Headache Management for the Pain Specialist

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Headache is a very common symptom caused by a wide variety of diseases. Primary headaches include migraine, cluster headache, tension-type headache, and other less common diseases. It is important to differentiate these headaches from secondary headaches caused by vascular, neoplastic, infectious, metabolic, or toxic disorders. Most primary headaches have a genetic basis, with environmental factors acting as triggers. Recent advances in basic research resulted in the development of more specific and effective therapies. Medication-overuse headache is a very common cause of chronic daily headache. Detoxification from the offending drug is essential for headache improvement. Cervicogenic headache is common and needs to be diagnosed correctly since it may require specific therapy. Nerve blocks are useful for some patients with primary, as well as secondary, headaches.

Key Words: Migraine, Cluster headache, Tension-type headache, Cervicogenic headache, Medication overuse, Nerve block.

Headache is a very common disease symptom that has a lifetime prevalence approaching 100%. Most headaches are benign (yet sometimes incapacitating), such as migraine and tension-type headaches (TTH). Headaches that have life-threatening causes are less frequent but important to recognize. Recent progress in the understanding of headache mechanisms has led to the development of new and effective treatments for primary headaches.

In this review, we discuss the clinical features and treatment of common primary headaches, as well as of secondary headaches, that are of special interest to the pain specialist. We also discuss symptoms and signs that should prompt a search for a potentially life-threatening cause of headache, and we review peripheral nerve blocks as a treatment for headaches.

Primary Headaches

Primary headaches are a disorder unto themselves. They are defined by the characteristics of the headache and its associated symptoms.

Migraine

Migraine is a neurovascular disorder characterized by episodes of headache accompanied by various combinations of gastrointestinal symptoms, autonomic nervous system dysfunction, and, in some patients, an aura consisting of transient neurologic symptoms.¹ ²

Epidemiology

Migraine is a very common disorder with a 1-year prevalence of 12% in the adult population (18% in women and 6% in men) and 4% in children in the United States and Western Europe.³ Migraine prevalence is highest between the ages of 25 and 55 years, which are the years of peak productivity.⁴ This age distribution, along with the high disability caused by migraine in a significant proportion of patients, explains the high economic impact of the disease. The World Health Organization rates migraine as one of the most disabling chronic diseases.⁵

Clinical Features

The 2 major subtypes of migraine are migraine without aura (MO) and migraine with aura (MA).⁶ Patients with both MO and MA may experience premonitory symptoms several hours to days before the attack. These symptoms include fatigue, depression, cognitive dysfunction, and food craving.⁷

MO is the most common subtype of migraine. It typically manifests as recurrent episodes of moderate to severe unilateral headache that is throbbing in quality and aggravated by physical activity. The headache may be associated with nausea or vomit-
ing and/or photophobia and phonophobia. Migraine headaches, however, may be nonthrobbing or bilateral.\(^1\) According to the International Headache Society (IHS) criteria, these episodes should last 4 to 72 hours (Appendix 1). A migraine attack that lasts longer than 72 hours is defined as status migrainosus.

MA manifests as attacks of headache similar to those of MO that are preceded by reversible focal neurologic symptoms called aura (Appendix 2). The aura develops gradually over 5 to 20 minutes and usually lasts for less than 60 minutes. The most common type of aura is visual, manifesting as scotoma (partial loss of vision), photopsia (unformed flashes of light), or fortification spectra (zig-zag lines). Less commonly, aura may be sensory (paresthesias) or motor (focal weakness) or may involve language function. Usually, the aura precedes the headache but, occasionally, it appears simultaneously with the headache. On rare occasions, the aura may occur without the headache.

Migraine attacks can occur from once in several months to several times a week and can last from a few hours to several days. Headache severity ranges from moderate to completely incapacitating. After the attack, the patient may feel tired, irritable, and listless.

Pathophysiology

Migraine is currently considered a primary brain disorder with secondary involvement of meningeal blood vessels.\(^2\)\(^,\)\(^8\) Evidence suggests the generator of migraine attacks is in the upper brain stem, which probably involves nuclei that modulate craniovascular pain afferents.\(^9\) During an attack, trigeminal sensory neurons are activated and release substance P, calcitonin gene–related peptide, and neurokinin A. This action results in neurogenic inflammation, meningeal blood vessel dilatation, and plasma protein extravasation. Some of these processes are mediated by serotonin released from trigeminal nerve endings adjacent to meningeal blood vessels.\(^10\) Evidence also suggests sensitization of neurons in the trigeminal nucleus caudalis in animal models of headache that may apply to migraine.\(^11\) Clinically, during migraine attacks, patients may experience cutaneous allodynia, probably related to central sensitization.\(^12\) Migraine aura appears to be related to the phenomenon of cortical spreading depression described by Leão.\(^13\) Aura is associated with neuronal events that reduce cerebral activity and with a wave of spreading oligemia that advances across the cerebral cortex from the occipital area forward at a characteristic rate of 2 to 3 mm/min. This oligemia is preceded by a short phase of hyperemia caused by central nervous system activation and is not confined to specific blood vessel territories.\(^14\)

Some individuals are known to have a genetic predisposition to migraine. The relative risk of first-degree relatives of migraine patients also experiencing the disease is 1.9 for MO and 3.8 for MA.\(^15\)

Management

Initial Approach to the Patient With Migraine Headache. The management of migraine begins with making a correct diagnosis. Laboratory and imaging studies should be performed in the appropriate cases to exclude secondary causes of headache.\(^16\) Symptoms, signs, and clinical settings that should raise suspicion of a worrisome underlying disease include the following (Table 1):

- New onset of headache in a patient older than 50 years,
- The sudden onset of headache,
- The occurrence of the worst headache ever,
- A progressively worsening headache,
- Headache in a patient with cancer or acquired immunodeficiency syndrome,
- Headache with fever or rash,
- Headache with papilledema, and
- Headache with focal neurologic signs.

In any of the above cases, a neurologic consultation should be obtained and the proper tests (e.g., neuroimaging, lumbar puncture, erythrocyte sedimentation rate) should be performed. Neuroimaging is not usually recommended for patients with a typical clinical picture of migraine and a normal neurologic examination.\(^17\)

Once the diagnosis of migraine is established, it should be explained to the patient and a treatment plan should be developed. Triggers for migraine attacks, such as emotional or mental stress, poor sleep patterns, skipped meals, and hormonal changes in women, should be addressed and corrected or avoided if possible.

Drug Therapy. Migraine pharmacotherapy may be acute, to reverse the symptoms of the acute attack, or preventive, to reduce the frequency, severity, and duration of attacks.

Treatment of the Acute Attack

Acute migraine treatment can be divided into nonspecific (drugs that are used to treat various pain disorders) and migraine-specific drugs. The nonspecific drugs include acetaminophen, aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), opiates, and antiemetic drugs. The migraine-specific drugs include the ergots and the serotonin (5-HT)\(_{1B/1D}\) agonists known as the triptans.
Several principles should be followed in acute migraine treatment. (1) The drug should be taken as early as possible into the attack. This action will increase treatment efficacy and accelerate the clinical response.\textsuperscript{18,19} (2) The dose should be adequate (e.g., 1,000 mg of acetaminophen, 500 to 1,000 mg of naproxen). (3) The route of administration should be appropriate. For patients with severe nausea or vomiting, a parenteral route is preferred. (4) The number of treatments should be limited to 2 to 3 a week to avoid analgesic-overuse headache. The choice of drug and the route of administration for the individual patient depends on the severity of the attack, its rate of evolution, associated symptoms, and coexisting diseases.

**Nonspecific Drugs**

NSAIDs and other simple analgesics are effective for some migraineurs.\textsuperscript{1} Opioid use should be minimized because of the potential risks of drug overuse with resultant headache exacerbation.\textsuperscript{20} The suggestion has recently been made that opioid therapy should not be the first-line treatment for acute headache in an emergency department setting.\textsuperscript{21} An analysis of 160 refractory headache patients treated with daily scheduled opioids in a referral headache center was recently performed.\textsuperscript{22} Only 26% of the patients had more than a 50% headache improvement. Despite careful screening and patient selection, problematic drug behavior occurred in 50% of patients, the most common of which was dose violation. The authors concluded that opioid therapy may provide significant long-term relief to selected patients, although most patients did not improve with this treatment.

Several antiemetics and neuroleptics are effective for acute migraine treatment. Prochlorperazine, chlorpromazine, promethazine, or metoclopramide can be used for both migraine headache and associated nausea and vomiting.\textsuperscript{23-25} Droperidol, a potent dopamine receptor antagonist, has recently been found effective for acute migraine treatment at a dose of 2.75 mg intramuscularly.\textsuperscript{26} Droperidol is associated with a dose-dependent prolongation of the QT interval. This effect may be seen within 10 minutes of drug administration.\textsuperscript{27} Droperidol has a black box warning that states the following: “Cases of QT prolongation and/or torsades de pointes have been reported in patients receiving Inapsine at doses at or below recommended doses. Some cases occurred in patients with no known risk factors for QT prolongation and some cases have been fatal.”\textsuperscript{27} QT interval, as well as calcium and potassium blood levels, should be measured before treatment.\textsuperscript{28}

**Migraine-Specific Drugs**

**Ergot Derivatives.** Ergots have been used for migraine treatment for more than 50 years.\textsuperscript{29} Since the introduction of the more pharmacologically specific triptans, the justification for the use of ergots has decreased. They remain, however, useful for some patients with prolonged attacks or high headache-recurrence rates. Dihydroergotamine (DHE) has fewer adverse events and is less likely to produce rebound headache compared with ergotamine. It can be given intranasally or intramuscularly in an outpatient setting. Repetitive intravenous DHE is the mainstay of treatment for refractory migraine in an inpatient setting.\textsuperscript{30}
Triptans. The development of the triptans and their introduction to clinical use in the early 1990s have dramatically changed acute migraine treatment.\(^2,28\) The triptans have a more specific pharmacologic profile than the ergots, and their efficacy has been established in well-designed clinical trials. Currently, seven triptans are available for acute migraine treatment: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan (Table 2). Triptans are 5-HT\(_{1B/1D}\)–receptor agonists. They relieve symptoms of acute migraine attack by several mechanisms: vasoconstriction of meningeal vessels, inhibition of primary trigeminal afferent fibers, and inhibition of second-order neurons in the trigeminal nucleus caudalis.\(^2\) The triptans differ in their pharmacokinetics, available formulations, and, to some extent, efficacy and tolerability. All triptans are available in an oral formulation. Some (rizatriptan and zolmitriptan) are also available in an orally dissolved formulation, and some (sumatriptan and zolmitriptan) are available as a nasal spray. Sumatriptan can also be injected subcutaneously. The triptans are effective and well tolerated for acute migraine treatment. Common side effects include dizziness, paresthesias, warmth sensation, and chest pressure, which is probably noncardiac in origin. Although 5-HT\(_{1B}\) receptors have been found in the coronary circulation, the triptans have proved to be very safe drugs with rare reports of adverse cardiovascular events.\(^31\) Still, they are contraindicated in patients with ischemic heart disease, cerebrovascular disease, uncontrolled hypertension, and hemiplegic or basilar migraine.

Preventive Treatment

Preventive drug therapy is administered to reduce attack frequency, duration, and severity.\(^32\) It may also render migraine attacks more responsive to acute treatment. Indications for starting preventive treatment include migraine that significantly interferes with the patient’s daily routine despite acute treatment; failure of, contraindication to, or troublesome adverse events from acute medications; acute medication overuse; very frequent headaches (>2/week); patient preference; hemiplegic migraine; or attacks with a risk of permanent neurologic injury.\(^33\) Drugs that are used for migraine prevention include the \(\beta\)-adrenergic blockers, antidepressants, anticonvulsants, calcium channel blockers, serotonin antagonists, and NSAIDs (Table 3).\(^1\) The choice of a preventive drug is based on efficacy, prior patient exposure, adverse-event profile, comorbidity, and concomitant drug therapy. In general, preventive drugs are started at a low dose that is increased gradually while the drug is monitored for tolerability and efficacy. Patients should be advised that a full therapeutic response may take several weeks to months. Recently, botulinum toxin type A (Botox; Allergan, Irving, CA) was found to be effective for migraine prophylaxis.\(^28,34\) The toxin is injected intramuscularly at different sites in the head or neck. Common injection sites are the glabellar, frontalis, and temporalis muscles. Treatment with botulinum toxin type A is safe, well tolerated, and has a long duration of action (of up to 4 months). It is particularly appealing for patients who have poor com-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Maximum Dose per Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>Oral</td>
<td>50 mg</td>
<td>200 mg</td>
<td>The triptan that has been used for the longest period of time</td>
</tr>
<tr>
<td></td>
<td>Nasal spray</td>
<td>5 mg</td>
<td>40 mg</td>
<td>More rapid onset of action than the oral formulation</td>
</tr>
<tr>
<td></td>
<td>Injection (s.c.)</td>
<td>6 mg</td>
<td>12 mg</td>
<td>Most rapid onset of action; highest efficacy</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>2.5 mg</td>
<td>10 mg</td>
<td>Efficacy and tolerability similar to sumatriptan</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Oral</td>
<td>5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Oral</td>
<td>1 mg</td>
<td>5 mg</td>
<td>Long half-life (6 h); few adverse events</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Oral</td>
<td>6.25 mg</td>
<td>25 mg</td>
<td>Efficacy similar to sumatriptan, slightly better tolerability</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Oral</td>
<td>2.5 mg</td>
<td>7.5 mg</td>
<td>Longest half-life (25 h)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
<td>80 mg</td>
<td>High bioavailability and efficacy</td>
</tr>
</tbody>
</table>
compliance with or are intolerant to daily drug treatment. Side effects are transient and include blepharoptosis, diplopia, and injection-site weakness. Nonpharmacologic preventive strategies include relaxation training, biofeedback, and cognitive-behavioral therapy.\textsuperscript{35}

**Cluster Headache**

Cluster headache (CH) is the most painful of the primary headaches.\textsuperscript{36,37} It is characterized by episodes of severe, strictly unilateral headache associated with symptoms and signs of cranial parasympathetic hyperactivity and sympathetic dysfunction.

**Epidemiology**

CH is less common than migraine; the estimated prevalence is 0.4%.\textsuperscript{36} In contrast to migraine, it is more common in men than in women; the male to female gender ratio is approximately 5:1. Recent studies, however, suggest that this ratio is decreasing.\textsuperscript{38} The disease onset is usually in the third decade of life.

**Clinical Features**

The hallmark of CH is its periodicity. In most patients, attacks occur during specific times called cluster periods. These periods last for several weeks to months and are separated by remission periods that may last several weeks to many years.\textsuperscript{36} In many patients, cluster periods occur with striking regularity at the same time of the year. A minority (10%) of patients have only short remission periods (<1 month) or none at all. They are classified as having chronic (as opposed to episodic) CH.

During a cluster period, the attack frequency ranges from 1 every other day to 8 per day. A CH attack is characterized by a rapidly developing, severe, unilateral pain in the periorbital, temporal, or frontal area. The pain usually lasts 45 to 90 minutes and is associated with symptoms and signs of autonomic dysfunction (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, miosis, or ptosis) ipsilateral to the pain. Unlike the migraine patient, the CH patient is restless during an attack. Attacks may occur at any time during the day and many times at the same hour for the individual patient. In patients with episodic, but not chronic, CH, a common time for an attack is at night, coinciding with the first rapid eye movement sleep period.\textsuperscript{39} The IHS diagnostic criteria for CH are listed in Appendix 3.

**Pathophysiology**

CH was previously thought to be a “vascular headache.” More recent studies, however, show evidence of activation of the trigeminovascular system in CH.\textsuperscript{36} The striking periodicity of CH attacks has led to the theory of a central generator for CH. Recent evidence for this theory comes from positron emission tomography studies that show activation of the ipsilateral posterior ventral hypothalamus during CH attack.\textsuperscript{40}

**Management**

The management of CH consists of patient support and education, treatment of the acute attack, and preventive treatment (Table 4).\textsuperscript{36} Treatment options for the acute attack include inhalation of 100% oxygen, sumatriptan injections, and intrave-
nous DHE. Oxygen should be administered at a high flow rate (≥7 L/min) via a nonrebreathing mask for at least 15 minutes. This treatment is very effective; however, it is not always readily available. Subcutaneous sumatriptan is very effective for the treatment of acute CH attack; it has a response rate of over 70%. DHE is best administered intravenously for prompt relief of CH attack. Because this treatment cannot be performed at home, this option is less attractive than sumatriptan. Intranasal lidocaine is less effective than the previously mentioned treatments for acute CH but may be used as an adjunctive therapy in severe cases.

The preventive treatment of CH is divided into transitional prophylaxis and maintenance prophylaxis. Transitional prophylaxis is administered at the beginning of a cluster period in an attempt to prevent attacks until the maintenance preventive drug is effective. This outcome is achieved either by an oral corticosteroid (e.g., prednisone 60 mg/day for 3 days, followed by a gradual taper-off over 3 weeks) or by oral ergotamine 2 mg/day for 2 to 3 weeks. Maintenance prophylaxis is administered throughout the time of the cluster period. It is started in parallel with the transitional prophylaxis and continued thereafter alone. The drug of choice for maintenance prophylaxis is verapamil. High doses (up to 720 mg/day) are occasionally needed. Other treatment options include lithium carbonate, methysergide, valproic acid, topiramate, and melatonin. A minority of patients who are refractory to medical treatment may need ablative surgical procedures directed at the trigeminal nerve root or ganglion. A novel approach to the preventive treatment of CH is deep-brain stimulation of the posterior-inferior hypothalamus, the area shown to be activated during CH attacks. Results with this treatment are encouraging, but the number of treated patients is still small.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Drug</th>
<th>Route</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Oxygen 100%</td>
<td>Nonrebreathing mask</td>
<td>&gt;7 L/min for 15 min</td>
<td>Effective but not always readily available</td>
</tr>
<tr>
<td></td>
<td>Sumatriptan</td>
<td>Injectable (s.c.)</td>
<td>6 mg</td>
<td>Very effective</td>
</tr>
<tr>
<td></td>
<td>Dihydroergotamine</td>
<td>Injectable (i.v.)</td>
<td>1 mg</td>
<td>Not available at home</td>
</tr>
<tr>
<td>Preventive transitional</td>
<td>Prednisone</td>
<td>Oral</td>
<td>60 mg/day, taper gradually</td>
<td>Multiple potential AEs</td>
</tr>
<tr>
<td>Preventive maintenance</td>
<td>Ergotamine</td>
<td>Oral</td>
<td>2 mg/day</td>
<td>Cannot be given with triptans</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>Oral</td>
<td>240–720 mg/day</td>
<td>Monitor ECG</td>
</tr>
<tr>
<td></td>
<td>Lithium carbonate</td>
<td>Oral</td>
<td>600–900 mg/day</td>
<td>Monitor drug levels and kidney and thyroid functions</td>
</tr>
<tr>
<td></td>
<td>Methysergide</td>
<td>Oral</td>
<td>2–12 mg/day</td>
<td>Cannot be used with ergots</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
<td>Oral</td>
<td>500–2,000 mg/day</td>
<td>Monitor drug blood levels, LFTs and CBC</td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td>Oral</td>
<td>50–125 mg/day</td>
<td>Potential cognitive AEs and renal calculi</td>
</tr>
<tr>
<td></td>
<td>Melatonin</td>
<td>Oral</td>
<td>10 mg</td>
<td>Few AEs</td>
</tr>
</tbody>
</table>

Abbreviation: AEs, adverse events.

**Tension-Type Headache**

TTH is the most common headache. TTH is divided into episodic (<15 days/month) and chronic (≥15 days/month) subtypes. In most patients, chronic TTH evolves from episodic TTH.

**Epidemiology**

In a Danish population-based study, the lifetime prevalence of TTH was as high as 78%. Many of these patients had short duration or infrequent headaches. Still, 10% had headache weekly and 2% to 3% had headache daily. In other studies, the prevalence of episodic TTH was 32% to 35% and that of chronic (daily or near daily) TTH was 2.2% to 2.7%. The prevalence of TTH peaks between the ages of 30 and 39 years and, in contrast to migraine, TTH has only a slight female preponderance (male to female ratio of 4:5).

**Clinical Features**

The pain of TTH is typically bilateral, pressing, or tightening in quality and of mild to moderate intensity. It is not worsened by routine physical activity. Nausea does not occur, but photophobia or phonophobia may be present. According to IHS criteria, the pain of TTH lasts 30 minutes to 7 days. Other symptoms include fatigue, sleep disturbances, and lightheadedness. Aura does not occur. The neurologic and physical examination is normal except for pericranial muscle tenderness in some patients. The IHS diagnostic criteria for chronic TTH are listed in Appendix 4 (for diagnostic criteria of episodic TTH, see reference 6).

Because both migraine and TTH are very common disorders, they may coexist in an individual patient. As with all primary headaches, the diagnosis of TTH should be made only when secondary
causes of headache are not suggested by history or by physical examination. When a secondary headache is suggested, it should be excluded by the appropriate investigation (see Table 1).

Pathophysiology

Little is known about the pathophysiology of TTH. It is likely that both peripheral and central mechanisms play a role. The increased pericranial muscle tenderness found in many patients with TTH probably represents activation of peripheral nociceptors. Myofascial tenderness has been shown to precede the headache and is, therefore, likely to be involved in the pathogenesis. Changes in central processing of sensory information are also likely to play a role. This hypothesis is supported by the observation of decreased threshold to pain and to thermal and electric stimuli in chronic TTH.

Patients with chronic TTH have a higher prevalence of depression and anxiety compared with the general population, but this condition may be secondary to the pain rather than the cause of it.

Management

Because the basic mechanisms are poorly understood, the treatment of TTH is still not satisfactory. Management includes pharmacologic and nonpharmacologic treatments. For mild to moderate acute episodes, acetaminophen (1,000 mg) and aspirin (500 to 1,000 mg) are effective. NSAIDs were also shown to be effective in relieving the pain of acute TTH and are recommended for moderate to severe pain. Recommended drugs and doses include ibuprofen, 200 to 400 mg; naproxen, 375 to 550 mg; and diclofenac potassium, 12.5 to 25 mg. Caffeine-containing combination analgesics may be superior to simple analgesics in relieving TTH pain. To avoid medication-overuse headache (MOH), the patient should be advised not to overuse acute medications.

The tricyclic antidepressant amitriptyline is the most widely used drug in the preventive treatment of TTH. Its efficacy has been shown in several well-designed trials, and it is considered the drug of choice for this indication. The recommended daily dose is 10 to 75 mg. The efficacy of the selective serotonin reuptake inhibitors in chronic TTH prevention is not well established. Other potential treatments that need further study include the muscle relaxant tizanidine and botulinum neurotoxin.

Nonpharmacologic treatments for TTH include relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy. Well-established evidence supports the efficacy of these treatment modalities in TTH. Used either as an adjunct or an alternative to pharmacologic treatment, they reduce headache frequency, affective distress, and headache-related disability. These treatments are particularly appealing to patients who do not tolerate, do not respond to, or have a contraindication to drug treatment.

Medication-Overuse Headache

Patients who suffer from frequent headaches often overuse pain medications. An estimated 4% of the population suffer from chronic daily headache, defined as headache occurring 15 or more days a month, and medication overuse is by far the most common cause of this type of headache.

The concept that pain medication overuse may cause or perpetuate chronic daily headache in headache-prone patients has long been recognized. This type of headache has been previously termed “rebound headache” or “drug-induced headache.” The IHS defined this headache as MOH and listed separate diagnostic criteria for headaches caused by each of the major overused drugs (ergotamine, triptans, simple analgesics, opioids, and combination analgesics).

Recently, Zwart et al. showed in a prospective study of 32,067 patients that analgesic overuse is a predictor of chronic pain and that the risk was highest for patients with migraine.

Making the diagnosis of MOH is extremely important because the primary measure in alleviating this type of headache is to stop the intake of the offending drug. Moreover, acute pain-medications overuse renders migraine-preventive drugs less effective or completely ineffective.

For a drug to be recognized as a cause of headache, several factors must be considered: treatment frequency, duration, regularity, and dose. These parameters are different for the various drugs, depending on their propensity to cause headache. In general, the treatment frequency required by the IHS is 10 to 15 days a month, the drug should be taken on a regular basis, and the duration of treatment should be 3 months or more.

Other important criteria in defining a headache as MOH are (1) the headache has developed or markedly worsened during treatment with the drug and (2) the headache resolves or improves within 2 months of discontinuation of the drug. Limmroth et al. calculated the mean critical treatment duration until the onset of MOH, the mean critical monthly intake frequency, and the mean critical monthly dosage in 98 patients with MOH. They found that the mean critical treatment duration until the onset of MOH was 1.7, 2.7, and 4.8 years for triptans,
ergots, and analgesics, respectively. The mean critical monthly intake frequency was lowest for triptans (18 doses/month) and highest for analgesics (114 doses/month). They concluded that triptan overuse leads to MOH faster and with lower doses compared with ergots and analgesics.

Clinical Features

According to IHS definition, MOH should be present in more than 15 days a month. Its characteristics vary depending on the type of offending drug. It can be bilateral and pressing/tightening in quality when simple analgesics or ergotamine are used, or it can be unilateral and pulsating when a triptan is used. Its intensity varies from mild to severe. Migraine-associated symptoms may or may not be present.

The mechanisms by which analgesics or antimigraine drugs cause or exacerbate headache are incompletely understood. Continued intake of acute medications may result in resetting the pain control mechanisms in susceptible individuals, perhaps by enhancing central sensitization or by blocking adaptive antinociceptive changes.

Management

The treatment of MOH consists of discontinuation of the offending drug and then starting the patient on a new pharmacologic regimen without exceeding the limits of drug dose and frequency. Bigal et al. studied 456 migraine patients who overused acute medications. At 1-year follow-up, those patients who stopped overusing acute medications had a 74% reduction in headache frequency compared with 17% for those who continued overusing acute medications. A significantly greater reduction also occurred in headache duration and headache intensity in patients who stopped overusing medications compared with those who did not.

During the washout period from the overused drug, headache may temporarily get worse before it gets better. This feature should be explained to the patient. Other withdrawal symptoms, such as nausea, vomiting, agitation, sleep disturbances, and, rarely, seizures, may also occur. This withdrawal period, which lasts 3 to 6 weeks, is usually followed by a significant headache improvement.

Detoxification may be done either in an outpatient or an inpatient setting. Two outpatient strategies are used for this purpose. One strategy is to taper-off the offending drug gradually over 2 to 3 weeks and replace it temporarily with a long-acting NSAID (e.g., naproxen sodium) while an effective longer-term preventive therapy is established. The second strategy is to discontinue the offending drug abruptly and replace it temporarily with an NSAID, prednisone, DHE, or a combination of NSAID and tizanidine. An example of such a bridging treatment is naproxen sodium 550 mg twice a day for a week which is tapered gradually. When butalbital-containing drugs are discontinued abruptly, low-dose phenobarbital (tapered from 60 to 15 mg/day for 1 week) is administered to prevent withdrawal symptoms. During detoxification, the patient should be administered a rescue medication for acute headache. Drugs used for this purpose are neuroleptics, antinausea drugs, or opioids (unless the patient is in the process of detoxification from them). When outpatient detoxification fails or when significant medical or psychiatric comorbidity is present, inpatient strategies are used. The most widely used drug for this purpose is repetitive intravenous DHE with metoclopramide. Alternative treatments used intravenously for patients who have contraindication to or cannot tolerate DHE include chlorpromazine, methylprednisolone, valproic acid, and lidocaine.

An important part of management is patient education. The patient should be encouraged to limit acute medication use to the recommended frequency; that is, for simple analgesics, less than 15 days/month and for ergotamine, triptans, opioids, and combination analgesics, less than 10 days/month.

Secondary Headache

Of the many types of secondary headache, cervicogenic headache (CEH) is of particular interest to the anesthesiologist.

Cervicogenic Headache

CEH is a term introduced by Sjaastad in 1983 and is defined as pain perceived in the head but with a source that lies in the neck. The IHS has accepted CEH as a type of secondary headache and included it in the International Classification of Headache Disorders. In the IHS criteria for CEH diagnosis, emphasis is placed on clinical and laboratory evidence for a source of pain in the neck and on abolition of headache after a diagnostic block of the presumed source of pain. The IHS criteria do not provide defining criteria for the features of CEH pain or its associated symptoms (Appendix 5). The criteria of The Cervicogenic Headache International Study Group also include head pain characteristics.

The anatomic basis for the concept of headache resulting from cervical pathology lies in neural convergence. Neurons in the dorsal horn of the upper 3 cervical segments of the spinal cord receive over-
lapping input from both cervical and trigeminal afferents.\(^6\) Thus, any structure innervated by neurons whose central processes reach the upper 3 cervical segments may be a source of headache. Clinical studies support this concept. In some patients with headache, the pain could be reproduced by stimulation of the C2-C3 intervertebral disc. In other patients, complete headache relief was achieved by anesthetic block of the lateral atlanto-axial joint.\(^6\)

**Epidemiology and Clinical Features**

The prevalence of CEH is estimated at 0.4% to 4.6%. CEH is more common in women compared with men (female to male ratio, 4:1), and the mean age is 42.9 years.\(^6\)

The hallmark of CEH is clinical evidence for neck involvement, which includes precipitation of pain by neck movement or external pressure on the neck or occiput; restricted neck range of motion; and ipsilateral neck, shoulder, or arm pain.\(^6\) The pain is typically unilateral without side shifts; it starts in the neck and spreads anteriorly to the ipsilateral orbital, frontal, and temporal areas. It is initially episodic but often becomes continuous and fluctuating. Pain intensity is usually moderate, and it is non throbbing in character. Nausea, vomiting, and photo/phonophobia may occur but are less frequent and less intense than in migraine. A history of head or neck trauma is common.

A positive response to anesthetic blocks is one of the diagnostic criteria to CEH. These blocks include greater occipital nerve (GON) block, lesser occipital nerve block, and C2-C3 facet joint blocks. The block should result in elimination or near-elimination of the pain, and the analgesic effect should be shown in nonanesthetized areas. Radiologic findings in CEH are usually nonspecific but may help in identifying a cervical pathology that is a potential source of pain (e.g., congenital abnormalities, bone tumors, rheumatoid arthritis, or ankylosing spondylitis). Cervical spine osteoarthritis has not been shown to be a cause of CEH.

**Management**

The approach to a patient with CEH includes a detailed history, physical and neurologic examination with an emphasis on signs of cervical pathology (local tenderness, limited range of motion and arm weakness, and paresthesias or hypoesthesia), and, in some cases, imaging studies to exclude lesions that would require specific therapy (e.g., tumor or rheumatoid arthritis). Anesthetic block of a cervical nerve or joint is recommended to support the diagnosis.

The management of CEH includes both pharmacologic and nonpharmacologic components.\(^7\) Pharmacologic treatment has not been evaluated in controlled trials, and, therefore, no evidence-based recommendations can be made. Medications are usually not significantly effective as the sole therapy and are used as an adjunct to physical and behavioral therapy. Drugs that have been used include the tricyclic antidepressants (amitriptyline and nortriptyline), anticonvulsants (valproic acid, carbamazepine, gabapentin, and topiramate), muscle relaxants (tizanidine and baclofen), and NSAIDs. Drugs from the last 2 groups can be used either for prevention or on an acute basis for pain exacerbation. The other drugs are used for prophylaxis. Cervical epidural injections of corticosteroids may be beneficial in some patients. Botulinum toxin, injected into cervical muscles, can be used but its efficacy has not been proved.

Physical therapy, an important part of CEH therapy, includes muscle stretching and cervical manipulation performed in a gradually progressing manner. Other treatments include biofeedback, relaxation techniques, and cognitive-behavioral therapy.

Nerve and anesthetic joint block are important in CEH, both as a diagnostic and a therapeutic tool.\(^7\) Possible sites include the GON, lesser occipital nerve, C2-C3 cervical spinal nerves, and upper cervical zygapophyseal joints. Anthony found that injection of depot methylprednisolone into the area of the GON and lesser occipital nerve resulted in complete headache relief in 169 of 180 patients with CEH. The mean duration of relief was 23.5 days. When an anesthetic block is effective, longer-acting neurolytic procedures (e.g., pulsed radiofrequency thermal neurolysis) may be considered. Surgical procedures (neurectomy, dorsal rhizotomy, and microvascular decompression of nerve roots) are reserved for patients with clear evidence of a correctable cervical pathology or who are refractory to all other treatment modalities. Nerve stimulation is increasingly used now for these purposes and may gradually replace the ablative procedures in the appropriate cases.

**Nerve Blocks for the Treatment of Headaches**

Peripheral nerve blocks have been used to treat headaches for decades.\(^7\) The most widely used procedure for this purpose is GON block. Other nerve blocks (supraorbital and lesser occipital) are occasionally used.

The GON is composed of sensory fibers that originate in the C2 and, to a lesser extent, C3 segments.
of the spinal cord. Its cutaneous sensory distribution is over the posterior part of the head and spreads anteriorly to the vertex. It becomes superficial 2.5 to 5 cm inferolaterally to the occipital protuberance. No standard protocol exists for GON block procedure. A 23-gauge needle is inserted 3.5 cm inferolaterally to the occipital protuberance, and the nerve is usually infiltrated with a local anesthetic (e.g., 1% to 2% lidocaine or 0.5% bupivacaine). At times, a corticosteroid (e.g., triamcinolone) is added.

The rationale for GON block comes from the convergence of sensory input to trigeminal nucleus caudalis neurons from both cervical and trigeminal fibers. This procedure may result in alleviation of pain even outside of the GON territory when the nerve is blocked. Supraorbital nerve block is performed by inserting the needle at the supraorbital notch, which is the point of emergence of this nerve to the epidermal tissue, and infiltrating the area with small volumes of the drugs mentioned previously.

Despite their widespread clinical use, the number of studies performed to assess the efficacy of nerve blocks for headache treatment is small. Caputi and Firetto found that 85% of 27 migraine patients had a beneficial response to repeated anesthetic blocks. They used 0.5 to 1 mL of bupivacaine 0.5% on alternate days for a maximum of 10 blocks. The therapeutic effect was maintained for the entire period of observation (6 months), and the treatment was very well tolerated. In another study, the diagnostic value and effects of GON and supraorbital nerve blocks in migraine patients, TTH patients, and CEH patients were examined in 52 subjects. A single injection of 0.5 to 1.5 mL of lidocaine 2% with adrenaline 12.5 µg/mL was used. GON block resulted in pain reduction of 54.5%, 14%, and 6% in the CEH, TTH, and migraine groups, respectively. Supraorbital nerve block resulted in corresponding response rates of 28%, 30%, and 16%. Gawel and Rothbart examined the effect of GON block combined with corticosteroid refractory patients with migraine and posttraumatic headache. All patients had been refractory to pharmacologic treatment. Seventy-two percent of the posttraumatic headache patients and 54% of the migraine patients reported being “significantly better” up to 6 months after the block. Peres et al. found that 64% of CEH patients who were treated with GON block combined with a corticosteroid had good or moderate response. Duration, frequency, and intensity of attacks were significantly lower 1 week after treatment compared with these parameters before treatment. The procedure was very well tolerated.

Peripheral nerve blocks are safe and easy-to-perform procedures that are beneficial for some patients with headaches. They appear to be most effective for CEH. More studies, however, are needed to evaluate their efficacy in primary headaches and to identify the patients who are most likely to benefit from this treatment.

**Summary**

The successful management of headache depends on arriving at a specific diagnosis and not treating the headache as a symptom. Clinicians must differentiate between primary and secondary headaches and recognize symptoms and signs that raise suspicion of life-threatening diseases. In the management of primary headaches, emphasis should be put on lifestyle alterations and avoidance of triggers to reduce attack frequency and severity. Acute pharmacologic treatments should be used at the appropriate dosages and time intervals to avoid MOH. Using this approach, most headache patients can achieve significant symptomatic relief.

**Appendix 1. IHS Diagnostic Criteria for Migraine Without Aura**

### 1.1 Migraine Without Aura

A. At least 5 attacks fulfilling criteria B to D
B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following conditions is present:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not attributed to another disorder

**Appendix 2. IHS Diagnostic Criteria for Migraine with Aura**

### 1.2 Migraine with Aura

A. At least 2 attacks fulfilling criterion B
B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1 to 1.2.6.
C. Not attributed to another disorder

### 1.2.1 Typical Aura with Migraine Headache

A. At least 2 attacks fulfilling criteria B to D
B. Aura consisting of at least one of the following but with no motor weakness:
   1. fully reversible visual symptoms that include positive features (e.g., flickering lights, spots, or lines) and/or negative features (e.g., loss of vision)
   2. fully reversible sensory symptoms that include positive features (e.g., pins and needles) and/or negative features (e.g., numbness)
   3. fully reversible dysphasic speech disturbance
C. At least two of the following conditions are present:
   1. homonymous visual symptoms and/or unilateral sensory symptoms
   2. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
   3. each symptom lasts ≥5 and ≤60 minutes
D. Headache fulfilling criteria B to D for 1.1 Migraine Without Aura begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder

Appendix 3. IHS Diagnostic Criteria for Cluster Headache

3.1 Cluster Headache
A. At least 5 attacks fulfilling criteria B to D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain that lasts 15 to 180 minutes if untreated
C. Headache is accompanied by at least one of the following conditions:
   1. ipsilateral conjunctival injection and/or lacrimation
   2. ipsilateral nasal congestion and/or rhinorrhea
   3. ipsilateral eyelid oedema
   4. ipsilateral forehead and facial sweating
   5. ipsilateral miosis and/or ptosis
   6. a sense of restlessness or agitation
D. Attacks have a frequency from 1 every other day to 8 per day
E. Not attributed to another disorder

Appendix 4. IHS Diagnostic Criteria for Chronic Tension-type Headache

2.3 Chronic Tension-type Headache
A. Headache that occurs on ≥15 days per month on average for ≥3 months (≥180 days per year) and fulfilling criteria B to D
B. Headache lasts hours or may be continuous
C. Headache has at least two of the following characteristics:
   1. bilateral location
   2. pressing/tightening (nonpulsating) quality
   3. mild or moderate intensity
   4. not aggravated by routine physical activity such as walking or climbing stairs
D. Headache has both of the following characteristics:
   1. no more than one of photophobia, phonophobia, or mild nausea
   2. neither moderate or severe nausea nor vomiting
E. Not attributed to another disorder

Appendix 5. IHS Diagnostic Criteria for Cervicogenic Headache

11.2.1 Cervicogenic Headache
A. Pain, referred from a source in the neck and perceived in one or more regions of the head and/or face, fulfilling criteria C and D
B. Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck known to be or generally accepted as a valid cause of headache
C. Evidence that the pain can be attributed to the neck disorder or lesion based on at least one of the following conditions:
   1. demonstration of clinical signs that implicate a source of pain in the neck
   2. abolition of headache after diagnostic block of a cervical structure or its nerve supply by use of a placebo or other adequate controls
D. Pain resolves within 3 months after successful treatment of the causative disorder or lesion

Appendix 6. The Cervicogenic Headache International Study Group Diagnostic Criteria for Cervicogenic Headache

I. Symptoms and signs of neck involvement
A. Precipitation of head pain similar to the usually occurring one
   1. by neck movement and/or sustained awkward head positioning, and/or
   2. by external pressure over the upper cervical or occipital region on the symptomatic side
B. Restriction of the range of motion in the neck
C. Ipsilateral neck, shoulder, or arm pain of a rather vague nonradicular nature or occasionally arm pain of a radicular nature
II. Confirmatory evidence by diagnostic anesthetic blockades

III. Unilaterality of the head pain, without side shift

References


