulation of potassium and glutamate in the extracellular matrix while sodium and calcium are brought intracellularly [4]. This disruption of neurochemical homeostasis is believed to result in the irritation of the trigeminovascular nociceptive pathway which in turn results in the throbbing headache patients frequently describe [4]. Genetic testing of patients with inherited forms of migraine headaches has implicated various other largely vasoactive peptides and molecules such as endothelin-1, calcitonin gene-related peptide (CGRP) as additional triggers [3, 4]. While the exact pathophysiology remains elusive, it is widely believed that this complex process is likely multifactorial [3].

Trigeminal Autonomic Cephalgias

Trigeminal autonomic cephalgias (TACs) are a group of headache disorders that are best categorized by their often severe and debilitating headache symptoms with craniofacial autonomic involvement. Although there remains substantial ambiguity regarding the exact pathophysiology of these debilitating diseases, there is increasing evidence localizing the abnormalities to the trigeminovascular, cranial autonomic, and/or hypothalamic systems [5]. There are currently five subtypes of TACs: cluster headaches, paroxysmal hemicranias, SUNCT, SUNA, and cervicogenic headaches. However, given the extensive similarities in symptoms, it's believed that they likely share many physiologic mechanisms.

Patients suffering from TACs will most commonly describe an intense unilateral headache with features such as tearing, rhinorrhea, and unilateral conjunctival injection indicative of autonomic involvement. Cluster headaches are the most common form of TACs and are unique in that they have a slight male predominance (3:1) and classically a clocklike, temporal aspect to the onset of their symptoms [5]. Knowing the hypothalamus and more specifically the suprachiasmatic nucleus is responsible for the circadian system, it has been postulated that these regions of the brain play a substantial role in the development of cluster headaches [6]. Multiple studies using magnetic resonance imaging, voxel-based morphometry, and positron emission tomography have demonstrated significant increases in both neuronal activation as well as the overall size of the anterior hypothalamus in patients with cluster headaches when compared to both control populations as well as those suffering from chronic migraine headaches [5, 6]. The recent study published by Arkink et al. illustrates that this trend may not be unique to cluster headaches but also to other TACs as well; however, their study lacked the power to make any significant statements in this regard [6].

Paroxysmal hemicranias will cause similar symptomatology as cluster headaches but classically have shorter durations and lack any sort of temporal regularity. Their most defining feature is their near complete resolution with the use of scheduled Indomethacin treatment. Indomethacin is a unique cyclooxygenase inhibitor in that it quickly crosses the blood–brain barrier, reduces intracranial pressure, and has direct effects of the hypothalamic, autonomic nuclei, and nitric oxide concentrations [5]. It's through knowing the pharmacology of this impressively effective treatment that many continue to postulate the exact mechanism of the headaches themselves.

SUNCT and SUNA headaches will once again present similar to the other TACs previously described. They have identical diagnostic criteria except that SUNCT headaches will display lacrimation and conjunctival injection while SUNA headaches will only have one or none of those features [5]. Their physiologic development is thought to be likely similar to the other TACs given the extensive overlap of symptoms. However, SUNCT and SUNA headaches both seem to be much more susceptible to tactile triggering mechanisms (chewing, or brushing one's teeth) when compared to the other TACs which provides a potential unique mechanism for their development [5].

The relationship between low intracranial pressure and headaches has been well described. The classic clinical presentation for a low-pressure headache is an orthostatic headache made worse in the erect position or during Valsalva maneuvers and better in the supine position [7]. There are many risk factors for the development of a low-pressure headache with the core mechanism nearly always traced to a defect in the spinal dura such that there is no longer a barrier preventing the extravasation of CSF fluid outside of the CNS. Direct

trauma to the dura such as postspinal or epidural anesthetic, spinal trauma, spinal surgeries, or degenerative disk disease places patients at risk for development of low-pressure headaches. Likewise, patients with hypermobility disorders such as Ehlers-Danlos or Marfan's syndrome with inappropriate compliance of the dura are at increased risk for the development of dural defects and these headaches [7]. If the defect is large enough such that the extravasation of CSF is faster than the formation of new CSF, the entire CNS falls out of equilibrium. Traction eventually develops on the upper cervical and cranial meninges, ligaments, and veins which in turn is interpreted as pain originating from the head itself rather than the true spinal defect [7]. MRI imaging consistent with decreased CSF volume and pressures such as cerebellar tonsillar descent, collapse of the ventricles, flattening of the anterior pons, and distention of the venous sinuses is typical, but nearly 25% of cases are reported to have normal neuroimaging [7].

The most common symptom of patient's suffering from high CSF pressure is also a headache, reported to be present in 80–90% of patients at the time of diagnosis [7]. In contrast to low-pressure headaches, these headaches will characteristically wake patients from their sleep, worsen in the supine position or at high altitudes. Visual disturbances and pulse-synchronous tinnitus are hallmarks of the disease and ought to act as red flags alerting the practitioner to investigate further. There are numerous causes for these headaches, but they all involve either increased CSF production or decreased CSF drainage creating a net increase in CSF and CSF pressure. Over time, this pressure will lead to papilledema and damage to the optic nerves as wall as pressure on the abducens nerve leading to abducens palsy [7].

Current Headache Treatments Options

Migraines

Many different treatment options are used by physicians for patients that suffer from chronic daily headaches. The type of headache the patient endures dictates which treatment type would be best for the patient. Most evidence suggest that patients suffering from mild to moderate migraine headaches can benefit with the use of NSAIDs, acetaminophen, or triptans, with dual therapy with either NSAID and triptan, or acetaminophen and triptan being superior to monotherapy alone. Data suggest that NSAIDs are superior to acetaminophen but are limited by their adverse profile [8]. The choice of NSAID should be driven by its side-effect profile, which may limit its use in patients with contraindications. There is also strong evidence to support the use of caffeine in combination with acetaminophen, and the latter can also be used as a first-line agent in these patients [9]. Patients with moderate-to-severe migraine headaches should be started on a triptan, as

it can target the pathophysiologic causes of migraines by constricting cerebral arteries, inhibiting neurogenic inflammation, and central inhibition of pain [10]. The choice of a triptan is one where head-to-head comparisons studies are limited, but there is strong evidence that 6 mg given subcutaneously shows the most benefit. In this regard, combination therapy has been shown to be superior by adding a triptan to one the agents previously described in this review. One should also consider that these agents are expensive, require education on the correct timing of administration, and vary in routes of administration (intranasal, oral, subcutaneous). Some patients benefit more from one of the other seven triptans described, related to variability in patient genetics [11]. Second-line agents should be considered in patients with refractory migraine headaches, which consist of antiemetics along with antiepileptics, but the latter are of limited utility related to their potential for abuse. The National Institute of Health and Care Excellence (NICE) recommends acute migraine abortive treatment with a triptan together with paracetamol (or a nonsteroidal antiinflammatory drug) plus an antiemetic [12]. It is important to note the lack of efficacy with one triptan does not mean that others will not work. Additionally, NICE guidelines for migraine prophylaxis suggest using topiramate or a beta blocker. Comorbidities or lack of efficacy often results in other agents being prescribed. Lastly, it is also recommended via these guidelines that providers should start migraine prophylactic agents at low dose, build the dose up progressively, and maintain a therapeutic dose for 3 months before judging its efficacy.

Acute exacerbations of migraine headaches can cause great amounts of pain and distress to patients. Treatment for acute migraines should start with non-steroidal antiinflammatories. If these medications prove to be ineffective, physicians should start patients on triptans for relief with every effect made to avoid opioid therapy. When prescribed for headaches, opioids can interfere with triptan effectiveness and lead to secondary medication overuse headaches [13]. Patients should be counseled on the deleterious side effects of medicine overuse [14]. Preventive therapy for chronic migraines is vital to patient well-being. A lifestyle change is the first line of therapy discussed with these patients. This starts with ensuring regular daily meal times and sleep cycles as well as avoiding triggering agents such as stress, certain types of food, and alcohol [14]. If lifestyle changes do not aid in prevention, first-line medication therapy should be beta blockers or tricyclic antidepressants with second-line therapy being anticonvulsants [14].

Tension Headaches

For tension-type headaches, current NICE guidelines recommend acetaminophen, or an NSAID, with data suggesting that tension headaches do not require a prophylactic regimen.

Treatment for tension-type headaches is also important in increasing the quality of life of patients. Tricyclic antidepressants have been proven to be superior to other medications in preventing tension headaches [15]. Amitriptyline is the most common tricyclic antidepressant prescribed to prevent onset of tension headaches. Cluster headaches are another type of headache with rapid onset painful episodes. Many studies have agreed that verapamil is the best first-line agent to prevent the onset of cluster headaches [16]. Treatment varies for acute onset cluster headaches. Triptans have been shown to be effective for cessation of acute cluster headaches [17]. Oxygen therapy is also used for abortive therapy for these acute headaches although evidence is limited [18]. Finally, paroxysmal hemicrania, a rare type of severe headache causing unilateral pain, has been shown to be relieved by the non-steroidal antiinflammatory medication indomethacin [19].

Medication-Overuse Headache

A common chronic headache disorder is medication-overuse headache (MOH). This public health problem has a worldwide prevalence of 1–2%. In this regard, many over the counter products have high doses of caffeine and when stopped, headache is an extremely common clinical manifestation, similar to people who consume large amounts of coffee daily and then stop abruptly. Further, chronic overuse of different headache medications can result in persistent cephalgia that is difficult to relieve. Three conditions need to be satisfied to diagnose medication overuse headache: a patient with a previously diagnosed primary headache must be overusing medication treatments for more than 3 months; a patient with a diagnosis of a previous primary headache must have a headache for 15 days or more out of the month; and finally, this headache and its symptoms cannot be attributed to any other primary headache conditions [20]. This condition seems to result from patients either taking simple analgesics such as non-steroidal antiinflammatories or acetaminophen for 15 days or more per month or using prescription medications such as triptans, opioids, or ergotamine for 10 days per month [20]. Treatment for this condition occurs by weaning patients off of the medication that they are overusing. Some studies have shown that best results occur once the offending agent has been weaned completely to cessation of use [20]. Prior to initiating any treatment, patient counseling and education is extremely important in preventing medication overuse headaches [20].

Novel Non-opioid Headache Treatments

There are several non-opioid treatments for headaches. Injection of botulinum toxin can increase the number of headache-free days experienced by patients suffering from

chronic, tension-type headaches [21]. For patients suffering from cluster headaches, suboccipital steroid injections have also been shown as a successful treatment option [22]. Botox is now FDA-approved to treat migraine headaches.

Interventional techniques, which consist of targeting peripheral nerves directly responsible for pain, include neurolysis or radiofrequency ablation, which temporarily eradicates the nerve until it regenerates approximately 3–6 months later, requiring repeat treatments. A new line of therapy is the use of electrical nerve stimulation, which has been shown to be beneficial in patients with chronic pain involving the trunk or extremities. There are studies examining its use in patients who suffer from chronic headaches and migraines [23]. Electric nerve stimulation technique works on the principle of gate control theory of pain as previously discussed. Currently, it is clearly warranted to conduct larger studies in order to better support this line of therapy, but case reports and smaller studies have shown some benefit in select patients.

Occipital nerve stimulation (ONS) has also been described as a treatment for all types of trigeminal autonomic cephalgias [24]. Percutaneous ONS is a minimally invasive (and reversible) approach to manage occipital neuralgia. This technique is performed by utilizing subcutaneous electrodes that are placed superficial to the cervical muscular fascia in the suboccipital area. Additionally, radiofrequency lesioning is another treatment used in the management of chronic pain syndromes of the head and neck. If a diagnostic sphenopalatine ganglion block successfully resolves the patient's symptoms, neurolysis can be used as a more permanent solution.

Studies on the efficacy of pulsed radiofrequency (PRF) in the treatment of occipital neuralgia (ON) [25–28] and cluster headaches (CH) [29] have regarded PRF to be superior with safer profile than foreknown treatments for refractory conditions. Choi et al. showed patients treated with PRF for refractory ON had declined in mean Visual Analog Scale by six units and total pain index scores by 192 units within a mean follow-up period of 7 months [25]. Huang et al. conducted a retrospective study to demonstrate the efficacy of PRF in ON and factors associated with the efficacy [30]. This large multicenter study showed 51% of positive outcomes with PRF treatment in patients with refractory ON and factors associated with the positive outcome are using lower volume of diagnostic block anesthetic, isolated greater occipital nerve involvement, having traumatic inciting event (66% success rate), patients receiving > 1 cycle of PRF (3-fold increase).

Contrarily, factors correlated with treatment failure are having pain anterior to the scalp apex and ongoing secondary gain issues. Basic science studies support the efficacy of PRF by modulatory pathways playing a role in antinociception [31]. Fang et al. demonstrated the superiority of sphenopalatine ganglion PRF over blockade in treating cluster headaches in

a prospective study were 85% percent of patients with episodic refractory cluster headache showed pain relief with sphenopalatine ganglion PRF, the mean duration of clusters decreased to 0.5 months and, the mean duration of remission increased up to 17 months [29]. Elahi et al. presented a case report of successfully managing refractory headache and facial pain secondary to cavernous sinus meningioma by using sphenopalatine ganglion blockade and radiofrequency technique [27].

Infection and bleeding are possible complications with any percutaneous intervention along with potential complications associated with sphenopalatine ganglion or occipital nerve involvement. Current pain medicine practice guidelines recommend the use of imaging guidance such as fluoroscopy, ultrasound, and CT scan to improve the precision, accuracy, and safety of PRF treatment.

CHAMP trial (childhood and adolescent migraine prevention study) was developed to examine the effectiveness of two widely prescribed migraine preventive drugs (amitriptyline and topiramate) in the pediatric population. This trial was aborted as neither of 2 drugs was more effective than placebo [32]. Due to the shorter duration of headaches and other characteristics, features in this population might lead to high response rates to placebo. Further research is needed to help understand the therapeutic benefits of placebo and methods of inducing and maintaining the therapeutic effect of placebo in a pediatric population.

Further, studies show deep brain neurostimulation is promising in the treatment of patients with chronic refractory pain which needs further validation for clinical utilization [33, 34]. Newer techniques like pulsed focused ultrasound are being studied in animal models [35]. More modern molecular methods like stem cell therapy especially treatment with mesenchymal stromal cells (MSCs) holds a great promising future in the management of chronic pain [34].

The triptans are a mainstay in the treatment of acute migraine attacks and were discussed in detail above; however, new formulations and modes of delivery are being created. For example, the release of serotonin included by 5-HT1B/1D receptor agonists [36]. Sumatriptan was used to treat migraines, but due to its low bioavailability and short half-life, other second generation triptans have been developed. These include almotriptan, eletriptan, frovatriptan, naratriptan, and rizatriptan. These are the current mainstays for treatment of a migraine attack.

Calcitonin-related peptide gene (CGRP) may play an important role in the molecular pathway of migraines. Studies have shown that CGRP levels are increased during a migraine and then normalized after treatment with triptans. This hypothesis shows that CGRP may be a target for migraine prevention [37]. There have been many studies regarding drugs that block CGRP in prophylactic migraine treatment. Current preventative medications used in migraine prevention are

treatments for other pathological processes. These include antidepressants, antihypertensives, and antiepileptic medications. Topiramate is recommended for migraine prevention [38]. Although CGRP blockade seems to be safe and efficacious for migraine prevention, there are a few considerations that need to be made. Most of the new formulations are monoclonal antibodies and need to be administered intravenously or subcutaneously [37]. Also, long-term side effects of these monoclonal drugs are unknown, including cardiovascular and cerebrovascular side effects. The exact target of the CGRP is not totally known, and these monoclonal drugs could potentially have effects on other areas of the body that could be deleterious. Finally, with any monoclonal drug, the development of antibodies is a distinct possibility, and long-term studies need to determine if this is of clinical significance [37]. Despite these concerns, the benefits of blockade of CGRP in those with chronic migraines seem to outweigh the risks. CGRP blockade is a novel target for migraine prevention.

Antileptics are also a treatment modality for the prevention of migraines. Divalproex sodium and sodium valproate showed a reduction in migraines over a 4-week period with minimal adverse effects. The most common adverse effect was weight gain. Additionally, gabapentin was also shown to reduce migraine number per month. Lamotrigine and oxycarbamazepine showed no benefit compared to placebo in migraine prevention. Topiramate showed a reduction in migraines as well [39].

Melatonin is a novel treatment in those with headache disorders. Melatonin levels have been shown to be lower in patients who have migraines and cluster headaches. Up to 3 mg nightly of melatonin immediate release has been shown to prevent migraines and up to 10 mg nightly has been shown to prevent cluster headaches [40].

Tonabersat inhibits cortical spreading depression. It acts as a stereoisomer binding site that could be associated with the glial gap junction. A small study demonstrated that tonebersat might be useful in the treatment of migraines with aura raising the possibility of a different mechanism of migraines with aura compared to those without aura [41]. However, in a separate study, Tonabersat failed to demonstrate a greater reduction in migraines compared to placebo, even though it was well tolerated [42].

Prochlorperazine is a superior treatment for migraines in the emergent setting compared to placebo. It is a dopamine antagonist with the chief side effect being drowsiness. Prochlorperazine outperforms magnesium, lidocaine, ketorolac, and sumatriptan. It is no more efficacious when combine with diphenhydramine [43].

Metoclopramide is another dopamine antagonist used in the acute treatment of migraines. Many studies show that it is superior to placebo in acute treatment and decreasing the need for rescue drugs [44]. Reviews state that metoclopramide should be used as a first-line agent in the acute setting as opposed to opioids especially due to the potential abuse of opioid medication [45]. See Table 1.

Table 1   Novel non-opioid headache treatments

Novel non-opioid headache treatments
Botox
Neurolysis
Radiofrequency ablation
Occipital nerve and vagal stimulation
Pulsed radiofrequency
Triptans
CGRP blockade
Antiepileptics
Melatonin
Tonabersat
Prochlorperazine
Metclopramide

Lastly, vagus nerve stimulation had been demonstrated to be effective for different headaches [46–48]. GammaCore, developed by ElectroCore, Inc., has been approved by the Food and Drug Administration for the treatment of pain associated with migraine headaches and as an adjunct in preventing cluster headaches in adult patients. The device is a twice-daily self-administered therapy which provides three consecutive 2-min electrical stimulations through the skin of the neck, activating the vagus nerve.

Conclusions

Headaches account for a large portion of annual emergency room and primary care visits. Along with the ever-growing opioid epidemic, it is important that clinicians use the best evidence to guide the clinical management of headaches. This is especially important given the complex nature of headaches which requires a personalized approach for each patient. When evaluating patients, it is important to first rule out headaches that raise suspicion that warrant further workup as outlined by the NICE guidelines. Once ruled out, one must consider the characteristics of the headache, onset, triggers, aggravating, and alleviating factors. Along with characterizing the headache, one must determine contraindications to specific treatment modalities through a detailed patient history, as failure to do so may lead to failure in treatment, or detrimental effects secondary to medication profile. Once treatment regimen is established, there should be an emphasis on establishing prophylactic treatment in those patients with chronic history of headaches to avoid debilitating episodes in advance. Along with the utilization of the non-opioid approach in the treatment of headaches, the clinician should consider identifying patients who would benefit from interventional treatments who are refractory to medical therapy or were previously well controlled, and now suffering from

medication overuse. Finally, there are several non-opioid treatments that are now available to treat patients who suffer from headache pain that can be used in a multimodal regimen.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

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

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