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Review Article

Headache Disorders: A Systematic Review of Pathophysiology, Diagnosis, and Therapeutic Approaches

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Abstract

Headaches represent a prevalent and often debilitating health concern, classified primarily into migraines, tension-type headaches (TTH), and cluster headaches (CH). This review synthesizes current pharmacological and non-pharmacological management strategies tailored to these three headache types, highlighting the necessity of personalized treatment based on individual patient characteristics and comorbidities. In migraine management, preventive therapies, including anticonvulsants (such as topiramate), beta-blockers, and antidepressants (notably amitriptyline), are recommended for patients experiencing chronic migraines. Non-pharmacological approaches, such as cognitive behavioral therapy, biofeedback, and acupuncture, have demonstrated efficacy in reducing headache frequency and enhancing quality of life. Additionally, addressing medication overuse headache (MOH) through patient education and the careful tapering of overused medications is essential to optimize treatment outcomes. For TTH, acute treatments typically include simple analgesics like acetaminophen and NSAIDs, with amitriptyline recommended as a first-line preventive option for frequent episodic and chronic cases. Non-pharmacological interventions, such as physical therapy, stress management, and lifestyle modifications, play a crucial role in long-term headache management. CH is characterized by its acute attacks, effectively treated with triptans and high-flow oxygen therapy, while transitional management often employs corticosteroids like prednisone. Long-term preventive treatments primarily include verapamil and newer monoclonal antibodies. Emerging therapies, such as non-invasive vagus nerve stimulation and occipital nerve stimulation, are promising adjuncts for patients who do not respond to conventional therapies.

Keywords: Migraine; Acupuncture; Medication Overuse; Vagus Nerve Stimulation

Introduction

Cephalalgia, commonly referred to as headache, is characterized by pain in the face, head, or neck region. It is a nearly ubiquitous condition and can manifest in various forms, including migraines, tension-type headaches, or cluster headaches. Moreover, headaches constitute approximately 3% of primary complaints in emergency departments [1]. While the majority of headaches (96%) are non-threatening, it is vital to identify less common, urgent causes, as prompt treatment can be lifesaving [2].

Historical texts, such as the Ebers Papyrus from 1200 B.C., contain references to headaches, migraines, and neuralgia, while evidence of trepanation in Neolithic skulls, dating back 9,000 years, suggests early attempts at headache treatment. Hippocrates documented visual disturbances associated with headaches around 400 B.C., and Aretaeus offered one of the earliest classifications of headaches around 200 A.D. Interest in headaches spans nearly the entirety of recorded history, making them one of the most prevalent complaints among patients seeking medical care. The direct and indirect socioeconomic impact of headaches on society is estimated at $14 billion each year. Given that primary care providers frequently encounter headache cases, timely and precise diagnosis along with effective treatment are crucial in alleviating pain and mitigating the associated economic burden.

Epidemiology

- The lifetime prevalence of headaches is 96%, with a higher occurrence in females. Globally, the active prevalence of tension-type headaches is around 40%, while migraines affect approximately 10% of the population [3].
- Migraine affected 1.1 billion people globally in 2019, with the highest prevalence in Belgium and Italy, and the lowest in Ethiopia and Djibouti. Over the past three decades, global migraine cases have increased, particularly in East Asia and Latin America, while declining slightly in North America and Southeast Asia. Migraine is more common in females, with peak incidence in the 10–14 age group and peak disability between ages 30-34 [4].
- While tension-type headaches are generally less severe than migraines, they are significantly more common, with a lifetime prevalence in the general population reaching up to 80%. These headaches often lead to some level of disability, and their high frequency results in considerable socioeconomic consequences [5].
- Trigeminal autonomic cephalgias are less common compared to migraines and tension-type headaches. The most prevalent form of trigeminal autonomic cephalgia is cluster headache, which has a population prevalence of 0.1% and a male-to-female ratio of 3.5 to 7:1 [6].
- Chronic daily headaches, characterized by daily or near-daily occurrences lasting for months or years, are frequently mentioned in the literature but are not recognized as an official diagnosis in the International Classification of Headache Disorders. Types of chronic daily headaches include chronic migraine, chronic tension-type headache, hemicrania continua, and new daily persistent headache. The global prevalence of chronic daily headache has remained steady at 3% to 5%, with most cases likely representing chronic migraine [4].

Classification

The International Classification of Headache Disorders, 3rd Edition (ICHD-3): [7]

Primary headache

- Migraine
- Tension-type headache (TTH)
- Trigeminal autonomic cephalalgias (TACs)
- Other primary headache disorders

Secondary headache

- Headache attributed to trauma or injury to the head and/or neck
- Headache attributed to cranial or cervical vascular disorder
- Headache attributed to non-vascular intracranial disorder
- Headache attributed to a substance or its withdrawal
- Headache attributed to infection
- Headache attributed to disorder of homoeostasis
- Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
- Headache attributed to psychiatric disorder

Neuropathies and facial pain and other disorders

- Painful lesions of the cranial nerves and other facial pain
- Other headache disorders

Appendix

Pathophysiology

The brain itself lacks pain receptors and is insensitive to pain. However, pain receptors are found in areas like extracranial arteries, veins, cranial nerves, meninges, and muscles. Headaches often stem from irritation or tension in the meninges and blood vessels, triggered by trauma, tumors, vascular spasms, meningitis, or muscle strain. Once activated, nociceptors send pain signals to the brain. Secondary headaches have clear causes, while the mechanisms behind primary headaches, such as migraines and tension headaches, remain uncertain with no definitive cause.

Migraine

Premonitory phase

The premonitory phase is the initial stage of migraine, which starts in CNS. Research indicates activation in key brain regions, such as the posterior and lateral hypothalamus and adjacent midbrain, which may explain why migraines are often triggered by disruptions in homeostasis (like changes in sleep-wake cycles or missed meals). Symptoms during this phase can include yawning, food cravings, polyuria, and mood changes. Additionally, areas like the periaqueductal gray and dorsal pons modulate the intensity of sensory stimuli (such as light and sound), cerebral blood flow, and nociception, which contributes to migraine symptoms [8].

Aura phase

The aura phase of a migraine is characterized by specific neurological symptoms that precede the headache, primarily driven by cortical spreading depression (CSD). CSD involves extreme depolarization of glial and neuronal membranes, leading to ionic disruption and changes in cerebral blood flow. Initially, CSD causes a transient increase in blood flow, followed by a decrease, resulting in symptoms such as visual disturbances. This wave of CSD propagates across the brain at a rate of 2-6 mm/min, correlating with the progression of these symptoms. Excessive release of glutamate, a neurotransmitter linked to excitatory signaling, plays a critical role in CSD, and genetic factors, including mutations associated with familial hemiplegic migraine (FHM), have been identified, indicating a genetic predisposition to heightened excitability. The activation of the trigeminovascular system during CSD is central to migraine pathophysiology, and preventive treatments (tonabersat and singlepulse transcranial magnetic stimulation (sTMS)- Both blocks CSD in animals) have shown efficacy in raising CSD thresholds [8].

Headache phase

During the headache phase, trigeminal sensory pathways are activated, causing pain in sensitive intracranial structures like the eye and dura mater. These pathways are supplied by unmyelinated fibers from the trigeminal nerve, which converge and synapse on second-order neurons in the trigeminal cervical complex, explaining the characteristic pain distribution associated with migraines. Neurotransmitters, including calcitonin gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide-38 (PACAP-38), are released, leading to cranial vessel dilation and further activation of pain pathways. Sensitization of these pathways can result in allodynia, where normally non-painful stimuli become painful. Central sensitization can persist even between migraine attacks, contributing to ongoing low-grade headaches and heightened sensitivity to sensory stimuli. This neural plasticity can be seen as a form of "pain memory," influenced by the frequency of attacks and changes in pain modulation systems. Chronic migraine and medication overuse may enhance cortical excitability, leading to a greater likelihood of migraine attacks triggered by various stimuli [8].

Tension type headache

The pathophysiology of tension-type headache (TTH) is complex and can be understood through three major categories: genetic factors, myofascial mechanisms, and mechanisms of chronification (involving central sensitization and altered descending pain modulation).

Genetic factors

Although the specific genes involved in TTH are still unknown, twin studies have shown varying heritability estimates. For example, in those with concomitant migraine, the heritability of TTH was 19%, while it was higher in those without migraine, 48% in male twins and 44% in female twins. There is evidence

suggesting that genetic factors may play a more substantial role in frequent episodic TTH (ETTH) than in infrequent ETTH, though direct comparisons are lacking. For chronic TTH (CTTH), studies suggest a threefold increase in risk among first-degree relatives, but these findings must be interpreted with caution as they did not account for concomitant migraine [9].

Myofascial mechanisms

A key aspect of TTH pathophysiology involves the myofascial tissues. Pericranial muscle tenderness is a hallmark of TTH, with higher tenderness scores observed in individuals with ETTH and CTTH compared to healthy controls. This muscle tenderness could either contribute to or result from TTH attacks. Interestingly, studies have shown that muscle tenderness can precede the onset of headaches, as seen in patients who experienced frequent ETTH over a 12-year period. Pericranial muscle hardness is also increased in patients with CTTH, even outside headache episodes. Nitric oxide (NO) is thought to play a role in this, as inhibiting NO production has been shown to reduce pain and muscle hardness. Myofascial trigger points, areas of hypersensitive muscle fibers that can radiate pain, are common in patients with TTH and may play a role in triggering or perpetuating TTH through peripheral nociception. These trigger points may also contribute to central sensitization-when the central nervous system becomes more responsive to pain [9].

Mechanisms of chronification and central sensitization

The transformation of TTH from an episodic to a chronic form is often linked to central sensitization, a process where the nervous system becomes hyper-excitable and overly responsive to stimuli. Patients with CTTH exhibit lower pain thresholds to various stimuli, indicating heightened pain sensitivity across both head and non-head regions. This phenomenon suggests that central sensitization is a key factor in the chronification of TTH. Increased activity in supraspinal structures, such as the thalamus and somatosensory cortex, is likely involved in this process. Nitric oxide (NO) also plays a central role in the pathophysiology of CTTH by increasing the excitability of central pain pathways. In studies where NO donors like glyceryl trinitrate were administered, patients with CTTH experienced immediate and delayed headache responses, reinforcing the idea that NO-related central sensitization is a common mechanism in both TTH and other primary headache disorders, such as migraine [10].

Vascular and Central Factors: Though vascular input is less significant in TTH compared to migraine, cerebral blood flow changes may still play a role. Alterations in the cerebral vasculature, as seen in increased blood flow velocities in some cerebral arteries, could lead to trigeminal activation and headache in TTH. Moreover, chronic TTH has been associated with both functional and structural brain changes, particularly in regions related to pain processing, such as the insula and anterior cingulate cortex. This indicates that frequent pain stimuli and central sensitization might contribute to long-term changes in brain structure and function [9].

Cluster headache

Cluster headache (CH) is a type of trigeminal autonomic cephalgia, characterized by severe, unilateral headaches and prominent cranial autonomic symptoms on the same side as the pain, such as eye redness and tearing. CH can be classified into episodic or chronic forms. Episodic CH involves attack periods lasting from 7 days to 1 year, while chronic CH persists for 1 year or longer, with remission periods shorter than 3 months. The pain typically centers around or behind the eye and can spread to the ipsilateral temple. During intense attacks, the pain is so severe it's referred to as a "suicide headache," causing patients to become restless, violent, or engage in self-harming behaviors. CH is also marked by a circadian rhythm and seasonal variation in attack periods [11].

Trigeminal-parasympathetic system

During cluster headache (CH) attacks, gasserian ganglion neurons release CGRP, a vasodilator that modulates trigeminal nociceptive neurons. Pain signals from cranial vessels and the dura are transmitted via the trigeminovascular system to the trigeminocervical complex, projecting to the thalamus and cortical areas. The trigeminocervical complex interacts with the hypothalamus and the superior salivatory nucleus (SSN), which is linked to facial parasympathetic fibers. These fibers, passing through the sphenopalatine and other ganglia, mediate symptoms like lacrimation, rhinorrhea, and vasodilation [11].

Activation of hypothalamus

The circadian rhythm, controlled by the suprachiasmatic nuclei in the ventral hypothalamus, regulates melatonin expression and

secretion. Studies show a reduced nocturnal melatonin peak in cluster headache (CH) patients, possibly explaining the frequent nighttime attacks [12]. PET scans reveal activation in the inferior hypothalamic grey matter during CH, suggesting it may trigger headaches rather than respond to trigeminal pain signals. The pathogenesis of CH is complex, with advanced neuroimaging suggesting interconnected cortical-hypothalamic-brainstem networks and diencephalic-mesencephalic involvement in CH pathophysiology [11].

Diagnosis

Physical examination

A thorough physical exam is essential, particularly focusing on neurological function and a complete HEENT (head, eyes, ears, nose, throat) assessment. This can help detect benign conditions like sinusitis or more serious issues, such as papilledema (a sign of elevated intracranial pressure) or temporal artery tenderness (suggesting giant cell arteritis).

Risk stratification: Low-risk vs. high-risk features

In many cases, patients exhibit low-risk features for serious underlying causes, such as being under 50, having a history of similar headaches, and presenting with a normal neurological examination. In such cases, the focus shifts to identifying the type of primary headache or benign secondary cause. For patients with high-risk features, such as new neurological symptoms, sudden onset, or older age, further diagnostic evaluation is warranted to rule out secondary causes.

Red Flags: SNOOP10 Mnemonic

The SNOOP10 mnemonic helps clinicians identify red flags for life-threatening conditions

- **S (Systemic):** Systemic symptoms like fever, weight loss, or immunosuppression can indicate infections, malignancy, or inflammatory diseases causing secondary headaches.
- **N (Neurologic):** Neurologic signs such as motor, sensory, or cognitive changes may suggest a serious underlying neurologic disorder.
- **(Onset, sudden):** Sudden onset or thunderclap headaches often signal conditions like subarachnoid hemorrhage or vascular issues.
- **(Onset, age):** Headache onset before 5 years or after 65 years raises concern for secondary causes like infection or neoplasm.
- **P (Pattern change):** A change in headache pattern, frequency, or associated symptoms can indicate a secondary etiology.
- **P (Precipitated by Valsalva):** Headaches triggered by coughing, sneezing, or straining may suggest structural abnormalities like Chiari malformation.
- **P (Postural aggravation):** Headaches worsened by posture changes may indicate abnormal intracranial pressure, either high or low.
- **P (Papilledema):** Swelling of the optic disc (papilledema) is a red flag for increased intracranial pressure and requires immediate evaluation.
- **P (Pregnancy-related):** Headaches in pregnancy, particularly with other symptoms, may indicate preeclampsia or other serious conditions.
- **P (Painful eye):** A painful eye with autonomic symptoms can suggest cluster headaches or glaucoma.
- **P (Posttrauma):** New headaches after trauma may indicate a brain injury or other complications like subdural hematoma.
- **P (Pathology):** Headaches associated with immune or oncologic pathology may signal infection, malignancy, or autoimmune disorders.
- **P (Phenotype change):** A change in the type or characteristics of a headache may suggest a new secondary cause.
- **P (Painkiller overuse):** Overuse of painkillers can lead to medication-overuse headaches, requiring a careful review of medication history.
- **P (Previous headache history):** Any significant change in a person's headache history should prompt consideration of a secondary headache [13,14].

ICHD-3 Diagnostic criteria for migraine [7]

Migraine without aura

At least five episodes that meet the following criteria

- Each headache lasts from 4 to 72 hours, whether untreated or inadequately treated.
- The headache must have at least two of the following features:
- Unilateral (one-sided) location
- Pulsating or throbbing quality
- Moderate to severe intensity
- Aggravation by or avoidance of routine physical activities (e.g., walking, climbing stairs)
- During the headache, at least one of the following symptoms must be present:
- Nausea, vomiting, or both
- Sensitivity to light (photophobia) and sound (phonophobia)
- The headache cannot be attributed to another disorder.
- Migraine With Aura (Classic Migraine)
- At least two episodes that fulfill the following criteria:
- The migraine aura meets the criteria for typical aura, hemiplegic aura, or basilar-type aura.
- The aura cannot be attributed to another disorder.

Typical aura

Fully reversible visual, sensory, or speech symptoms (or any combination), with no motor weakness.

Visual symptoms may include homonymous or bilateral disturbances, which can present as positive features (e.g., flickering lights, spots, lines) or negative features (e.g., loss of vision). Sensory symptoms may involve unilateral disturbances, including positive features (e.g., pins and needles) or negative features (e.g., numbness), or any combination thereof.

At least one of the following criteria must be met

- At least one symptom that develops gradually over a minimum of 5 minutes, or different symptoms occurring in succession, or both.
- Each symptom lasts for at least 5 minutes and does not exceed 60 minutes.

A headache that meets the criteria for migraine without aura begins during the aura or follows it within 60 minutes.

ICHD-3 diagnostic criteria for tension type headache [7].

Infrequent Episodic Tension-Type Headache (ETTH)

To meet the criteria, the following must be satisfied:

- **Frequency:** At least 10 headache episodes occurring on average less than 1 day per month (i.e., fewer than 12 days per year).
- **Duration:** Each episode lasts between 30 minutes and 7 days.
- Additional criteria that must also be met.

Frequent Episodic Tension-Type Headache (ETTH)

To meet the criteria, the following must be satisfied

- **Frequency:** At least 10 headache episodes occurring on average 1 to 14 days per month for more than 3 months (i.e., between 12 and 180 days per year).
- **Duration:** Each episode lasts between 30 minutes and 7 days.
- Additional criteria that must also be met.

Chronic tension-type headache (CTTH)

To meet the criteria, the following must be satisfied

- **A: Frequency:** Headaches occurring on 15 days or more per month on average for more than 3 months (i.e., at least 180 days per year).
- **B: Duration:** Episodes can last from hours to days, or they may be continuous.

At least two of the following four characteristics must be present

- Bilateral location
- Pressing or tightening (non-pulsating) quality
- Mild or moderate intensity
- Not worsened by routine physical activities such as walking or climbing stairs

Both of the following must be true

For infrequent and frequent ETTH

- No nausea or vomiting
- No more than one of photophobia or phonophobia

For CTTH

- No more than one of photophobia, phonophobia, or mild nausea
- No moderate or severe nausea or vomiting
- The headaches are not better explained by another diagnosis in the ICHD-3 classification.

ICHD-3 Diagnostic criteria for Cluster Headache [7].

At least five episodes that meet the following criteria

- The pain is severe, unilateral, and located in the orbital, supraorbital, and/or temporal regions, lasting between 15 to 180 minutes if left untreated.
- One or both of the following symptoms must be present:
- At least one of the following, occurring on the same side as the headache: conjunctival injection and/or tearing; nasal congestion and/or runny nose; eyelid swelling; sweating on the forehead and face; miosis (constricted pupil) and/or ptosis (drooping eyelid).
- A feeling of restlessness or agitation.
- The frequency of attacks ranges from once every 2 days to up to eight times per day.
- The episodes cannot be better explained by another diagnosis in the ICHD-3 classification.

Laboratory and imaging studies

Routine lab tests are not typically useful for diagnosing headaches unless specific conditions are suspected, such as checking ESR and CRP for suspected giant cell arteritis or carboxyhemoglobin for carbon monoxide poisoning. Neuroimaging is indicated in high-risk patients, with non-contrast head CT often being the first step for emergent headaches. Advanced imaging like CT angiography (CTA) or MRI with MR venography (MRV) is used for conditions like SAH, arterial dissection, or dural sinus thrombosis. Lumbar puncture (LP) may be necessary when infection, subarachnoid hemorrhage, or idiopathic intracranial hypertension is suspected. [15,16].

Management

- When addressing secondary headaches, the primary goal is often to manage the underlying cause. For instance, if the headache is due to a sinus infection, treating the infection itself will typically resolve the headache symptoms. In certain cases, such as post-traumatic headaches, the treatment approach may align with migraine therapy, as post-traumatic headaches frequently resemble migraines in their clinical presentation.
- For primary headaches, such as migraines, the treatment strategy is more individualized and depends on the severity and impact of the symptoms. Patients with mild or occasional headaches may benefit from conservative approaches like lifestyle modifications, stress management, and the use of over-the-counter medications. However, when symptoms are more severe or disabling, prescription medications may be introduced to restore function and minimize the impact of the headache.
- In clinical management, it's essential to differentiate between abortive and preventive medications. Abortive treatments are designed to relieve acute headache attacks, offering immediate symptom relief, while preventive medications are intended to reduce the frequency, duration, and intensity of headaches over time. The ultimate goal of preventive therapy is to minimize disability and enhance the patient's quality of life by preventing future attacks.

Primary headache management

Migraine

Pharmacological management

Acute treatment

The acute treatment of migraines focuses on a combination of pharmacological therapies and behavioral techniques, aimed at alleviating pain as early as possible. The key to effective treatment is prompt administration of the correct dose and, in some cases, choosing a non-oral route (e.g., nasal spray, injection, or suppository) to bypass issues like nausea, vomiting, or rapid pain escalation. A combination of medications targeting different mechanisms can be useful in difficult cases. Educating patients with frequent migraines about the risk of medication-overuse headaches is crucial. They should limit simple analgesics (e.g., NSAIDs, paracetamol) to fewer than 15 days per month and

triptans, ergots, or combination analgesics to fewer than 10 days per month.

General principles

- **Early intervention:** Administer medication when the pain is mild to improve outcomes.
- **Non-oral routes:** These are often necessary for patients with severe nausea, vomiting, or rapid pain progression.
- **Combination therapy:** Using medications with different actions may help if initial relief is incomplete or if headache recurrence occurs within 24-48 hours [3].

Key medications

Simple analgesics

- First-line for mild to moderate migraines.
- Common examples include Ibuprofen 400mg tablet and Naproxen 500mg tablet [8].

Triptans

- First-line for moderate to severe migraines, acting on serotonin (5-HT) receptors.
- They work by constricting blood vessels and blocking pain pathways in the brain.
- Available in various forms (oral, nasal, subcutaneous injections), giving flexibility based on patient preference and migraine severity.
- Examples: Sumatriptan PO (50mg), nasal (20mg), SC (6mg); Rizatriptan PO 10mg, Zolmitriptan PO 2.5mg [8].

Triptan safety considerations

- **Contraindications:** Patients with vascular diseases (e.g., peripheral, coronary, cerebrovascular diseases) or severe hypertension should avoid triptans.
- **Vascular Risk:** FDA has identified rare associations between triptans and vascular events (e.g., strokes, aneurysms, artery dissections).
- **Patient-specific selection:** Formulation choice depends on the attack's onset, severity, and recurrence potential.

Dihydroergotamine

- Useful in patients who do not respond to triptans or are prone to medication-overuse headaches.
- Administered as a nasal spray or injection.

Ergotamine tartrate

Rarely used due to poor bioavailability and frequent side effects, such as nausea.

Opioids and Butalbital-containing analgesics

Generally avoided due to high risk of adverse events, addiction, and medication-overuse headache [8].

Preventive treatment

Preventive medications are essential in the management of frequent migraines, significantly reducing their frequency, severity, and duration. Understanding the criteria for their use, patient adherence, and alternative treatment options is critical for effective migraine management.

Indications for preventive medications

Preventive medications should be considered for individuals who:

- Experience Frequent Attacks: Those suffering from four or more migraine attacks per month (or eight headache days per month) are at an increased risk of developing chronic migraines. Early intervention can help manage this risk effectively.
- Have Substantial Quality of Life Impairment: If migraine attacks disrupt daily life despite adequate use of acute medications and lifestyle changes, preventive medications should be pursued.
- Suffer from Rare Migraine Subtypes: Patients with specific migraine types, such as hemiplegic migraine or migraine with brainstem aura, may benefit from preventive treatments, regardless of attack frequency.
- Have a History of Poor Response to Acute Medications: Individuals who find that acute treatments are ineffective or cause significant side effects may require preventive strategies [3].

Importance of patient adherence

Adherence to preventive medications is often poor, even among those with chronic migraines. Factors contributing to low compliance include:

- Side Effects: Patients may experience adverse effects from preventive medications, leading to discontinuation.
- Complex Regimens: The need for consistent medication intake can be burdensome, especially if the treatment involves multiple medications or dosing schedules.
- Lack of Immediate Relief: Unlike acute treatments that provide quick pain relief, preventive medications may take weeks to show benefits, which can discourage patients [8].

When prescribing preventive medications for migraines, healthcare providers should follow these general principles to ensure optimal efficacy and safety

- Begin with the lowest possible dose and gradually increase it. This helps minimize the risk of adverse effects. Dose escalation should stop if side effects become problematic or once the desired efficacy is achieved.
- Take into account other conditions the patient may have, such as depression, epilepsy, hypertension, or obesity, when selecting a medication. While some medications may address multiple conditions (e.g., a tricyclic antidepressant for both migraine and depression), monotherapy might not always be optimal. Combining therapies may be necessary to achieve effective management.
- A trial of 2–3 months is usually required to determine whether the medication is effective. In some cases, it may take up to 6 months for the full benefit to be realized. Patience is essential to observe the maximal response.
- The primary goals should be a reduction in the frequency, severity, or duration of migraine attacks, or a combination of these factors. Establishing specific targets helps in evaluating the success of the preventive therapy.
- For female patients of childbearing potential, discuss the implications of using migraine medications, including potential risks to a fetus. Some preventive drugs may have teratogenic effects, and family planning must be a key consideration.
- It is essential to explain the possible side effects of the prescribed medications. Patients should be aware that some side effects are self-limiting (resolve over time) and dose-dependent. Encouraging open communication about any adverse effects can help in managing treatment adjustments [8].

Recommended preventive medications

Several classes of medications are recommended for migraine prevention, with strong evidence supporting their efficacy. These include

Anticonvulsants

- **Topiramate (50-200 mg BD or before bed):** Effective in reducing the frequency of migraines and is well-studied for this purpose.
- **Gabapentin (600-3600 mg in two-three divided doses):** Evidence is conflicting, with some studies showing efficacy while others do not.

Beta-blockers

- Propranolol (40–240 mg OD for long-acting formulation), Nadolol (20–160 mg OD), and Metoprolol (50–200 mg OD for long-acting formulation) are often first-line options due to their effectiveness and safety profiles.

Antidepressants

- Amitriptyline (10–50 mg before bed) has been shown to be effective for migraine prevention, particularly in patients with comorbid depression or anxiety.

Other agents

- Candesartan and Lisinopril are sometimes considered, but the evidence for their efficacy is not as strong.

Nutritional supplements

- Riboflavin (Vitamin B2), Coenzyme Q10 (ubidecarenone), and Magnesium citrate have shown promising results and are often used as adjunctive therapies [8].

Management of chronic migraine

In patients with chronic migraines, preventive medications are often essential. Onabotulinum toxin A has emerged as a highly effective treatment option, even in cases where acute medications are frequently overused [8]. The American Academy of Neurology recommends onabotulinum toxin A as a first-line preventive treatment for chronic migraines [17].

Managing medication overuse headache

Medication overuse headache (MOH) presents a unique challenge in migraine management. It occurs when patients frequently use acute migraine treatments, leading to a cycle of worsening headaches. Management strategies include

- **Reducing Acute Medication Use:** Establishing guidelines for limiting the number of days acute medications can be taken each week is crucial.
- **Gradual Withdrawal:** Patients should work with their healthcare providers to gradually reduce their reliance on overused medications, which can help alleviate MOH.
- **Initiating Preventive Therapy:** Research suggests that starting preventive medications during the withdrawal process may improve outcomes and reduce the likelihood of recurrent headaches [18].

Non-pharmacological management

Nutraceuticals

- Nutraceuticals are dietary supplements that offer potential health benefits and are increasingly popular, especially among patients with chronic diseases like migraines who seek alternatives to long-term prescription medications. Common nutraceuticals used in migraine prevention include riboflavin (Vit B2), coenzyme Q10 (CoQ10), butterbur root extract (Petasites hybridus), and feverfew (Tanacetum parthenium) [19].

Behavioral methods

Behavioral methods encompass a variety of strategies designed to help patients manage migraines by improving coping skills and identifying potential headache triggers. Key techniques include

- **Relaxation Techniques:** These may involve progressive muscle relaxation, autogenic training, and meditation, aimed at reducing stress and tension, which can trigger migraines.
- **Biofeedback:** This approach uses electronic devices to help patients monitor physiological processes such as muscle tension, blood pressure, and heart rate. By providing real-time feedback, patients can learn to control these responses and potentially alleviate pain.
- **Cognitive Behavioral Therapy (CBT):** A form of brief psychotherapy focused on managing stress and addressing cognitive patterns associated with pain. Evidence supports its effectiveness, [20] especially in situations where pharmacological treatments are less suitable, such as during pregnancy or in patients with certain medical comorbidities.

Research has demonstrated that these behavioral strategies can be effective, particularly when combined with traditional pharmacological treatments. For instance, a randomized trial involving 135 children and adolescents with chronic migraines found that participants receiving CBT alongside amitriptyline experienced a significant reduction in headache days compared to those receiving headache education with the same medication [21].

Acupuncture

Acupuncture as a treatment for migraines has produced mixed results across studies. Several RCTs have compared acupuncture to sham acupuncture or standard care. While some studies indicate a positive effect on headache improvement, the overall strength of evidence remains low, largely due to challenges in blinding and study design. One notable trial conducted in Germany with 960 participants (794 in the intention-to-treat population) compared verum acupuncture, sham acupuncture, and standard therapy. While all three treatments demonstrated effectiveness in reducing migraine days from baseline, no significant differences were observed between the groups. This suggests that the therapeutic effect of acupuncture may not solely depend on needle placement, raising questions about the mechanisms underlying its efficacy [19].

Non-invasive neuromodulation

Non-invasive neuromodulation is an emerging field in migraine treatment that stimulates the nervous system to modulate pain mechanisms involved in headaches. These techniques can be applied through the skin using either electrical currents or magnetic fields, offering potential immediate relief for acute migraine symptoms, with chronic use possibly providing longer-term preventive effects. They present a promising alternative to traditional oral or invasive therapies, generally exhibiting favorable

side effect profiles. However, caution is necessary due to the limited size of existing randomized controlled trials and concerns regarding blinding effectiveness.

Transcutaneous cranial nerve stimulation

- Transcutaneous cranial nerve stimulation, such as with the Cefaly® device (Cefaly Technology, Belgium), targets the supraorbital nerve. A RCT involving 67 subjects indicated a significant 30% reduction in migraine days over three months of daily treatment [22]. In a post-marketing survey, 54% of users reported that the device was beneficial [23]. Mild and reversible paresthesia was the most common side effect, which may affect treatment adherence.

Non-Invasive Vagus Nerve Stimulation (nVNS)

- The gammaCore® device (electroCore, LLC; Basking Ridge, NJ, USA) is a handheld stimulator delivering current to the cervical vagus nerve branch. Initially, invasive vagus nerve stimulation was used for refractory epilepsy and depression. Observations of migraine improvement in patients with implantable devices led to the development of gamma Core. Early studies indicated a pain-free rate of 21% at two hours post-treatment [24]. Subsequent open-label studies showed similar results, with the most common side effects being mild twitching and tingling sensations at the stimulation site [25].
- The EVENT study, the only randomized controlled trial evaluating nVNS for migraine prevention, did not show significant differences between the active and sham groups after two months. However, participants who continued treatment during the open-label phase reported a significant reduction in headache days, suggesting nVNS may be effective for acute treatment but lacks robust evidence for preventive use [26].

Single-pulse transcranial magnetic stimulation (sTMS)

sTMS is a safe, non-invasive technique that utilizes fluctuating magnetic fields to modify the excitability of cortical neurons. Post-marketing studies reported significant reductions in headache days for both episodic and chronic migraine patients, suggesting its potential as an effective treatment [27].

Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation modulates cortical excitability through anodal (excitatory) or cathodal (inhibitory) currents applied to the scalp. Anodal stimulation has shown promising results in reducing migraine frequency and pain intensity, particularly in early studies [28]. However, the effectiveness of cathodal currents has not been established, with recent studies failing to show significant reductions in migraine attacks.

Percutaneous mastoid stimulation (PMES)

The PMES device delivers an electric current through the skin behind the ear to stimulate the fastigial nucleus in the cerebellum. Recent trials indicated a significant reduction in migraine days, though the effectiveness of blinding in these studies remains uncertain [29].

Non-painful brachial electric stimulation

Research on non-painful electrical stimulation applied to the arm as an acute migraine treatment revealed modest therapeutic gains, with a 24% pain-free rate at two hours compared to sham stimulation. While this approach has the added advantage of being discreet and remotely controlled, further studies are necessary to confirm its efficacy [19].

Invasive neuromodulation

Invasive neuromodulation techniques aim to modulate pain pathways and provide relief for chronic migraine patients through direct electrical stimulation.

Occipital nerve stimulation (ONS)

ONS targets the greater occipital nerve, modulating central pain transmission through the trigeminocervical complex. Three randomized controlled trials (RCTs) have evaluated ONS for chronic migraine. The ONSTIM study, which included 75 participants, compared ONS with sham stimulation and medical management, showing a responder rate of 39% in the active group compared to 6% in the sham group [30]. Adverse events, including pain, infections, and lead migration, are common, and the high cost of the procedure limits its widespread use.

Sphenopalatine ganglion (SPG)

The sphenopalatine ganglion (SPG) is involved in the trigeminal-autonomic reflex, contributing to the autonomic symptoms of trigeminal autonomic cephalalgias and migraine. While lidocaine application to the SPG can abort migraine attacks, initial trials of electrical stimulation for acute migraine therapy yielded unsatisfactory results [19].

High cervical spinal cord stimulation

- Cervical spinal cord stimulation delivers electrical currents to the trigeminocervical complex using implantable leads. An open-label study showed promising outcomes, with over 30% reduction in headache days reported by many participants. The high-frequency stimulation (10 Hz) used in this technique reduces the likelihood of paresthesia, a common side effect of other neurostimulators [31]. Despite these promising results, further randomized controlled trials are necessary to establish the efficacy and safety of cervical spinal cord stimulation for chronic migraine treatment.

Tension type headache

Pharmacological management

Tension-type headache (TTH) treatment should be personalized and may include pharmacotherapy, behavioral therapies, physical and occupational therapies, lifestyle changes, and stress management. Infrequent TTH can often be managed with acute medications and lifestyle modifications, while frequent episodic (ETTH) or chronic TTH (CTTH) may require preventive medications and behavioral interventions.

Education on TTH triggers, progression, and treatment goals is essential. Treatment decisions should consider patient preferences and comorbidities, with an emphasis on shared decision-making to improve adherence. It's important for patients to understand that the aim is to manage TTH rather than cure it. Additionally, attention should be paid to potential nocebo effects and medication overuse, particularly regarding acute treatment frequency [9].

Acute treatment

- **Simple Analgesics:** Acetaminophen and aspirin have both been studied for treating TTH and are considered safe. However, acetaminophen can cause liver dysfunction, while aspirin may lead to bleeding [9]. The European Federation of Neurological Societies Task Force (EFNS-TF) recommends both for acute TTH treatment. NSAIDs like ibuprofen and ketoprofen are particularly effective and hence EFNS-TF also recommends the oral use of these NSAIDs for acute TTH treatment [32].
- **Combination Analgesics:** While caffeine alone is ineffective for TTH, its combination with analgesics like acetaminophen or ibuprofen can enhance their efficacy. A meta-analysis found that a combination of aspirin, acetaminophen, and caffeine was more effective than acetaminophen alone, with minimal side effects [33]. Common side effects included nervousness, nausea, and abdominal discomfort. Caffeine may also facilitate the absorption of analgesics [9]. EFNS-TF endorses caffeine combinations for acute TTH treatment [32].
- **Medications to Avoid:** Opioids should be avoided due to the risk of medication overuse headache (MOH) and potential misuse [34]. Triptans are generally ineffective for TTH unless the headache exhibits migraine-like features [32]. Muscle relaxants are not recommended for treating TTH due to their low efficacy. In specific populations such as children, pregnant or breastfeeding women, and the elderly, NSAIDs and caffeine combinations should be used with caution.

Preventive treatment

Preventive treatment is recommended for patients with frequent episodic tension-type headache (ETTH) and chronic tension-type headache (CTTH). Infrequent TTH does not typically require preventive measures unless specific comorbidities (like depression or fibromyalgia) are present, symptomatic treatments are ineffective, or daily functioning is compromised. Determining the duration of prophylaxis for TTH remains challenging, as studies generally last between 2 to 6 months, but many patients may need longer treatment. Factors such as comorbidity, treatment response, individual characteristics, previous headache history, and patient preferences should guide the decision on how long to continue treatment. For those showing a significant response (50–75% reduction in headache days), a common strategy is to pause treatment after 3 to 6 months and monitor for recurrence, unless other comorbidities warrant prolonged treatment [9].

Amitriptyline

Amitriptyline, a tricyclic antidepressant, has moderate to high efficacy in preventing TTH and is rated as level A by the EFNS-TF [32,35]. Its analgesic properties are attributed to mechanisms such as noradrenaline reuptake inhibition and NMDA receptor antagonism. Common side effects include drowsiness, weight gain, dry mouth, and dizziness. Amitriptyline is the first choice for TTH prevention in both elderly and younger patients, although those with cardiac arrhythmias should be excluded. Elderly patients should be monitored with electrocardiograms at baseline and during dosage adjustments [36].

Mirtazapine

Two RCTs support mirtazapine's efficacy for TTH prevention, granting it a level B rating [32]. The exact mechanism of mirtazapine is unclear, but it may involve the descending noradrenergic and serotoninergic pathways. Its side effects include drowsiness and weight gain, but it generally has a better tolerability profile than amitriptyline.

Venlafaxine

The evidence for venlafaxine, a serotonin-noradrenaline reuptake inhibitor, is limited, with only one small RCT supporting its level B rating [9]. Its mechanism of action is also unclear but is thought to be similar to that of mirtazapine. Common side effects include nausea, vomiting, and dizziness, but it tends to have better tolerability than amitriptyline [32].

Other agents

Other third-line treatments recommended with a level B rating include clomipramine, maprotiline, and mianserin. Additionally, a trial indicated that combining pindolol with amitriptyline may enhance treatment efficacy [37]. Evidence suggests that botulinum toxin type A and ibuprofen are ineffective or harmful for CTTH prevention [32].

Medication overuse

Medication overuse and medication-overuse headache (MOH) can occur in TTH patients, though less frequently than in those with migraines. Up to 20% of patients with MOH have TTH as their primary headache disorder. Management strategies for patients with MOH include education, cognitive behavioral therapy, and addressing risk factors like frequent headache attacks, anxiety, and specific medication use. Withdrawal from overused medications can be abrupt or gradual, depending on the drug, patient preferences, and comorbidities. Using preventive medications during withdrawal can improve outcomes, but 25–35% of patients may relapse, necessitating careful monitoring and potentially a multidisciplinary approach involving headache specialists, physiotherapists, and mental health professionals. In severe cases, hospitalization for detoxification may be necessary [9].

Nonpharmacological treatments

All individuals with TTH can benefit from education on healthy lifestyle habits. Non-pharmacological therapies with strong evidence for safety and efficacy include physical and occupational therapies, behavioral therapies (such as cognitive behavioral therapy (CBT), biofeedback, and relaxation therapy), complementary and integrative medicine (acupuncture and massage), and lifestyle modifications (sleep management, healthy diet, hydration, stress management, and regular exercise).The EFNS guidelines recommend considering non-pharmacological treatments before pharmacological options [32].

Behavioral therapies

Biobehavioral therapies, including CBT, biofeedback, and relaxation techniques, are effective for TTH management. Meta-analyses indicate that biofeedback significantly improves headache frequency, muscle tension, and self-efficacy. Stress management therapy has shown efficacy comparable to that of medications like amitriptyline or nortriptyline for CTTH prevention. Long-term group behavioral treatment combined with pharmacotherapy has shown promise in reducing headache frequency and disability [38].

Trigger management/prevention

Identifying and managing headache triggers can help prevent TTH. Common triggers reported by patients include sleep disturbances, negative emotions, and environmental factors like sunlight exposure [9]. However, relying excessively on self-reported triggers is not evidence-based and can lead to unnecessary avoidance behaviors. Instead, clinicians should focus on providing advice about trigger management, promoting graduated exposure to triggers to reduce sensitivity, and addressing sleep disorders associated with TTH.

Acupuncture

Acupuncture is effective for treating frequent ETTH or CTTH, with many patients experiencing significant reductions in headache frequency. While there are methodological limitations in the studies, the safety profile of acupuncture is favorable compared to pharmacological treatments like amitriptyline [34].

Interventional therapies

Anaesthetic injections at myofascial trigger points may reduce headache frequency. Myofascial trigger point dry needling is also effective for chronic TTH, improving headache intensity, frequency, and overall function [9].

Cluster headache

Pharmacological management

Patients with cluster headache (CH) can benefit from a variety of effective pharmacological and non-pharmacological treatments, although the clinical trial designs are quite varied. These interventions are categorized into acute, transitional (short-term preventive or bridging), and long-term preventive treatments. Acute episodes are commonly managed with triptans, oxygen therapy, and non-invasive transcutaneous vagal nerve stimulation, particularly for those with episodic cluster headaches. In the transitional phase, prednisone has been the most extensively researched. Verapamil and monoclonal antibodies are the primary options for preventive care, with additional pharmacological and non-pharmacological treatments available [40].

Acute treatment

- Triptans, especially a 6 mg subcutaneous dose of sumatriptan, are highly recommended for treating acute cluster headache attacks, with alternative options including a 20 mg intranasal sumatriptan and intranasal zolmitriptan (5 mg or 10 mg). These medications have an approximately 80% response rate, but their vasoconstrictive effects limit their use in patients with cardiovascular conditions, and they can only be taken twice within 24 hours.
- High-flow oxygen therapy is another effective option, delivering 100% oxygen via a non-rebreather mask at a flow rate of 7 to 15 liters per minute, with response rates ranging from 62% to 100% and relief typically occurring within 12 to 15 minutes. Both triptans and oxygen therapy are considered first-line treatments for acute CH attacks [40].

Bridging treatment

For transitional management, an oral regimen of prednisone at 100 mg per day for five days, followed by a gradual tapering of the dosage, is recommended [41]. Alternatively, a greater occipital nerve block may provide similar effectiveness with better tolerance [42].

Preventive treatment

- Verapamil, a calcium channel blocker, is the primary pharmacological treatment recommended for both episodic and chronic CH, typically at a minimum dosage of 240 mg per day. It is crucial to perform electrocardiograms prior to starting treatment and after any increase in dosage to monitor for potential cardiac side effects. Regular ECGs should continue even after reaching a stable dose, as cardiac issues can arise after a delay. Interestingly, in Mexico and some other Latin American countries, the standard maximum daily dose of verapamil is capped at 240 mg, whereas in other regions, doses can go up to 720 mg, possibly due to genetic factors [40].
- The FDA has also approved the monoclonal antibody galcanezumab as a preventive treatment for CH, with a dosing regimen of 300 mg per month for the first two months. In clinical trials, this treatment reduced the average weekly attack frequency from 8.7 in the treatment group to 5.2 in the placebo group by the third week. The most common side effects reported were nasopharyngitis and pain at the injection site [43,44].
- For second-line treatments, options include lithium, civamide, melatonin, topiramate, sodium valproate, baclofen, gabapentin, and non-invasive transcutaneous vagal nerve stimulation. Botulinum toxin and sphenopalatine ganglion stimulation may serve as third-line treatments [40].

Non-pharmacological management

Non-invasive VAGUS nerve stimulation (nVNS)

- Cluster headache (CH) is associated with unilateral cranial autonomic symptoms, such as tearing, nasal congestion, and drooping eyelids. These symptoms result from the trigeminal autonomic reflex involving nociceptive input and parasympathetic output. The use of nVNS for CH treatment

stems from its known effects on the parasympathetic system and a case report indicating headache improvement in patients treated with invasive VNS for depression.

- Double-blind studies show that nVNS is effective in aborting acute attacks in patients with episodic CH (eCH) but has limited efficacy in chronic CH (cCH).
- Side effects include a brief facial pulling sensation, and exclusion criteria for its use involve various cardiovascular and neurological conditions. Although the precise mechanism of nVNS remains unclear, it likely affects the trigeminal autonomic reflex by modulating parasympathetic output and trigeminal sensitivity [40].

Occipital nerve stimulation (ONS)

- The effectiveness of suboccipital steroid injections for treating CH has led to exploring greater occipital nerve (GON) stimulation as a long-term treatment for cCH patients. A recent RCT demonstrated over 40% improvement in headache frequency after GON stimulation; however, the results were similar for both the experimental and sham groups, indicating a potential placebo effect [45].
- Adverse events were mostly related to the hardware used for stimulation, and long-term follow-up indicated that a majority of patients maintained response rates for over six years [46].

Sphenopalatine ganglion stimulation (SPG)

- The sphenopalatine ganglion (SPG) plays a critical role in the trigeminal autonomic reflex. Stimulation of the SPG provide both acute and preventive benefits for CH [40].
- In two randomized trials, significant improvement was noted in a substantial percentage of cCH patients, with long-term follow-up revealing that many continued to respond positively [47].
- However, the SPG stimulator is currently unavailable due to financial issues. The mechanism by which SPG stimulation alleviates headaches is not fully understood, although it appears to influence parasympathetic output and may also modulate trigeminal nociception directly.

Deep brain stimulation (DBS)

- DBS of the posterior hypothalamus is considered for patients with medically refractory CH, based on evidence of hypothalamic activation during attacks.
- The risk of severe complications, such as intracranial hemorrhage, limits the use of DBS, making peripheral stimulation methods more favorable [40]. However, the potential for hypothalamic DBS to modulate pain indicates its relevance as a treatment target in future studies.

Conclusion

In conclusion, the management of headaches including migraines, tension-type, and cluster headaches, demands a multifaceted and patient-centered approach, underscoring the importance of personalized treatment plans tailored to the specific characteristics of each headache type. An integrated approach that combines pharmacological treatments with non-pharmacological methods, such as behavioral therapy and lifestyle adjustments, is essential for effective and sustainable headache management. Additionally, addressing the challenge of medication overuse headaches through vigilant monitoring and comprehensive patient education is crucial to preventing relapse and optimizing long-term outcomes.

Future work in headache management should focus on advancing our understanding of headache pathophysiology and identifying novel therapeutic targets. Continued exploration of neuromodulation and other emerging technologies holds the potential to expand the range of effective treatments available, especially for patients who do not respond well to conventional therapies. Moreover, future clinical guidelines should evolve to prioritize truly patient-centered care by incorporating individualized treatment strategies that account for patients' unique preferences, comorbidities, and headache profiles. Collaborative research efforts, including large-scale clinical trials and real-world studies, will be essential to refining treatment paradigms, developing innovative therapies, and enhancing the overall quality of life for those affected by chronic headaches.

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