VIII HEADACHE

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Headaches are a near-universal experience, with a 1-year prevalence of 90% and a lifetime prevalence of 99%. Each year in the United States, 9% of adults see physicians for headaches and 83% self-medicate. Headaches are one of the most common complaints of patients seen by primary care physicians and account for 20% of outpatient visits to neurologists.

The differential diagnosis of headaches is one of the longest in medicine, with over 300 different types and causes. Although most headaches are of benign (and still poorly understood) origin, some headaches can have serious and even potentially life-threatening causes. Thus, it is critical for the physician to diagnose headaches as precisely as possible.

The International Headache Society (IHS) criteria, which were introduced in 1988 and updated in 2004 (*International Classification of Headache Disorders Second Edition* [ICHD-2]),[1] are the worldwide standard for headache classification. IHS criteria categorize headaches as primary or secondary. Primary headaches—those with no other underlying cause—account for 90% of headaches. This category includes migraine, tension, cluster, and miscellaneous headaches, such as primary exertional headaches. There are a large number of secondary headaches, which are classified according to their causes [*see Table 1*].

A careful history, examination, and, in some cases, diagnostic testing will usually provide the accurate diagnosis of a headache, although a precise diagnosis is not always possible. For example, some benign headaches have both migraine and tension-type features. Chronic daily headaches (CDHs) may also be difficult to classify.

This chapter reviews pain-sensitive structures in the head, the history and examination in patients with headache, and many of the primary and secondary headaches. The interested reader may wish to refer to a headache textbook for more comprehensive information (see the reference list at the end of the chapter).[2–4]

Table 1 Major Categories of Headache Disorders[1]

Primary Headaches
- Migraine
- Tension-type headache
- Cluster headache and chronic paroxysmal hemicrania
- Miscellaneous headaches unassociated with structural lesion: idiopathic stabbing, external compression, cold stimulus, benign cough, benign exertional, associated with sexual activity

Secondary Headaches
- Headache associated with head trauma
- Headache associated with vascular disorder: acute ischemic cerebrovascular disorder, intracranial, hematoma, subarachnoid hemorrhage, unruptured vascular malformation, arteritis, carotid or vertebral artery pain, venous thrombosis, arterial hypertension, associated with other vascular disorder
- Headache associated with nonvascular intracranial disorder: high and low cerebrospinal fluid pressure, intracranial infection, intracranial sarcoidosis and other noninfectious inflammatory disease, related to intrathecal injections, intracranial neoplasm, associated with other intracranial disorder
- Headache associated with substances or their withdrawal: acute and chronic substance use or exposure, withdrawal after acute and chronic use, associated with substances with uncertain mechanism
- Headache associated with noncephalic infection: viral infection, bacterial infection, other infection
- Headache associated with metabolic disorder: hypoxia, hypercapnia, mixed hypoxia and hypercapnia, hypoglycemia, dialysis, other metabolic abnormality
- Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
- Cranial neuralgias, nerve trunk pain, and deafferentation pain
- Persistent pain of cranial nerve origin, trigeminal neuralgia, glossopharyngeal neuralgia, nervus intermedius neuralgia, superior laryngeal neuralgia, occipital neuralgia, central causes of head and facial pain other than tic douloureux

Pain-Sensitive Structures

Similar headaches can have different causes because there are a limited number of pain-sensitive structures in the head. Although all pain is registered in the brain, the brain parenchyma itself is not pain sensitive. The arachnoid, ependyma, and dura (except portions near blood vessels) are also insensitive to pain. The following are sensitive to pain: cranial nerves V, VII, IX, and X; the circle of Willis and proximal continuations; meningeal arteries; large veins in the brain and dura; and structures external to the skull (including scalp and neck muscles, cutaneous nerves and skin, the mucosa of paranasal sinuses, teeth, cervical nerves and roots, and the external carotid arteries and branches).

Headache pain may be felt at its source (e.g., cheek or forehead pain from maxillary or frontal sinusitis) or be referred from another site. For example, supratentorial structures are innervated by the ophthalmic division of the trigeminal nerve, whereas infratentorial and posterior fossa structures are supplied by C_2 and C_3. Thus, a cerebellar hemisphere lesion generally refers pain posteriorly and an occipital lobe lesion refers pain anteriorly. The caudal nucleus of the trigeminal nerve, which is located from the midpons to the third cervical segment, receives pain messages from the upper cervical roots and the trigeminal nerve. Thus, pain from the upper cervical spine or posterior fossa can also be referred to the front of the head.

Headache History

The headache history is usually essential to establishing the diagnosis.[5] Key elements of the history include not only the features of the headache but also the patient's own diagnosis, past history, psychosocial history, and family history

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[*see Table 2*]. In gathering the key elements, both open-ended ("What are your headaches like?") and closed-ended ("Do you have nausea with the headache?") questions are necessary [*see Table 3*]. Often it is helpful to ask about a history of mild headaches and bad headaches. Some patients are not able to clearly remember or articulate features of the headache ("It's just a headache, doctor."). With patients who have chronic headaches, it may be necessary to provide a headache diary or have them record features of their headaches and then return for a later appointment.

Physical Examination

A directed physical examination may be informative. Examples of significant abnormal findings include hypertension, fever, cervical lymphadenopathy in infectious mononucleosis, cervical trigger points in tension-type headache, and maxillary sinus tenderness in sinusitis. Every patient seen for headaches should have, at the least, a screening neurologic examination; this takes only a few minutes to perform. Although the results of this examination are usually normal, the examination can point to significant underlying disease by revealing abnormalities such as papilledema, a mild lateral rectus paresis, unequal pupils, a mild hemiparesis, or a Babinski sign.

Clinical Classification

In most cases, the findings on the history and physical examination will point the clinician toward the diagnosis of primary headache. The three most common primary headaches are migraine, episodic tension type, and cluster headache [*see Table 4*]. Much less often, the clinical features suggest secondary headache [*see Table 5*].

Diagnostic Testing

The vast majority of headaches require no diagnostic testing; they can be diagnosed accurately on the basis of a detailed history and a physical examination.[6,7] For example, patients who meet IHS criteria for migraine rarely have abnormal neuroimaging findings to explain the headache. In patients with headache of any type and a normal neurologic examination, the yield of a computed tomographic (CT) or magnetic resonance imaging (MRI) scan is only about 2% or less. However, certain clinical features, patient

Table 2 Key Elements of the Headache History

Element	*Examples*
Temporal profile	
Age at onset	Migraine, usually ≤40 yr; temporal arteritis after age 50
Time to maximum intensity	Gradual in migraine; immediate in thunderclap headache
Frequency	Up to 8 per day with cluster; daily or only a few in a lifetime with migraine
Time of day	Cluster or migraine may be present on awakening; tension in the afternoon
Duration	Migraine, 4–72 hr; cluster, 15 min to 3 hr
Recurrence	Migraines recur about 30% of the time after relief with a triptan
Headache features	
Location	Cluster always unilateral; migraine unilateral or bilateral
Quality of pain	Migraine, throbbing; tension, pressure; cluster, boring
Severity of pain	Most severe headaches are migraine or cluster
Associated symptoms and signs	
Before headache	Migraine aura or prodrome, fever before meningitis
During headache	Nausea/vomiting in migraine, eye redness and tearing in cluster
After headache	Mental dullness after migraine
Aggravating or precipitating factors	
Trauma	Migraine, subdural hematoma
Medical conditions	Obesity in pseudotumor cerebri
Triggers	Present in 85% of migraineurs; stress in tension type
Trigger zones	Trigeminal neuralgia
Activity	Exertional headache, primary orgasmic cephalalgia
Pharmacologic	Oral contraceptives, medication overuse headaches
Relieving factors	
Nonpharmacologic	Sleep for migraine, relaxation for tension type
Pharmacologic	Prescription and over-the-counter drugs, herbs, and vitamins
Previous evaluation and treatment	Obtain medical records as appropriate
Psychosocial history	
Substance use	Medication overuse headaches from too much caffeine
Occupational and personal life	Stress, occupational toxin exposures
Psychological history	Depression, anxiety
Sleep history	Deprivation causing headaches; sleep apnea
Impact of headache	Missed school, work, family activities
Patient's own diagnosis	May incorrectly self-diagnose as brain tumor, sinus headache, aneurysm
Family history	70% of migraineurs have a first-degree relative with migraine
Complete medical and surgical history	Asthma as a contraindication to beta blockers for migraine

Table 3 Helpful Questions to Ask for the Headache History[5]

Do you have different types of headaches or just one?
Where does the headache hurt?
When did you first start having these headaches?
What were you doing when the headache started?
How long before the headache reaches maximal intensity?
How long does the headache last?
Does the headache recur? If so, how often?
What is the pain like? Is it a pressure, throbbing, pounding, aching, or stabbing?
Is the pain mild, moderate, or severe?
On a scale of 1 to 10, with 10 the worst and 1 the least, how would you rate the headache?
Do you have trouble with your vision before or during the headache?
Do you have other symptoms (e.g., nausea, vomiting, light sensitivity, noise sensitivity, discomfort with eye movement) with the headache?
During a headache, would you prefer to be in bright sunlight or in a dark room?
During a headache, would you prefer to be in a room with loud music or in a quiet room?
Are signs present (e.g., fever, ptosis, miosis)?
Do you have triggers of your headaches (e.g., menses, stress, foods, beverages, lack of sleep, oversleeping, strong odors, trigger zones)?
What makes the headache worse (e.g., coughing, bending over, physical activity)?
What makes the headache better (e.g., sleep, lying down in a quiet room)?
Do your headaches have any impact on your life?
Do you take over-the-counter medications, vitamins, or herbs for your headaches? If so, how much and how often?
Do you drink caffeinated beverages? If so, what types and how many?
What prescription drugs have you tried, what doses, for what duration, and with what effect?
What doctors have you seen in the past for your headaches?
What other treatments have you tried and with what success (e.g., acupuncture, chiropractic, biofeedback, stress management, massage)?
Have you been under much stress lately?
Have you been depressed?
Do you have any parents or siblings with a history of migraines or bad headaches?

Table 4 Features of Selected Primary Headaches[5]

Feature	*Migraine*	*Episodic Tension Type*	*Episodic Cluster*
Female-to-male ratio	1:1 before puberty, 3:1 after	5:4	1:4
Family history	First-degree relatives affected in 80% of cases	Frequent	Rare
Typical age at onset (yr)	92% before age 40, 2% after age 50	20–40	20–40
Visual aura	20% of cases	No	Occasional
Location	Unilateral 60%, bilateral 40%	Bilateral > unilateral; anywhere on the head, posterior neck, face	Unilateral, especially orbital, periorbital, frontotemporal
Quality	Pulsatile or throbbing in 85%	Pressure, aching, tight, squeezing	Boring, burning, or stabbing
Severity	Mild to severe (moderate to severe [untreated] in 80%)	Mild to moderate	Severe
Triggers	Present in 85%; numerous	Stress, lack of sleep	Alcohol, nitrates
Duration	4–72 hr; duration > 24 hr (untreated) in 62%; may be < 1 hr in children	Hours to days	15 min to 3 hr
Frequency	Rare to frequent	Rare to frequent	1–8 a day during clusters, usually 1–3
Periodicity	Menstrual migraine	No	Yes; average bout, 4–12 wk; average 1 or 2 bouts yearly
Associated features	Nausea in 80%, vomiting in 30%, light and noise sensitivity in 80%	Occasional nausea	Ipsilateral conjunctival injection, tearing, and nasal congestion or drainage; ptosis and miosis in 30%
Behavior during headache	Still, quiet, tries to sleep	No change	Often paces, agitated
Awakens patient from sleep	Can occur	Rare	Frequently

Table 5 Features of Selected Secondary Headaches[5]

Headache Type	*Epidemiology*	*Age at Onset*	*Location*	*Quality and Severity*	*Frequency*	*Associated Features*	*Comments*
Trigeminal neuralgia	4.3/100,000/yr; male-to-female ratio, 1:1.5	Usually > 40 yr; if < 40 yr, consider multiple sclerosis	Unilateral, 96%; second or third trigeminal division greater than first	Stabbing; electrical bursts; burning; lasts few seconds to < 2 min	Few to many a day	Trigger zone present in > 90% of cases	Usually due to vascular compression of CN V; scan needed to exclude occasional tumor
Brain tumor	Persons/yr; 41,000 primary, 170,000 metastatic	Any age	Often bifrontal, unilateral or bilateral; any location	Can be pressure or throbbing, mild to severe	Occasional to daily; usually progressive	Papilledema in 40%; at time of diagnosis, headache present in 30–70%	Primary tumors in adults; lung, 64%; breast, 14%; unknown, 8%; melanoma, 4%; colorectal, 3%; hypernephroma, 2%
Idiopathic intracranial hypertension (pseudotumor cerebri)	1–2/100,000/yr; 90% are female; 90% are obese	Mean of 30 yr	Often bifronto-temporal but can occur in other locations and unilaterally	Pulsatile; moderate to severe	Daily	Papilledema in 95%; transient visual obscurations in 70%; intracranial noises in 60%; CN VI palsy in 20%	MRI preferred to better exclude cortical venous thrombosis and posterior fossa lesions
Subarachnoid hemorrhage	30,000/yr caused by saccular aneurysm	Mean of 50 yr	Usually bilateral; any location	Usually severe but can be mild and gradually increasing	Paroxysmal	Often with nausea, vomiting, stiff neck, focal findings, syncope; stiff neck absent in 36%	CT scan abnormal on first day in 95%; third day, 74%; 1 wk, 50%; lumbar puncture may be essential for diagnosis
Temporal arteritis	In age > 50 yr, annual incidence of 18/100,000; female-to-male ratio, 3:1	Rare before 50 yr; mean age of 70 yr	Variable, unilateral, or bilateral; often tempofrontal	Often throbbing; may be sharp, dull, burning, or lancinating; mild to severe	Intermittent to continuous	50% have PMR; jaw claudication in 38%; 50% have absent pulse or tender STA	ESR WNL in up to 36%; CRP usually elevated; STA biopsy false negative in up to 44%
Acute paranasal sinusitis	More common in children (in whom frontal and sphenoid sinusitis are rare) than in adults	Any age	Frontal (forehead), maxillary (cheek), ethmoid (between eyes), sphenoid (variable)	Dull, aching; can be severe	Lasts from 1 day to 3 wk	Fever in about 50%; nasal congestion and purulent nasal drainage usually present (less often in sphenoid)	Well visualized on routine MRI but not on routine head CT scan; sinus CT is the best study
Subdural hematoma	Occurs in 1% after mild head injury; in chronic cases, up to 50% without history of head injury	Any age	Unilateral or bilateral	Mild to severe; may be aching, dull, or throbbing	Paroxysmal to constant	Normal neurologic examination in 50%; alteration in consciousness and focal findings may be present	MRI may detect the occasional isodense subdural hematoma, which can be missed on CT scan

CN = cranial nerve; CRP = C-reactive protein; CT = computed tomography; ESR = erythrocyte sedimentation rate; MRI = magnetic resonance imaging; PMR = polymyalgia rheumatica; STA = superficial temporal artery; WNL = within normal limits.

characteristics, and associated symptoms and signs justify neuroimaging for headaches [*see Table 6*].

Although a CT scan of the head will detect most pathologic conditions that cause headaches and is the preferred study for acute head trauma and subarachnoid hemorrhage (SAH), an MRI scan is generally preferred for evaluation of headaches. An MRI may demonstrate pathology not seen on a standard CT scan, including abnormalities of the paranasal sinuses, pituitary, posterior fossa, cortical veins (e.g., superior sagittal sinus thrombosis), cervicomedullary junction (e.g., Chiari I malformation), intracranial aneurysms, carotid dissection, infarcts, white matter abnormalities, congenital abnormalities, and neoplasms.

CT of the head also exposes the patient to ionizing radiation with an effective radiation dose of 2.0 millisieverts (mSv) (double this dose for a scan with and without contrast), which is equivalent to 100 chest x-rays.[8] The Food and Drug Administration (FDA) has estimated that exposure to 10 mSv (the equivalent of one CT scan of the abdomen) may be associated with an increased risk of developing fatal cancer for one patient in 2,000, with a greater risk for children and young adults.[9]

Electroencephalography (EEG) is not useful for the routine evaluation of patients with headache. However, EEG may be helpful if the patient has headaches and symptoms suggesting a seizure disorder or alteration of consciousness.

Blood tests are generally not helpful for the diagnosis of headaches, but specific tests are indicated when certain conditions are suspected. Such conditions, along with their indicated tests, include arteritis (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP] in temporal arteritis [TA]); infection (tests for infectious mononucleosis, Lyme disease, and HIV); and antiphospholipid antibody syndrome, which should be considered in patients with white matter lesions on MRI. Complete blood counts and metabolic studies are indicated in suspected anemia, renal failure, or hypercalcemia, and endocrine studies are indicated in suspected hypothyroidism or pituitary tumors. Blood studies are also valuable as a baseline for monitoring the adverse effects of certain medications for preventing headache (e.g., valproic acid and carbamazepine).

Lumbar puncture can be helpful in diagnosing meningitis, encephalitis, meningeal carcinomatosis, lymphomatosis, SAH, high cerebrospinal fluid (CSF) pressure (e.g., pseudotumor cerebri), and low CSF pressure. MRI or CT is always performed before a lumbar puncture for the evaluation of headaches, to rule out mass lesions, except in some cases in which acute meningitis is suspected. Lumbar puncture is often indicated for the first or worst headache, to exclude SAH [*see* First or Worst and Thunderclap Headaches, *below*]; headache with fever or other findings that suggest an infectious cause; a subacute or progressive headache in a patient with HIV infection or carcinoma; and an atypical chronic headache (e.g., to rule out idiopathic intracranial hypertension [IIH] [pseudotumor cerebri] in an obese woman without papilledema).

Table 6 Reasons to Consider Neuroimaging for Headaches[5]

Temporal and clinical features	First or worst headache Subacute headaches with increasing frequency or severity A progressive or new daily persistent headache Chronic daily headache Headaches always on the same side Headaches not responding to treatment
Patient characteristics	New-onset headaches in patients with cancer or HIV infection New-onset headaches after age 50
Associated symptoms and signs	Fever, stiff neck, nausea, and vomiting Aura and focal neurologic symptoms or signs, in nonmigraine headache Papilledema, cognitive impairment, or personality change Seizures

Migraine

EPIDEMIOLOGY

The 1-year prevalence of migraine is 18% in women, 6% in men, and 6% in children (both boys and girls). In the United States, 35 million persons have migraine each year.[9,10] The lifetime incidence is 43% in women and 18% in men.[11] Migraine begins before the age of 35 in 75% of cases and after the age of 50 in 2%; the highest prevalence is from 25 to 55 years of age. Interestingly, there is a high prevalence in neurologists (lifetime of 47% in males and 63% in females).[12]

The frequency of migraine can range from once in a lifetime to daily. The frequency of attacks in migraineurs is as follows: one to 12 a year, 38%; one to three a month, 37%; one a week, 11%; and two to six a week, 14%. Two percent of adults have migraine headaches 15 days per month or more with a duration of greater than 3 months, which is defined by the ICHD-2 as chronic migraine[1]; episodic migraine is less than 15 headache days per month. Half of migraineurs do not know that they have migraine, with 42% of undiagnosed patients self-diagnosing themselves with so-called sinus headache and 43% having received a diagnosis of sinus headache from a physician.[10]

There are many disorders with a greater-than-coincidental association (comorbidity) with migraine, including the following: vascular (hypertension or hypotension, Raynaud disease, mitral valve prolapse, patent foramen ovale, angina, myocardial infarction, and stroke); neurologic (epilepsy, essential tremor, benign positional vertigo, and restless legs syndrome); psychiatric (depression, generalized anxiety disorder, panic disorder, and bipolar); and other (irritable bowel syndrome, asthma, atopic allergies, systemic lupus erythematosus, and fibromyalgia).[13]

ETIOLOGY AND PATHOPHYSIOLOGY

Although the mechanism of migraine remains incompletely understood, there is growing evidence that migraine is an inherited, episodic disorder involving sensory sensitivity.[14] About 70% of migraineurs have a positive family history in a first-degree relative. The mode of transmission of susceptibility to migraine remains unclear; there is probably genetic heterogeneity.

The aura that precedes some migraines is a slow march of visual or other neurologic symptoms associated with changes in neuronal activity that result in spreading neural depression from the occipital cortex. Excitatory changes produce increased blood flow, followed by reduced blood flow caused by neuronal inhibition.

The trigeminal nerve and the blood vessels it innervates may constitute the anatomic substrate for migraine pain. Input from the pain-sensitive cranial nerves and dura passes through the ophthalmic division of the trigeminal ganglion to the trigeminocervical complex (the trigeminal nucleus caudalis and dorsal horns of C_1 and C_2) that produces referred pain in the head (especially the ophthalmic division) and upper posterior neck. When the peripheral branches of the trigeminal nerve are activated during migraine, pain results from neurogenic inflammation that is produced by the antidromic release of calcitonin gene–related peptide by trigeminal nerve endings and that is associated with the release of other pain substances from plasma, platelets, and mast cells (e.g., histamine, prostaglandin, and serotonin). These substances induce vasodilatation and extravasation of plasma proteins and the sensitization of trigeminal nociceptive nerve endings. Throbbing pain and exacerbation by activities such as bending over, head movement, coughing, and walking may reflect mechanical hypersensitivity of meningeal C-fiber nociceptors. Nitric oxide released from blood vessels, perivascular nerve endings, or brain tissue can be a trigger for migraine pain.

Pain signals in the trigeminocervical complex undergo central processing, with second-order neurons receiving input and projecting rostrally to the contralateral thalamus (ventrobasal complex and medial nuclei) and then to the activating cortex (anterior cingulate, insular, and frontal), the periaqueductal gray matter (dorsal raphe nuclei), and the locus coeruleus. Aminergic areas in the periaqueductal gray matter and locus coeruleus influence the incoming pain and cortical blood flow. A continuous discharge in this pain-control system may occur from stimulation from the cortex or hypothalamus caused by stress or by excessive afferent input from the special senses or from cerebral or extracranial vessels. The migraine prodrome may originate in the hypothalamus.

CLINICAL FEATURES

Migraine can occur with or without an aura [*see* Migraine Aura, *below*]. Migraine without aura (formerly referred to as common migraine) occurs in 80% of migraineurs, and migraine with aura (formerly referred to as classic migraine) occurs in 20%. Most patients who have migraine with aura also have migraine without aura.

According to the ICHD-2 criteria for migraine without aura, the duration of untreated or unsuccessfully treated episodes ranges from 4 to 72 hours.[1] The headaches are associated with at least two of the following pain characteristics: unilateral location; pulsating quality; moderate or severe intensity; and aggravation by, or resultant avoidance of, routine physical activity (e.g., walking or climbing stairs). The pain is accompanied by nausea, vomiting, or both, as well as by sensitivity to light (photophobia) and sound (phonophobia). Also, the patient has a history of at least five previous attacks that meet these criteria. If there are no indications that other primary etiologies may be responsible for the headaches, a diagnosis of migraine without aura can be reasonably established.[1]

Although the IHS criteria have been very useful for research purposes, most clinicians recognize migraine through familiarity with the general features [*see Table 4*]. Migraine pain is unilateral in 60% of cases and bilateral in 40%. About 17% of migraineurs report so-called side-locked headaches, with migraine always occurring on the same side. The pain will often be more intense in the frontotemporal and ocular regions before spreading to the parietal and occipital areas. Any region of the head or face may be affected, including the parietal region, the upper or lower jaw or teeth, the malar eminence, and the upper anterior neck. Throbbing pain is present in 85% of episodes of migraine, although up to 50% of patients describe nonthrobbing pain during some attacks. Along with having head pain, up to 75% of migraineurs report having unilateral or bilateral tightness, stiffness, or throbbing pain in the posterior neck. The neck pain can occur during the migraine prodrome, the attack itself, or the postdrome and is typically relieved by migraine medication such as a triptan.

Migraine persisting for more than 72 hours is termed status migrainosus. Without treatment, 80% of patients have moderate to severe pain and 20% have mild pain. The pain, which is usually increased by physical activity or movement, is associated with nausea in about 90% of episodes, vomiting in about 30%, photophobia in about 90%, and phonophobia in about 80%.[10] Diarrhea occurs in about 16%; lightheadedness is also common. In children, migraine pain is bilateral in 60% and unilateral in 40%. The duration of the untreated headache in children can be 1 hour or more, much shorter than that in adults.

During an attack, 45% of migraineurs have at least one autonomic symptom (i.e., lacrimation, eye redness, ptosis, eyelid edema, nasal congestion, or rhinorrhea). These symptoms are caused by parasympathetic activation of the sphenopalatine ganglion, which innervates the tear ducts and sinuses, and these symptoms can lead to confusion of migraine with so-called sinus headaches.[15] Of patients with autonomic symptoms, 45% have both nasal and ocular symptoms, 21% have nasal symptoms only, and 34% have ocular symptoms only.

Cutaneous allodynia, pain elicited by nonpainful stimulation of the skin such as brushing the hair, touching the scalp, shaving, wearing contact lenses, or wearing tight clothes, occurs in 63% of those with episodic migraine and 68% with chronic migraine and becomes less frequent with older age.[16] The symptoms are usually cephalic (scalp, face, neck, ears), but in about 15% of cases, they are extracephalic (extremities or trunk). The most common symptoms are sensitivity to touching the scalp and abnormal soreness or tenderness of the pericranial muscles. Extremity allodynia can be unilateral or bilateral. Cutaneous allodynia results from an increase in the responsiveness (sensitization) of central pain neurons that process information from intracranial structures and extracranial skin and muscles. Cutaneous allodynia is a predictor of poor response for triptan therapy and a risk factor for disease progression.

Prodromal symptoms (premonitory phenomena) may be present in up to 87% of cases and precede the migraine

attack by hours or by up to 1 or 2 days. Prodromal symptoms include changes in mental state such as depression, hyperactivity, euphoria, talkativeness, irritability, drowsiness, and restlessness. Neurologic symptoms may include photophobia, difficulty concentrating, phonophobia, dysphasia, hyperosmia, and yawning. General symptoms may include fatigue, stiff neck, food cravings, feeling cold, anorexia, sluggishness, diarrhea or constipation, thirst, and fluid retention.

Postdrome or resolution symptoms occur in about 80% of migraineurs. Symptoms include asthenia, tiredness, somnolence, and concentration difficulties, although some people feel refreshed or euphoric after an attack.

Triggers or Precipitants

Migraines are often triggered by environmental or other factors; as many as 85% of migraineurs report triggers. Patients typically have multiple triggers, with a mean as high as 6.7.[17] Up to 80% of patients report stress as a trigger, but letdown after stress, vacations, and crying can also be precipitants for some. Missing a meal (57%), lack of sleep, oversleeping, and fatigue are also commonly reported as triggers. Half of women with migraine report menses as a trigger, and 14% have migraines associated only with their menses. About 50% of migraineurs report that a change of weather is a trigger. Other environmental triggers are heat, high humidity, and high altitude.

Sensory triggers include bright lights, glare, flickering lights, loud noise, and strong smells such as perfume or cigarette smoke. Up to 50% of patients report alcohol as a trigger; this can be all forms of alcohol or only one type, such as red wine or beer. Up to 45% report food triggers such as chocolate, dairy products (particularly cheese), citrus fruits, fried foods, and nitrates and nitrites in cured meats or fish (e.g., frankfurters, bacon, and smoked salmon). Other triggers include minor head trauma, exertion, and nitroglycerin.

Migraine Aura

The migraine aura has a total duration of usually less than 1 hour and frequently less than 30 minutes.[18] An aura lasting more than 1 hour but less than 1 week is termed migraine with prolonged aura, or complicated migraine. The most common aura is a vision-related one, which is present in 99% of cases. There are two types: (1) positive visual phenomena, with hallucinations, and (2) negative visual phenomena, or scotomas, with either an incomplete or a complete loss of vision in a portion or all of the visual field. Most visual auras have a hemianoptic distribution. Photopsias consist of small spots, dots, stars, unformed flashes or streaks of light, or simple geometric forms and patterns that typically flicker or sparkle.

A scintillating scotoma, also called a fortification spectrum (because of its resemblance to a medieval fortified town as viewed from above) or teichopsia (seeing fortifications), is present in about 10% of cases. The scotoma, which is frequently semicircular or horseshoe shaped, usually begins in the center of the visual field and then slowly extends laterally. The scotomatous arc or band is a shimmering or glittering, bright, zigzag border. Most visual auras consist of flickering, colored or uncolored, unilateral or bilateral zigzag lines or patterns; semicircular or arcuate patterns; wavy lines; or irregular patterns. Rare visual auras include metamorphopsia (objects appear to change in size and shape), macropsia, micropsia, telescopic vision (objects appear larger than normal), teleopsia (objects appear to be far away), mosaic vision, Alice in Wonderland syndrome (distorted body image), and multiple images. Headaches, when unilateral, usually occur on the side contralateral to the visual symptoms but can occasionally be ipsilateral.

A sensory aura, which is present in about 30% of episodes of migraine with aura, consists of numbness, tingling, or a pins-and-needles sensation. The aura, which is usually unilateral, commonly affects the hand and then the face, or it may affect either one alone. Paresthesia of one side of the tongue is typical. Less often, the leg and trunk may be involved. A true motor aura is rare, but sensory ataxia or a heavy feeling is often misinterpreted as weakness.

Speech and language disturbances may occur in up to 20% of cases. Patients often report a speech disturbance when the spreading paresthesias reach the face or tongue. Slurred speech may be present. With involvement of the dominant hemisphere, paraphasic errors and other types of impaired language production and comprehension may occur. Rarely, other aura symptoms may be described, including déjà vu and olfactory and gustatory hallucinations.

Although visual symptoms frequently occur by themselves, combinations of aura symptoms can occur. Sensory, speech, and motor symptoms are usually associated with visual symptoms or with one or more other symptoms. When two or more aura symptoms are present, they almost always occur in succession rather than simultaneously.

Migraine aura can occur without headache (acephalgic migraine), often in patients whose migraine episodes typically involve headache (with or without aura). A visual aura is the most common in such cases. Another type of migraine without aura is episodic vertigo (migrainous vertigo or vestibular migraine) without a headache, auditory disturbances, or other neurologic symptoms, lasting minutes to days.[19] In older persons, the aura—termed late-life migraine accompaniment—can be confused with a transient ischemic attack (TIA) [*see* Geriatric Headache, *below*]. Rarely, migraineurs have persistent visual aura. This usually consists of simple, unformed hallucinations in the entire visual field of both eyes, including innumerable dots, television static, clouds, heat waves, flashing or flickering lights, lines of ants, a rainlike or snowlike pattern, squiggles, bubbles, and grainy vision. Occasionally, palinopsia (the persistence of visual images), micropsia, or formed hallucinations occur.

Migraine Variants

Migraine variants include familial hemiplegic; basilar type; benign paroxysmal vertigo of childhood; abdominal; confusional; so-called footballer's migraine; benign episodic mydriasis; and retinal. Familial hemiplegic migraine (FHM) is a rare variant of migraine with aura accompanied by hemiplegia or hemiparesis and other manifestations. Attacks may occur on the same side as previous episodes or on another side and typically feature a slow spread of paresis involving the face, arm, and leg. Alteration of consciousness, ranging from confusion to coma and aphasia, may be

present. There are three types: FHM1 is caused by an autosomal dominant mutation in a brain-specific P/Q-type calcium channel subunit on chromosome 19p13; FHM2 arises from a mutation in the α_2 subunit of the Na/K pump on chromosome 1q23; and FHM3 is caused by a missense mutation in *SCN1A*, which encodes an α_1 subunit of a neuronal voltage-gated Na^+ channel on chromosome 2q24.

Basilar-type migraine is a rare disorder that most often occurs in children and rarely occurs in patients older than 50 years.[20] According to IHS criteria, attacks are marked by two or more of the following fully reversible aura symptoms: dysarthria, vertigo, tinnitus, hypacusia, diplopia, visual symptoms simultaneously in the temporal and nasal fields of the two eyes, ataxia, decreased level of consciousness, and simultaneous bilateral paresthesias. These symptoms, which originate from the brainstem or both occipital lobes, are not accompanied by motor weakness. There is also at least one of the following: bilateral paresthesias; gradual development of at least one aura symptom over 5 minutes or longer, the occurrence of different aura symptoms in succession over 5 minutes or longer, or both; or persistence of each aura symptom for 5 to 60 minutes. Patients with basilar-type migraine may also have other types of migraine. Visual symptoms—which usually take the form of blurred vision, shimmering colored lights accompanied by blank spots in the visual field, scintillating scotoma, and graying of vision—may start in one visual field and then spread to become bilateral. Diplopia occurs in up to 16% of cases. Vertigo may be present, either alone or accompanied by various combinations of tinnitus, dysarthria, gait ataxia, and paresthesias (usually bilateral but sometimes affecting alternate sides in successive episodes). Impairment of consciousness is common and may include obtundation, amnesia, syncope, and, albeit rarely, prolonged coma. A severe throbbing headache, typically with a bilateral occipital location, is present in 96% of cases. Nausea and vomiting typically occur, with light and noise sensitivity in up to 50% of cases.

Benign paroxysmal vertigo of childhood presents as episodes of vertigo without headache. Abdominal migraine also occurs in children and features recurring episodes of abdominal pain without headache that may be associated with nausea, vomiting, pallor, and flushing. Confusional migraine presents with a headache, which can be minimal, associated with a confusional state that can last from 10 minutes to 2 days. Agitation and impaired memory may be present. The patient may exhibit inattention, distractibility, and difficulty maintaining coherent speech or action. So-called footballer's migraine (originally described in soccer players) refers to the triggering of migraine by acute minor head trauma in children or adolescents.

Benign episodic mydriasis is a transient, isolated mydriasis. This disorder typically occurs in young adults or children. Patients have normal vision and pupillary reactivity to light that may occasionally accompany migraine headaches. The episodes last 15 minutes to 24 hours, are often associated with blurred vision, and can average two or three a month. Eyelid or ocular motility abnormalities are absent. Angle-closure glaucoma should be excluded. Dilatation of the pupil is secondary either to parasympathetic insufficiency of the iris sphincter or to sympathetic hyperactivity of the iris dilator. Retinal migraine, a rare diagnosis of exclusion, produces episodes of transient monocular visual loss lasting minutes to hours, which may or may not be associated with headache.

ACUTE TREATMENT

Certain general principles apply to the use of medications for acute (symptomatic) treatment of migraine. Early treatment, when the headache is mild, is much more effective than later treatment, when the migraine is moderate or severe in intensity. Frequent use of acute-treatment medications can lead to medication overuse headache (MOH); for that reason, acute therapy should be restricted to a maximum of 2 or 3 days a week. Different patients may respond to different medications at different times. Patients benefit from stratified care.[21] Treatment is based on the characteristics of the patient's episodes (including peak intensity, time to peak intensity, associated symptoms, and disability) and is tailored to specific patient needs. Nasal, parenteral, or rectal administration of medication should be used in patients with significant nausea or vomiting or gastroparesis. Antinausea medications such as promethazine and prochlorperazine may help in such cases. Many migraineurs respond to over-the-counter medications for acute symptoms [*see Table 7*]. Over-the-counter drugs are often more effective if taken when the pain is mild rather than when it has become more intense.

Patients who do not respond or who respond incompletely to over-the-counter medications may require a prescription medication. The combination of isometheptene mucate, dichloralphenazone, and acetaminophen (Midrin) can be highly effective, especially for mild to moderate headache.[22] Combination medications that include butalbital (e.g., Fiorinal) may also be effective. Surprisingly, despite their common use, the butalbital combinations have not been studied in a placebo-controlled trial.[23] Oral and intranasal opiates may also be effective. Butorphanol nasal spray (Stadol) may be very effective for some patients who have severe migraine with nausea or vomiting and cannot keep an oral medication down, do not respond to triptans, or require a rescue medication when the usual medication is ineffective. Side effects include dizziness, nausea, vomiting, and drowsiness. However, frequent use of medications such as butalbital and opiates can lead to MOHs and habituation.

Triptans

The introduction of the triptans has dramatically improved the acute treatment of migraine. Triptan medications are selective 5-hydroxytryptamine ($5\text{-}HT_{1B/1D}$) receptor agonists that share a basic indole ring structure with different side chains. Triptans have three potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex. These mechanisms inhibit the effects of activated nociceptive trigeminal afferents and control acute migraine attacks.[14]

Seven triptans are available in the United States: almotriptan, eletriptan, frovatriptan, naratriptan, sumatriptan, rizatriptan, and zolmitriptan. [*see Table 8*].[24] In migraineurs who take oral triptans when their pain is moderate to severe in

Table 7 Efficacy of Selected Over-the-Counter Medications for Relief of Moderate to Severe Migraine Pain[77–80]

Medication and Dose	*Percentage of Responders at 2 hr (% Placebo)*		*Percentage of Responders at 6 hr (% Placebo)*	
	Mild or No Pain	*No Pain*	*Mild or No Pain*	*No Pain*
Ibuprofen, 400 mg	42 (28)	15 (8)	49 (32)	31 (20)
Acetaminophen, 1,000 mg	58 (39)	22 (11)	77 (46)	46 (28)
Acetaminophen, 500 mg, plus aspirin, 500 mg, plus caffeine, 130 mg	59 (33)	22 (7)	79 (52)	51 (23)
Aspirin, effervescent, 1,000 mg	55 (37)	29 (17)	Not assessed	

Percentages are rounded.

intensity, the 2-hour response rate (i.e., no pain or mild pain) is about 45% for naratriptan and frovatriptan and about 65 to 70% for the five others. Sumatriptan 85 mg with naproxen sodium 500 mg in a rapid-release formulation is also available and is more effective than placebo or either drug given as monotherapy at achieving headache relief at 2 hours after migraine onset. With all of the triptans, the 2-hour pain-free response rates are much higher if the drug is taken when the headache is mild; depending on the drug, the response rate may exceed 70%.

The oral triptans may not be equally effective for all patients. If a patient has an unsatisfactory or inconsistent response, unpleasant side effects, or an initial good response but later a poor response with one triptan, a different triptan may prove to be effective and tolerable. Patients who have prominent vomiting or nausea or who desire the quickest relief may benefit from subcutaneous sumatriptan (at 2 hours, 79% of patients show a response and 60% are pain free) or intranasal sumatriptan or zolmitriptan. About 25% of migraineurs will not respond to any of the triptans.[25]

Patients may experience a recurrence, which is defined as the return of headache (usually of moderate or severe intensity) within 24 hours after an initial response to acute treatment in about 20 to 40% of patients depending on the triptan. The time to recurrence is generally about 12 hours.[26]

Triptans can stimulate 5-HT_{1B} receptors on coronary arteries and result in constriction, which may become clinically significant in patients with coronary artery stenosis or vasospastic disease.[27] Consequently, triptans as a class are contraindicated in patients with known or suspected ischemic heart disease, Prinzmetal angina, or uncontrolled hypertension. In view of the potential adverse cardiovascular events associated with triptans, a functional cardiac evaluation is recommended for patients with more than one Framingham risk factor for unrecognized coronary artery disease. Triptans are also contraindicted in patients with cerebrovascular or peripheral vascular disease, hemiplegic or basilar migraine, and within 24 hours of dihydroergotamine (DHE).

Table 8 Triptans Available in the United States

Drug (Brand Name)	*Formulation*	*Doses* (mg)*	*Maximum Daily Dose (mg)*
Almotriptan (Axert)	Tablet	6.25, **12.5**	25
Eletriptan (Relpax)	Tablet	20, **40**	80
Frovatriptan (Frova)	Tablet	2.5	5
Naratriptan (Amerge)	Tablet	1, 2.5	5
Rizatriptan (Maxalt)	Tablet Orally disintegrating preparation‡ (Maxalt MLT)	5,† **10** 5,† **10**	30† 30†
Sumatriptan (Imitrex)	Tablet Tablet with 500 mg naproxen sodium (Treximet) Nasal spray Subcutaneous injection	25, 50, **100** 85 5, **20** 4, **6**	200 170 40 12
Zolmitriptan (Zomig)	Tablet Orally disintegrating preparation‡ (Zomig ZMT) Nasal spray	2.5, 5 2.5, 5 5	10 10 10

*Optimal dose, when known, in boldface.
†5 mg single dose and 15 mg maximum dose if on concomitant propranolol.
‡Dissolves on the tongue; can be taken without water (efficacy similar to that of tablet form).

The common triptan side effects—tightness, heaviness, pressure, or pain in the chest, neck, or throat—are not associated with electrocardiogram changes and are not caused by coronary vasoconstriction. There are rare case reports of atrial fibrillation triggered by sumatriptan possibly caused by transient elevations in atrial pressure.[28]

In 2006, the FDA issued an alert warning that there is the potential for life-threatening serotonin syndrome in patients taking triptans and selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs) concomitantly. It is estimated that some 700,000 people in the United States receive these coprescriptions annually. However, of the 29 cases of possible serotonin syndrome from coprescriptions of concern to the FDA, only seven met the Sternbach criteria and none met the more rigid Hunter criteria for serotonin syndrome.[29] No cases have been published since meeting these criteria.

INTRACTABLE MIGRAINE AND MIGRAINE STATUS

People with migraine often seek help in the emergency department, where they account for around 2% of visits and may receive a less than warm welcome when they present with "just a headache."[30] This challenging group of people is made up of those with their first or worst attacks, those who have not taken or not responded to drugs, frequent attendees, those with acute exacerbation of chronic migraine, and those with migraine with neurologic symptoms and signs (with aura). Intravenous fluids and electrolyte replacement may be necessary for patients with intractable vomiting associated with migraine.

Evidence-based guidelines recommend the first-line use of DHE, subcutaneous sumatriptan, dopamine antagonists (metoclopramide, prochlorperazine, and chlorpromazine), and ketorolac, which have response rates of up to 70%. Narcotic analgesics, recommended as rescue drugs, are still widely used, even though their administration may result in significantly longer stays in the emergency department compared with non-narcotic treatments. Migraine pain persists or recurs within 24 hours of discharge from the emergency department regardless of treatment in over half of patients. Intravenous dexamethasone (10 to 24 mg) has a modest effect (the number needed to treat is nine) on preventing recurrence and is not effective for acute treatment of migraine pain.[31]

Medication options include the following:

1. Sumatriptan, 4 or 6 mg SC
2. DHE, 0.5 to 1 mg by SC, IM, IV (DHE and triptans should not be used within 24 hours of each other).
3. Metoclopramine 10 IV
4. Ondansetron 4 to 8 mg IV
5. Prochlorperazine, 5 to 10 mg IV
6. Ketorolac, 30 mg IV, 30 to 60 mg IM
7. Dexamethasone, 10 mg IM or IV
8. Parenteral narcotics, which may be combined with promethazine
9. Valproate sodium, 500 to 1,000 mg IV
10. Droperidol (2.5 mg IM or IV)

There is a very small risk of torsades de pointes with the use of neuroleptics such as prochlorperazine and droperidol.

PREVENTIVE TREATMENT

A number of factors may justify daily preventive medication for patients with migraines [*see Table 9*].[32] Indications for preventive treatment are as follows:

1. The headaches significantly interfere with the patient's daily routine, despite acute treatment (such as two or more attacks a month producing disability lasting 3 or more days)
2. Acute medications are contraindicated, ineffective, or overused or have intolerable side effects
3. Frequent migraines (two or more attacks a week)
4. Uncommon migraine types (hemiplegic, basilar, prolonged aura, or migrainous infarction)
5. The cost of acute medications is significantly greater than the cost of preventive medication
6. Patient preference (i.e., the patient is willing to risk the possibility of side effects from the preventive medication to reduce the frequency of headaches)

There are general principles for the use of preventive medications[32]:

1. The clinician should start with a low dose of medication and increase it slowly, depending on the response and whether adverse effects occur, until the target dose is reached or significant adverse events occur.
2. Each medication should be given a trial of 2 to 3 months at adequate doses.
3. Overused medications that may be causing MOH and may decrease the efficacy of preventive treatment should be discontinued or tapered (depending on the drug).
4. Patients should keep a headache diary to monitor their headaches.
5. The clinician should educate the patient about the rationale for treatment and possible adverse effects and should address the patient's expectations for treatment. Many early adverse events are self-limited and dose-dependent if patients can be encouraged to continue the medication. Many patients want a complete cure, and although this is certainly understandable, it is usually not possible as success is defined as a 50% or greater reduction in the frequency of headaches.
6. Coexistent or comorbid conditions should be considered. Some medications may be effective against both migraine and another disorder. Other disorders, along with the migraine medications that may be effective against them, include epilepsy (divalproex sodium, topiramate, and gabapentin), hypertension (beta blockers), depression (tricyclic antidepressants, venlafaxine), bipolar disorder (divalproex sodium), insomnia (tricyclic antidepressants), essential tremor (beta blockers and topiramate), and overweight or obesity (topiramate). On the other hand, coexistent diseases such as depression or asthma may be relative contraindications to the use of beta blockers.
7. In a woman of childbearing potential, the potential for teratogenesis should be considered.
8. Patients who are somewhat responsive to one preventive agent may benefit from the addition of a second agent.

Table 9 Preventive Medications for Migraine			
Drug Class	*Agent*	*Dosage*	*Typical Side Effects*
Beta blockers	Atenolol	50–100 mg/day	Hypotension, tiredness, dizziness, decreased exercise tolerance, nightmares, memory disturbance, exacerbation of asthma
	Metoprolol*	50–200 mg/day	
	Nadolol	40–160 mg/day	
	Propranolol*	40–120 mg b.i.d.	
	Propranolol long acting*	60–240 mg/day	
	Timolol*	10–30 mg/day	
Antidepressants	Amitriptyline*	25–150 mg h.s.	Drowsiness, dry mouth, weight gain, constipation
	Nortriptyline	25–150 mg h.s.	
	Protriptyline	10–60 mg am as single or divided dose	
	Venlafaxine XR	75–225 mg/day	Nausea, insomnia, drowsiness
Anticonvulsants	Divalproex sodium*	500–1,000 mg in divided doses or once daily with extended release formulation	Nausea, tremor, drowsiness, weight gain, alopecia, fetal abnormalities, rare hematologic and liver abnormalities, pancreatitis
	Topiramate*	50–200 mg/day in divided doses	Weight loss, paresthesias, cognitive disturbances, kidney stones
	Gabapentin	300–800 mg t.i.d.	Dizziness, fatigue, drowsiness

*Evidence from at least two class I studies indicates that these are the most effective.

9. If a medication does not work or has significant side effects, withdrawal of the agent may need to be done slowly if the patient has been receiving moderate or high doses of tricyclic antidepressants, venlafaxine, and beta blockers.
10. Consider patient preferences for medications that may improve adherence.

Compliance indicates the patient's correct following of medical advice. Adherence refers to the extent to which patients follow agreed-upon treatment recommendations, a term that emphasizes the importance of patient participation in effective treatment.[33] Up to 50% of patients are nonadherent with migraine preventive medications, and perhaps 10% do not even fill the initial prescription. Approaches that may improve adherence include patient involvement in selecting a medication (considering adverse events, cost, and dosing schedule); detailed recommendations on the use of the medications, including how to deal with the most common adverse events; monitoring (headache diary, medication counts, and follow-up visits); and involvement of family members or friends. On follow-up visits, you can nonconfrontationally ask if they take their medications regularly or, instead, sometimes forget. Then you can emphasize the importance of daily use.

Evidence from at least two class I studies indicates that the beta blockers propranolol, metoprolol, and timolol; the tricyclic antidepressant amitriptyline; and the antiseizure medications divalproex sodium and topiramate are the most effective preventive medications, reducing the frequency of migraines by more than 50% in about 50% of patients. In general, preventive medications are more effective when patients are placed on a titration schedule with a minimum target dose. Titration schedules and minimum target doses are as follows: propranolol (either regular or long acting), 40 mg daily, increased weekly by 40 mg to a maximum daily dose of 120 to 240 mg; amitriptyline, 10 to 25 mg at bedtime, increased weekly by 10 to 25 mg to a maximum daily dose of 150 mg; divalproex sodium (either regular or extended release), 500 mg daily for 1 week and then 1,000 mg daily; and topiramate, 25 mg daily for the first week, increased by 25 mg/wk in divided doses, to a maximum daily dose of 100 mg administered at a dosage of 50 mg twice daily (anecdotally, once-daily dosing is effective; the half-life is 21 hours).[34] At dosages greater than 200 mg daily, topiramate may produce a dose-related reduction in the estrogen component of oral contraceptives. The incidence of kidney stones on topiramate is about 1.5%, which is a two to four times increase over the occurrence in the general population.

Table 9 lists beta blockers that may be effective. The use of beta blockers may be limited in patients with erectile dysfunction, peripheral vascular disease, Raynaud syndrome or disease, or erectile dysfunction and in patients with baseline bradycardia or low blood pressure. They must be used cautiously as well in those with asthma, diabetes mellitus, chronic heart failure, and cardiac conduction disturbances or sinus node dysfunction.

The tricyclic antidepressants nortriptyline (taken at bedtime) and protriptyline (may be activating, taken in the morning) may be efficacious with less sedation than amitriptyline. The SNRI venlafaxine may be as effective as amitriptyline, with fewer side effects.[35] SSRIs are probably not effective for migraine prevention, and verapamil and gabapentin are only modestly effective.[32]

Changes of weight can occur with preventive medications.[36] Weight increase can occur with amitriptyline (in a 26-week trial, 65% gained > 1% and 29% had a weight gain

of > 5% body weight on a mean dose of 88.9 mg/day); propranolol (in a 26-week trial, a 2.3% increase in body weight on a median dose of 130 mg/day); and divalproex sodium (after 18 months on 500 mg/day, 21% gained weight). Timolol and venlafaxine are typically weight neutral. Topiramate is associated with weight loss (in a 26-week trial on a mean dose of 90.6 mg daily, 65% lost > 1% and 30% lost more than 5% of their baseline weight), and protriptyline may be as well.

There are natural products that may be beneficial for migraine prevention, including the extract from the butterbur plant, *Petasites hybridus* (Petadolex, 75 mg twice daily), riboflavin (400 mg a day), and coenzyme Q_{10} (100 mg three times daily).[37] The evidence for the herb feverfew (*Tanacetum parthenium*) and magnesium supplements is not conclusive. Botulinum toxin injections may be of benefit in chronic migraine ((by modulating release of neuropeptides such as calcitonin gene–related peptide and influencing the process of central sensitization associated with migraine) but is not effective in episodic migraine. The relative benefit of these treatments may become clearer with additional studies, but for now, some migraineurs may prefer them because they have few, if any, side effects.

For many migraineurs, the avoidance of triggers may be useful. Examples include adequate sleep at set hours, routine exercise, regular meals, avoiding triggering foods and beverages, and wearing sunglasses in bright sunlight or glare. Some patients may benefit from biofeedback, relaxation training, and psychotherapy.[38] Although patent foramen ovale is associated with migraine with aura, closure has not been proven to decrease the frequency of migraine.[39]

If the migraines are improved for at least 6 to 9 months, you may then discuss tapering or discontinuing the medication with the patient. Only one study provides information on this issue. Comparing patients who continued topiramate for a total of 12 months with those who stopped after 6 months and were placed on placebo, the number of migraine days increased by 2% and 26%, respectively.[40] The decision should be individualized based on patient preference, baseline frequency and severity of headache, and response to the preventive medication.

WOMEN AND MIGRAINE

There are issues specific to the treatment of female migraineurs.[41] During pregnancy, the frequency of migraines decreases (especially during the second and third trimesters) in 60%, remains the same in 20%, and increases in 20%. Migraines may occur for the first time when women start using oral contraceptives (OCs). Low-estrogen OCs usually have no effect on migraine or may even improve it, although the frequency can increase. Of patients with new-onset migraine or increased frequency of migraine associated with OCs, 30 to 40% may improve when OCs are discontinued, although improvement may not occur for up to 1 year. Two thirds of women with prior migraine improve with physiologic menopause. Surgical menopause results in worsening of migraine in two thirds of cases.

Menstrual migraine is treated with the same acute-treatment medications as other migraines (see above). Interval or short-term preventive treatment of menstrual migraine, starting 2 or 3 days before menses and continuing during the menses, may be helpful for some women with regular menses and migraines that are poorly responsive to symptomatic medications. Potentially effective medications include the following: amitriptyline or nortriptyline, 25 mg at bedtime; long-acting propranolol, 60 to 80 mg daily, or nadolol, 40 mg daily; nonsteroidal antiinflammatory drugs (NSAIDS) such as naproxen sodium, 550 mg twice daily; ergotamine, 1 mg once or twice a day, or DHE, 1 mg subcutaneously or intramuscularly; naratriptan, 1 mg orally twice daily, or frovatriptan, 2.5 mg twice daily, for 6 days perimenstrually; transdermal estradiol, 100 µg applied 3 days before the expected start of menses and replaced after 3 days; continuous combined OC use, with a lower estrogen dose given during the menses; and extended-duration OC use.

Although low-estrogen OCs may be associated with a small increase in ischemic stroke risk, most women who have migraine without aura can safely take low-estrogen OCs if they have no other contraindications or risk factors. When taking low-estrogen OCs, women younger than 35 years who have migraine with aura (e.g., visual symptoms lasting less than 1 hour) have a risk of ischemic stroke of about 30 per 100,000 annually, which is twice the risk of those women who have migraine without aura.[42] An IHS task force concluded that OCs may be contraindicated in women with migraine who have additional risk factors that cannot easily be controlled, including migraine with aura, because of a possible increase in the risk of ischemic stroke, and that these risks must be assessed and evaluated on an individual basis.[43] Women with aura symptoms such as hemiparesis or aphasia or prolonged focal neurologic symptoms and signs lasting more than 1 hour should avoid starting low-estrogen OCs and should stop the medication if they are already taking it. Progestin-only OCs and the many other contraceptive options can be considered, as appropriate. Cigarette smoking should be strongly discouraged because female migraineurs who smoke one or more packs of cigarettes a day raise their risk of ischemic stroke by a factor of about 10.

Estrogen replacement therapy has a variable effect on migraine: 45% of patients show improvement, 46% show worsening of migraine, and 9% show no effect. If migraines increase when a patient starts estrogen replacement, the following strategies may be beneficial:

1. Reduce the estrogen dose.
2. Change the estrogen type to one less likely to promote migraine. From most to least likely to promote migraine, these are, in order, conjugated estrogens (Premarin), pure estradiol (Estrace), synthetic estrogen (Estinyl), and pure estrogen (Ogen).
3. Convert from interrupted to continuous dosing in the case of estrogen-withdrawal migraine.
4. Convert from oral to parenteral administration (e.g., a transdermal patch).
5. Add androgens.

Management of migraine during pregnancy and breast-feeding[41] is beyond the scope of this chapter.

Tension-Type Headaches

The 1-year prevalence of tension-type headaches has been variably reported as being from 30 to 90%. The lifetime

prevalence is 78% (63% in males and 86% in females; the male-to-female ratio is about 4:5). The prevalence peaks in the fourth decade of life, with an average age at onset between 25 and 30 years.

CLINICAL FEATURES

Tension-type headache may be episodic or chronic.[44] The ICHD-2 criteria for episodic tension-type headache are as follows: at least 10 previous headache episodes fulfilling the criteria, number of days with the headache being less than 180 a year or 15 a month, and headache lasting from 30 minutes to 7 days. At least two of the following pain characteristics should be present: pressing or tightening (nonpulsating quality), mild or moderate severity, bilateral location, and no aggravation of headache by walking up and down stairs or performing similar types of routine physical activity. There should be no nausea or vomiting (anorexia may occur), and either photophobia or phonophobia may be present, but not both.

The pain is variably described as pressure, soreness, tightness, a band or cap on the head, or a weight on the head. During severe episodes, a pulsating sensation is occasionally present. Although 90% of episodic tension-type headaches are bilateral, these headaches can be unilateral in patients with trigger points or oromandibular dysfunction.

In chronic tension-type headache, according to IHS criteria, the average headache frequency is 15 days or more a month for at least 6 months or 180 days or more a year. The pain characteristics are the same as for episodic tension type. There should be no concomitant vomiting, and no more than one of the following features should be present: nausea, photophobia, or phonophobia. Some patients may have continuous headaches for years. Secondary causes of episodic and chronic tension-type headaches should be excluded, as appropriate.

TREATMENT

Acute headaches may respond to the following: aspirin or acetaminophen, alone or in combination with caffeine; NSAIDs; isometheptene in combination with other agents; and butalbital with other agents. Overuse of any of these medications, however, may lead to MOHs. Frequent butalbital use can also result in dependency. Muscle relaxants are not effective for acute treatment.

Frequent headaches may require preventive medications. Tricyclic antidepressants (especially amitriptyline titrated up to 75 mg given at bedtime but also nortriptyline or protriptyline) may be the most effective. Other antidepressants such as mirtazapine (15 to 30 mg per day) and venlafaxine (150 mg/day) may be effective, whereas the SSRIs are probably not effective. Topiramate may be effective for chronic tension-type headaches. Psychological treatment strategies such as relaxation training, biofeedback, and cognitive behavioral therapy (stress management) may be effective. Physical therapy may produce modest improvement.

Chronic Daily Headache

CDH has a frequency of 15 or more days a month for greater than 3 months' duration. The 1-year prevalence of CDH in adults is about 3% in males and 5% in females, of whom 0.5% have severe daily headaches, and about 2% in adolescents.

HEADACHE TYPES IN CDH

CDH of long duration (4 or more hours per attack) includes four different headache types: chronic, or transformed, migraine and chronic tension-type headache, which each account for about 50% of those with CDH, and the rare hemicrania continua and new daily persistent headache (0.1% of the general population).

Chronic or transformed migraine is a complication of intermittent migraine, with 2.5% progressing yearly from episodic to chronic migraine. About 75% of those with chronic migraine are age 40 or older. It may occur with or without medication overuse. The pain is often mild to moderate; is not always associated with photophobia, phonophobia, nausea, or vomiting; and may resemble a mixture of migraine and tension-type headaches with intermittent severe migraine-type headaches. Depression is present in 80%. Risk factors for transformation include medication overuse (especially opiates and barbiturate combinations), high caffeine consumption, female gender, stressful life events, anxiety, baseline high attack frequency, individuals with lower educational and socioeconomic levels, white patients, those previously married, lifetime injuries to the head or neck, obesity, snoring, arthritis, and diabetes.[45]

Hemicrania continua, with or without medication overuse, is a rare entity with constant, unilateral pain of variable intensity that responds dramatically to indomethacin. Painful exacerbations are associated with autonomic symptoms in 75% of cases (such as conjunctival injection, tearing, rhinorrhea, nasal stuffiness, eyelid edema, forehead sweating, and ptosis), migrainous features (nausea, vomiting, light and noise sensitivity), and a sharp pain lasting less than 1 minute (ice-pick headache) in 40%.

New daily persistent headache (NDPH), with or without medication overuse, is daily and unremitting from (or almost from) the moment of onset in patients with no past history of increasingly frequent migraine or tension-type headache.[46] There may be a self-limited form resolving without therapy within several months and a refractory type resistant to treatment. NDPH, which usually begins in the second and third decades in females and fifth decade in males, has a female preponderance of 2.5:1. This is probably a heterogeneous disorder of uncertain cause, which in about 50% of cases may be triggered by a viral infection or stressful life event. The pain may be unilateral or bilateral, and more than half of patients report migrainous symptoms (such as nausea, light and noise sensitivity, and vomiting). The diagnosis is one of exclusion as there is a long list of secondary causes of NDPH, including the following: postmeningitis headache, chronic meningitis, primary with medication overuse, neoplasms, chronic subdural hematoma, posttraumatic, sphenoid sinusitis, hypertension, spontaneous intracranial hypotension, cervical artery dissections, idiopathic and secondary intracranial hypertension, cerebral venous thrombosis, arteriovenous malformation, Chiari malformation, temporal arteritis, cervicogenic, and temporomandibular joint dysfunction).

If medication overuse or rebound headaches (see below) are a possibility, medications that may be responsible should be tapered. Some acute-treatment medications that may be effective are longer-acting NSAIDs (e.g., naproxen sodium) and hydroxyzine (50 mg p.o., t.i.d., p.r.n.), which may not be associated with medication overuse.

The muscle relaxant baclofen might also be effective, but carisoprodol can be habituating. Another muscle relaxant that may be effective is tizanidine, given at a dosage of 2 mg three times a day, or it can be started as 2 mg at bedtime and titrated upward to the maximum tolerated dose or a maximum dosage of 18 mg in three divided doses daily, depending on the response. Because about 5% of patients on tizanidine develop abnormally elevated transaminase levels, which reverse after discontinuance of the drug, baseline measures and periodic monitoring of liver function for the first 6 months are recommended. Triptans may be used as appropriate but should be limited to 2 or 3 days a week because of the risk of medication overuse.

For prevention of CDH and NDPH, the same medications are used as for chronic tension-type headache and migraine. Fluoxetine may be effective for chronic migraine. Combination therapy may be helpful in some cases. The effect of treatment may not be apparent for weeks. Some data suggest that preventive medications may not be effective for chronic migraine until medication overuse is eliminated, although two studies have suggested that topiramate may be effective in those overusing acute medications.

Hemicrania continua is treated with indomethacin 25 mg t.i.d. for 3 days. If there is no total relief of pain, the dose is increased to 50 mg t.i.d. for 3 days. If there is no response and the diagnosis is still highly suspected, then 75 mg t.i.d. for 3 days can be tried. The addition of a proton pump inhibitor should be considered for those on long-term treatment with indomethacin. If there is no response, then an alternative diagnosis should be considered. If the patient cannot tolerate indomethacin or there are contraindications, other possibly effective medications include celecoxib, verapamil, and melatonin (3 to 15 mg h.s.).

For detoxification or if there is significant medical or psychiatric comorbidity, inpatient treatment may be indicated if outpatient therapy fails. Options include intravenous DHE (0.5 to 1.0 mg IV), usually given with an antiemetic (e.g., metoclopramide, 5 to 10 mg IV) every 8 hours. DHE may be combined with other medications, such as NSAIDs, oral or intravenous corticosteroids, intravenous prochlorperazine, and intravenous valproate sodium [*see* Intractable Migraine and Migraine Status, *above*]. One or more of these treatments can be used in patients who cannot tolerate DHE or patients in whom DHE is contraindicated.

Behavioral therapy and psychological or psychiatric referral may be beneficial. Physical therapy may be useful if there is a myofascial contribution to the headaches. Trigger-point injections and occipital nerve blocks may be worthwhile in some cases.

Even with optimal therapy, about one third of patients who show improvement will experience recurrence of their daily headache and medication overuse pattern. Some patients have intractable CDH that is resistant to all treatments.

Medication Overuse Headaches

Migraineurs are particularly susceptible to MOHs or rebound headaches, which can occur with frequent use of symptomatic medications, including acetaminophen, aspirin, caffeine, NSAIDs with short half-lives (e.g., ibuprofen), butalbital, ergotamine, opiate agonists, and triptans.[47] One study found that migraine progression is associated with opiates (with use 8 or more days per month more pronounced in men) and butalbital (with use 5 or more days per month more pronounced in women). Triptans and NSAIDs induce migraine progression when used by those with 10 to 14 days of migraine at baseline.[48] Frequent use of symptomatic medications may also result in tolerance (the decreased effectiveness of the same dose of an analgesic, often leading to the use of higher doses to achieve the same degree of effectiveness) and in habituation and dependence (respectively, the psychological and physical need to repeatedly use drugs).

According to ICHD-2, MOH may occur when simple analgesics are taken 15 or more days a month for 3 months; when triptans are taken 10 or more days a month; when combination analgesics containing simple analgesics plus opioids, butalbital, or caffeine (alone or together) are taken for 10 or more days a month for 3 months; and when opioids are used 10 or more days a month.[48]

In the treatment of suspected MOH, the medications acetaminophen, aspirin, NSAIDs with short half-lives, and triptans can be stopped abruptly. Caffeine use should be tapered off, to avoid withdrawal symptoms. Opiates and butalbital should be tapered because of the risk of a serious withdrawal syndrome. If butalbital is abruptly discontinued, phenobarbital can be substituted to prevent withdrawal; the phenobarbital is tapered down from 60 mg to 15 mg at night over 1 week. After medication withdrawal, the duration of MOHs from triptans is about 4 days and from other analgesics is about 9 days. A migraine preventive medication can also be started, but it may not be effective when patients are overusing symptomatic medications.

The combination of tizanidine and a long-acting NSAID such as naproxen may be effective in reducing headaches during the withdrawal period. It is not certain if a short course of corticosteroids is beneficial. Inpatient treatment is the same as for CDH (see above).

Drug-Induced Headache

Many drugs can induce acute headache, with some examples including the following: antibiotics (especially amphotericin, griseofulvin, tetracycline, and sulfonamides); nitroglycerin; cardiovascular agents (angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, dipyridamole, hydralazine, methyldopa, and nitroglycerin); erectile dysfunction agents (phosphodiesterase-5 inhibitors such as sildenafil); gastrointestinal medications (histamine receptor antagonists cimetidine and ranitidine and proton pump inhibitors omeprazole and lansoprazole); NSAIDs (especially indomethacin); oncologic agents (anagrelide, cyclosporine, and tacrolimus); and oral contraceptives.

Drug-induced aseptic meningitis, a rare occurrence, has numerous possible causes, including NSAIDs; antibiotics

(e.g., trimethoprim-sulfamethoxazole, sulfasalazine, cephalosporins, ciprofloxacin, isoniazid, and penicillin); intrathecal drugs and diagnostics (e.g., antineoplastic agents such as methotrexate and cytarabine; gentamicin; corticosteroids; spinal anesthesia; baclofen; repeated iophendylate for myelography; and radiolabeled albumin); intraventricular chemotherapy; intravenous immunoglobulin; vaccines (polio; measles, mumps, and rubella; and hepatitis B); and other drugs, such as carbamazepine, muromonab-CD3, and ranitidine.[49,50]

The clinical presentation of drug-induced aseptic meningitis is the same as that of viral meningitis. CSF findings are the same as those in viral meningitis, except for a neutrophil predominance; however, in cases induced by intravenous immunoglobulin, eosinophils are present.

Cluster Headaches

Cluster headaches are an uncommon headache type, occurring in only about 0.2% of the general population, and are four times more common in men than in women.[51,52] The headaches can occur at any age, including childhood and adolescence (although they are rare in children younger than 10 years), but usually begin in the third or fourth decade of life. As the name denotes, this condition is marked by periods of recurrent headaches (one to eight a day) interspersed with periods of remission. In 90% of patients, the clusters occur episodically. In the remaining 10%, the clusters are chronic, with cluster periods lasting for more than 1 year without remission or with remission lasting less than 14 days.

CLINICAL FEATURES

Cluster headaches are one sided and severe. The most common types of pain, in order of decreasing frequency, are orbital, retro-orbital, temporal, supraorbital, and infraorbital. The headache may alternate sides between cluster periods or, rarely, within the same period. The pain is described as constant, boring, pressing, burning, or stabbing; about 30% of patients describe throbbing or pulsating pain. Cluster headaches have a rapid onset, with peak intensity in 5 to 10 minutes, and usually a short duration of 30 to 45 minutes, although a minority of patients may have pain persisting up to 3 hours (rarely longer). During attacks, most patients prefer to walk, sit, kneel, stand, or jog in place. Many find it difficult to lie down, and they feel restless and agitated.

Autonomic symptoms are present in over 97% of cases. Lacrimation and conjunctival injection are each present in about 80% of cases, and ipsilateral nasal congestion or clear drainage is present in 75%. A partial Horner syndrome with a slight ipsilateral ptosis or miosis or a combination of both is present in about 65% of cases and, in some patients, may persist between attacks in later stages of the disorder. Increased forehead sweating may occur in some patients during attacks. Erythema of the eyelid or a circumscribed area of the face or forehead may be present. Nausea and sensitivity to light and noise accompany the headache in up to 50% of cases. An aura, usually visual, occasionally precedes the headache. Small quantities of alcohol, nitroglycerin, and histamine can trigger attacks during cluster periods but not during remission.

DIAGNOSTIC TESTING

Although the yield is small, neuroimaging, preferably MRI with pituitary views, is suggested as the initial evaluation as cluster headache mimics may be extremely difficult to distinguish clinically from the primary type. Those with an abnormal neurologic examination or suspicion of a pituitary abnormality should certainly be imaged.

Symptomatic or secondary cluster headache can result from many causes, including the following: vascular (carotid or vertebral artery dissection or aneurysm; arteriovenous malformations; subdural hematomas; and infarcts); tumors (pituitary lesions and meningiomas); infections (maxillary sinusitis and herpes zoster ophthalmicus); posttraumatic or surgery (facial trauma or following enucleation of eye); dental (following extraction or impacted molar); and other (Chiari malformation, cervical syrinx, or IIH). These headaches are usually atypical in their lack of periodicity or response to medications or their accompaniment with abnormal neurologic signs.

TREATMENT

For acute attacks of cluster headache, inhalation of 100% oxygen administered through a nonrebreathing face mask at a rate of 7 to 15 L/min for 15 to 20 minutes with the patient sitting upright is effective in up to 80% of cases. (However, those with severe chronic obstructive pulmonary disease should not be treated with inhaled oxygen because of the risk for developing severe hypercapnia and CO_2 narcosis.) Sumatriptan, 6 mg subcutaneously, is effective in about 75% of all cluster headache patients, with no tachyphylaxis or rebound effect in most patients. Intranasal sumatriptan and zolmitriptan are less efficacious with oral triptans, having modest efficacy. Intravenous DHE, 1 mg, may provide relief in less than 10 minutes; onset is slower with intramuscular or intranasal administration. Triptans and DHE should not be used within 24 hours of each other. Ergotamine may also be effective. Topical lidocaine 4%, administered as nosedrops, may be modestly effective.

Transitional treatments are medications that may induce rapid suppression of attacks before a preventive medication takes effect. Transitional treatments include prednisone, 80 mg daily for 2 days, followed by 20 mg decrements every 2 days, 10 mg for 2 days, and then stopping (the drug is given in the morning to prevent interference with sleep); ergotamine tartrate, 1 mg orally twice a day, including a bedtime dose if nocturnal attacks occur (the drug is contraindicated in patients with peripheral vascular and cardiovascular disease; ergotamine and triptans should not be used within 24 hours of each other); DHE, 0.5 to 1.0 mg subcutaneously or intramuscularly every 8 to 12 hours; and a greater occipital nerve block on the side ipsilateral to the attacks, using a corticosteroid (such as 120 mg of methylprednisolone) and an anesthetic (such as 3 mL of 1% lidocaine).

A number of medications may be effective for prevention of cluster headaches. Verapamil is the drug of choice for both episodic and chronic types. It is started at 120 to 240 mg a day and slowly increased (80 mg increase every 3 to 7 days as tolerated) to 480 mg if necessary. The drug can be given in both a regular formulation three times daily and an

extended-release formulation once a day. In some cases of chronic cluster headache, a daily dose up to 960 mg may be necessary. With daily doses of 480 mg or higher, baseline and serial electrocardiograms are indicated to monitor for the development of heart block, which becomes more frequent at higher doses.

Other medications that may be effective include topiramate (50 to 100 mg daily); divalproex sodium ER (500 to 3,000 mg daily depending upon response); lithium carbonate (150 to 300 mg t.i.d. with monitoring of blood levels), especially for chronic rather than episodic cluster; baclofen (10 mg t.i.d.); and melatonin, 9 mg at bedtime. For chronic or intractable cases, combination therapy can be used.

Surgical treatment may be useful for patients with total resistance to medical treatment and strictly unilateral pain. Options include percutaneous radiofrequency retrogasserian rhizotomy, gamma-knife radiosurgery to ablate the trigeminal nerve root, and percutaneous retrogasserian glycerol rhizolysis.

Geriatric Headache

Older persons have fewer headaches than younger ones. The prevalence of headaches at different ages in women and men, respectively, is as follows: 21 to 34 years, 92% and 74%; 55 to 74 years, 66% and 53%; and after age 75, 55% and 22%.[53] Although 90% of headaches in younger patients are of the primary type, only 66% of headaches in the elderly are primary.[54] There is a decreasing prevalence of migraine with older age. Past the age of 70 years, only 5% of women and 2% of men still have migraine. There are many causes of new-onset headaches in the elderly, some of which can be particularly worrisome.[55] The risk of serious secondary disorders in persons older than 65 years is 10 times higher than that in younger persons.[56]

LATE-LIFE MIGRAINE ACCOMPANIMENTS

Late-life migraine accompaniments are transient visual, sensory, motor, or behavioral neurologic manifestations that are similar or identical to migraine aura.[57] Headache is associated with only 50% of cases and may be mild. These accompaniments occur more often in men than in women. From most to least common, migraine accompaniments consist of visual symptoms (transient blindness, homonymous hemianopsia, and blurring of vision); paresthesias (numbness, tingling, pins-and-needles sensation, or a heavy feeling of an extremity); brainstem and cerebellar dysfunction (ataxia, clumsiness, hearing loss, tinnitus, vertigo, and syncope); and disturbances of speech (dysarthria or dysphasia).

Other causes of transient cerebral ischemia should be considered, especially when the patient is seen after the first episode or if the case has unusual aspects. The usual diagnostic evaluation for TIAs or seizures is performed [*see 11: IV Cerebrovascular Disorders and 11:XII Epilepsy*].

Features that help distinguish migraine accompaniments from TIAs include a gradual buildup of sensory symptoms; a march of sensory paresthesias; serial progression from one accompaniment to another; longer duration (90% of TIAs last for less than 15 minutes); and multiple stereotypical episodes.

If the episodes are frequent, the usual preventive medications can be considered. However, medication use can be problematic in the elderly because of comorbidity, changes in pharmacokinetics where lower doses may be indicated, accentuation of side effects, and concerns over polypharmacy.

CEREBROVASCULAR DISEASE

Headaches commonly accompany stroke. Headache may occur in up to 34% with ischemic infarcts, 57% with parenchymal hemorrhage, 36% with TIAs, and 23% with lacunar infarcts.[58] Women and patients with a history of recurrent throbbing headaches are more likely to have headaches associated with stroke. The headache begins before the stroke in up to 60% of cases and at its onset in 25%. The quality, onset, and duration of stroke-associated headaches vary widely. The headaches are equally likely to be abrupt and to be gradual in onset. In patients presenting with what they consider to be the worst headaches of their lives, SAH should be excluded.

Headache accompanying stroke is usually unilateral, focal, and of mild to moderate severity, although up to 45% of patients may have a severe headache. The headache may be throbbing or nonthrobbing and, in rare cases, may be stabbing. The headache is more often ipsilateral than contralateral to the side of the cerebral ischemia. Migraine features (including nausea, vomiting, light, and noise sensitivity) are present in up to 40%.

Headache is more common in ischemia of the posterior circulation than of the anterior circulation and more common in cortical than in subcortical events. The headache is of longest duration in cardioembolic infarcts and thrombotic infarcts, of medium duration in lacunar infarction, and of shortest duration in TIAs.

HEAD TRAUMA

Although there are numerous causes of head trauma, falls are of particular concern in the elderly. Approximately 30% of all persons older than 65 years fall at least once a year. Subdural hematomas follow approximately 1% of mild head injuries, even those involving no loss of consciousness, such as a bump on the head or riding a roller coaster. Chronic subdural hematomas occur more often in the elderly because of brain atrophy that causes stretching of the parasagittal bridging veins and a predisposition to tearing. The atrophy in an older person also permits hematomas to accumulate without symptoms for a longer period of time than it does in a younger person. Other risk factors include use of aspirin or warfarin[59] and alcoholism.

Headaches are present in up to 90% of patients with head trauma. The headaches are nonspecific; they can range from mild to severe and from paroxysmal to constant and can be bilateral or unilateral. They may be exacerbated by coughing, straining, or exercise and may be associated with vomiting or nausea. About 50% of patients with chronic subdural hematomas will have altered mental status. A strokelike presentation with a transient or persistent hemiparesis can also occur. Only about 50% of patients with a chronic subdural hematoma will have a history of a head injury. The history may also be inaccurate in patients with dementia.

TEMPORAL ARTERITIS

TA (giant cell arteritis) is a systemic panarteritis that selectively involves arterial walls with significant amounts of elastin. Approximately 50% of patients with TA have polymyalgia rheumatica, and about 15% of patients with polymyalgia rheumatica have TA. Both conditions occur almost exclusively in patients older than 50 years, with a mean age at onset of about 70. The ratio of women to men with TA is 3 to 1. The annual incidence is about 18 per 100,000 population in persons older than 50 years.

Headaches are the most common symptom of TA, reported by 60 to 90% of TA patients.[60] The pain is most often throbbing, although many patients describe a sharp, dull, burning, or lancinating pain. The pain may be intermittent or continuous and is more often severe than moderate or slight. For some patients, the pain may be worse at night when lying on a pillow, while combing the hair, or when washing the face. Tenderness or decreased pulsation of the superficial temporal arteries is present on physical examination in about half of all patients with TA. The location of the headache is variable and may be unilateral or bilateral. Intermittent jaw claudication occurs in 38% of cases.

The diagnosis of TA is based on clinical suspicion, which is usually but not always confirmed by laboratory testing.[61] The three best tests are the Westergren ESR, the CRP level, and temporal artery biopsy. For elderly patients, the ESR range of normal may vary from less than 20 mm/hr to 40 mm/hr. Elevation of the ESR is not specific for TA; elevation of the ESR can be seen in any infectious, inflammatory, or rheumatic disease. TA with a normal ESR has been reported in 10 to 36% of patients. When abnormal, the ESR averages 70 to 80 mm/hr and may reach 120 or even 130 mm/hr. If the ESR is elevated at the time of diagnosis, it can be followed to help guide the corticosteroid dosage.

CRP is an acute-phase plasma protein from the liver. As with the ESR, elevation of CRP levels is nonspecific and can be seen with numerous disorders. The CRP level is not influenced by various hematologic factors or age and is more sensitive than the ESR for the detection of TA. The combination of ESR and CRP levels gives the best specificity (97%).

The diagnosis of TA is made with certainty when a superficial temporal artery biopsy demonstrates necrotizing arteritis characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells. The false negative rate of temporal artery biopsies ranges from 5 to 44%. Some physicians obtain bilateral temporal artery biopsies for greater yield depending on the degree of clinical suspicion.

In patients without contraindications, treatment of TA is typically started with prednisone at a dosage of 40 to 80 mg a day. The headache will often improve within 24 hours. The initial dose is maintained for about 4 weeks and then slowly reduced over many months, depending on the clinical effect, the ESR, and the occurrence of side effects. Long-term treatment is often required.

TRIGEMINAL NEURALGIA

Trigeminal neuralgia has an annual incidence of 4 to 5/100,000 with a male to female ratio of 1:1.5 and begins after the age of 40 in 90% of cases. About 80% of cases result from vascular compression of the trigeminal nerve at the root entry zone; most commonly, such compression is caused by a branch of the superior cerebellar artery. As about 15% of cases are caused by tumors (vestibular schwannoma [acoustic neuroma], meningioma, epidermoid or other cyst) and 5% by other etiologies (arteriovenous malformation, aneurysms, and multiple sclerosis), routine imaging of the brain should be obtained, preferably with MRI, which is more sensitive than CT.

The pain is a severe, sharp, shooting, or electric shock–like sensation lasting seconds to 2 minutes. It is usually in a unilateral maxillary or mandibular trigeminal distribution and uncommonly in the ophthalmic division. In about 90% of cases of trigeminal neuralgia, the patient has trigger zones, usually in the central part of the face around the nose and lips. Normally, nonpainful stimuli in these zones can trigger pain. Stimuli can include talking, chewing, washing the face, brushing the teeth, shaving, facial movement, and cold air. After a paroxysm of pain, there is a refractory period lasting up to several minutes, during which stimulation of the trigger zone will not trigger pain. Facial grimacing or spasm may accompany the pain (tic douloureux). Between painful paroxysms, the patient is usually pain free, although dull aching may persist for a few minutes after attacks of long duration or multiple clustered attacks. Multiple attacks may occur for weeks or months. About 50% of patients with trigeminal neuralgia will have spontaneous remissions for at least 6 months. Physical examination is usually normal except for trigger zones, although up to 25% of patients will have sensory loss.

Carbamazepine (100 to 200 mg b.i.d. with slow titration as tolerated to a maximum dose of 1,200 mg/day) is effective, and oxcarbazepine (300 mg b.i.d. with slow titration as tolerated to a maximum dose of 1,800 mg/day) is probably effective for treatment.[62] Baclofen (5 mg t.i.d. gradually titrated to 20 mg t.i.d. as necessary), lamotrigine (titrated up to 400 mg/day), and pimozide (rarely used because of side effects) are possibly effective for controlling pain, although there is insufficient evidence to support or refute the efficacy of clonazepam, gabapentin, phenytoin, tizanidine, topical capsaicin, and valproate. The medications can be used alone or in combination. For example, if a patient fails or has an incomplete response to carbamazepine or oxcarbazepine, some evidence supports add-on therapy with lamotrigine or a switch to baclofen. About 30% of patients do not respond to medical treatment but may respond to one of the many surgical approaches available, including percutaneous procedures on the gasserian ganglion, gamma knife, and microvascular decompression.

POSTHERPETIC NEURALGIA

Although herpes zoster most commonly occurs in the thoracic region, the second most commonly involved area is a trigeminal distribution, usually in the ophthalmic division (herpes zoster ophthalmicus), which occurs in 23% of cases.[63] The zoster is almost always unilateral. The incidence of postherpetic neuralgia (PHN) (i.e., the persistence of pain for more than 1 month after the initial outbreak) greatly increases with older age, to about 1,000 per 100,000 population for those who are 80 years of age or older. PHN develops in 50%

of persons older than 50 years and in 80% of those older than 80 years. Zoster involving the face nearly doubles the risk of developing facial PHN, which lasts longer than PHN in other locations.

Typically, the vesicles crust, the skin heals, and the pain resolves within 3 to 4 weeks after the onset of the rash of herpes zoster. PHN involves three types of pain: a constant burning or deep aching; an intermittent spontaneous pain with a jabbing or lancinating quality; and a superficial, sharp, or radiating pain or itching provoked by light touch (allodynia), which is present in 90% of persons with PHN and often interferes with sleep. The type of pain experienced varies from patient to patient.

Treatment with oral corticosteroids (e.g., prednisone, starting at 60 mg/day and tapering off over 2 weeks) may modestly reduce acute pain in herpes zoster but does not lower the risk of PHN and is not used by many physicians because of concern over possible side effects. One week of therapy with famciclovir (500 mg every 8 hours) or valacyclovir (1,000 mg every 8 hours), ideally started within 72 hours after onset of acute zoster, mildly reduces the risk and duration of PHN.

Numerous treatments may be effective for PHN, including tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine), duloxetine, venlafaxine, gabapentin, pregabalin, topical agents (capsaicin, lidocaine, and aspirin), opioids, and tramadol.

Unfortunately, PHN persists for 1 year or more in over 20% of patients. For this reason, the live attenuated vaccine, Zostavax, is recommended by the Advisory Committee on Immunization Practices for those age 60 years or older because it reduces the incidence of herpes zoster by 51%, the burden of illness from herpes zoster by 61%, and the risk of PHN by 66%.[64]

CARDIAC ISCHEMIA

In rare cases, cardiac ischemia can cause a unilateral or bilateral headache brought on by exercise and relieved by rest.[65] The headache can occur alone or can be accompanied by chest pain. Angina is generally believed to be caused by afferent impulses that traverse the cervicothoracic sympathetic ganglia, enter the spinal cord via the first to the fifth thoracic dorsal roots, and produce the characteristic pain in the chest or inner aspects of the arms. Cardiac vagal afferents, which mediate anginal pain in a minority of patients, join the tractus solitarius. A potential pathway for referral of cardiac pain to the head would be convergence with craniovascular afferents.

HYPNIC HEADACHE

Hypnic headache is a rare disorder that occurs more often in the elderly (but with a range of 36 to 83 years of age) and predominantly in women.[66] The headache occurs only during sleep and awakens the sufferer at a consistent time. Nausea is infrequent, and autonomic symptoms are rare. The headache can be unilateral or bilateral, throbbing or nonthrobbing, and mild to severe in intensity. The headaches can last 15 minutes to 3 hours and can occur frequently, as often as nightly, for many years. Medications reported to be effective include caffeine (one or two cups of caffeinated coffee or a 40 to 60 mg caffeine tablet before bedtime); lithium carbonate (300 to 600 mg at bedtime); indomethacin (50 mg t.i.d. tapering off after several weeks); atenolol (25 mg at bedtime); melatonin (3 mg at bedtime); cyclobenzaprine; prednisone (25 mg daily for 15 days and then 12.5 mg daily for 15 days); topiramate (25 to 100 mg daily); botulinum toxin; pregabalin (titrated to 150 mg at bedtime); amitriptyline (titrated to 50 mg at bedtime); and flunarizine (5 mg at bedtime; not available in the United States).

The diagnosis of hypnic headache is one of exclusion. Secondary causes of nocturnal headaches that must be ruled out include drug withdrawal, temporal arteritis, sleep apnea, oxygen desaturation, pheochromocytoma, primary and secondary neoplasms, communicating hydrocephalus, subdural hematoma, and vascular lesions. Migraine, cluster, and chronic paroxysmal hemicrania are other primary headaches that can cause awakening from sleep. Migraine typically has associated symptoms and very uncommonly occurs only during sleep. Cluster headaches have autonomic symptoms and may occur during the day as well as during sleep. Chronic paroxysmal hemicrania occurs both during the day and at night, lasts for less than 30 minutes, and occurs 10 to 30 times a day.

Other Headaches

Numerous other types of headache have been identified. The more common of these are briefly discussed.

FIRST OR WORST AND THUNDERCLAP HEADACHES

The term *first or worst* refers to severe headache of a type the patient has never experienced before, which may be the first episode of a primary headache such as migraine or cluster, or to the worst headache the patient has ever had, which can be caused by numerous primary and secondary disorders [*see Table 10*].[5]

Headache in SAH

Headache is present in 90% of cases of SAH.[67] The classic headache is sudden, severe, and continuous, often with nausea, vomiting, meningismus, focal neurologic findings, and loss of consciousness [*see 11:IV Cerebrovascular Disorders*].

Thunderclap Headache

A sudden severe headache with maximal onset within 1 minute without evidence of SAH is termed a thunderclap headache.[68] Possible causes of thunderclap headaches include the following: SAH, sentinel headache, cerebral venous thrombosis, cervical artery dissection (carotid or vertebral), spontaneous intracranial dissection, pituitary hemorrhage, retroclival hematoma, ischemic stroke, acute hypertensive crisis, reversible cerebral vasoconstriction syndrome, colloid cyst of the third ventricle, acute complicated sinusitis, and primary thunderclap headache.

COUGH, EXERTIONAL, AND SEXUAL HEADACHES

Primary cough, exertional, and sexual headaches have lifetime prevalence rates of 1% each. All three types occur more often in men.[46,69]

Primary cough headache is a bilateral headache of sudden onset that is precipitated by coughing and typically lasts a few seconds to a few minutes but occasionally can last up to

Table 10 Differential Diagnosis of the Acute, Severe, New-Onset Headache

- Primary headache disorders
  - Migraine
  - Cluster
  - Primary exertional headache
  - Primary orgasmic cephalalgia
- Posttraumatic
  - Subdural and epidural hematomas
  - Retroclival hematoma
  - Parenchymal hemorrhage
- Associated with vascular disorders
  - Acute ischemic cerebrovascular disease
  - Unruptured saccular aneurysm
  - Subarachnoid hemorrhage
  - Systemic lupus erythematosus
  - Temporal arteritis
  - Internal carotid and vertebral artery dissection
  - Cerebral venous thrombosis
  - Acute hypertension
    - Pressor response
    - Pheochromocytoma
    - Preeclampsia
  - Reversible cerebral vasoconstriction syndrome
  - Primary thunderclap headache
- Associated with nonvascular intracranial disorders
  - Intermittent hydrocephalus
  - Idiopathic intracranial hypertension
  - Post–lumbar puncture
- Spontaneous intracranial hypotension
  - Related to intrathecal injections
  - Intracranial neoplasm
  - Pituitary apoplexy
- Acute intoxications
- Associated with noncephalic infection
  - Acute febrile illness
  - Acute pyelonephritis
- Cephalic infection
  - Meningoencephalitis
  - Acute sinusitis
- Acute mountain sickness
- Disorders of eyes
  - Acute optic neuritis
  - Acute glaucoma
- Cervicogenic
  - Greater occipital neuralgia
  - Cervical myositis
- Trigeminal neuralgia

several hours.[70] About 25% of patients have the onset after a respiratory infection with cough. This is an infrequent type of headache, with patients having a mean age at onset of about 63 years. The diagnosis is one of exclusion. Patients should undergo neuroimaging with MRI of the brain with and without contrast to exclude pathology such as Chiari malformation, platybasia, basilar impression, brain tumors, subdural hematoma, and spontaneous intracranial hypotension. Although there are scattered case reports of unruptured intracranial aneurysms, carotid stenosis, and vertebrobasilar disease, these may be incidental findings rather than causes of cough headache. Treatments that may be effective include indomethacin (25 mg b.i.d. or t.i.d. increased as needed to 50 mg t.i.d.), a single lumbar puncture, and acetazolamide.

Primary cough headache also includes headache brought on by sneezing, blowing the nose, laughing, crying, weightlifting, bending, stooping, or straining with a bowel movement. Weightlifting can also produce a benign acute bilateral nuchal-occipital or nuchal-occipital-parietal headache that can persist as a residual ache for days or weeks. SAH should be considered a cause with the initial presentation.

Primary exertional headache is a bilateral, usually throbbing, headache brought on by prolonged physical activity and lasting from 5 minutes to 24 hours. Some of the activities that can cause this headache are running, rowing, tennis, and swimming. In some persons, the headache may be precipitated by one activity but not others. Exercise can trigger a migraine in migraineurs. Depending on the clinical scenario and number of headaches, secondary causes may need to be excluded, such as SAH, sinusitis, brain tumors, pheochromocytoma, cardiac ischemia (anginal headache), and intracranial arterial dissection. The headaches may be prevented by a warm-up period or by avoiding particular activities. Indomethacin may be taken as a preventive (daily dose range of 25 to 150 mg) or 25 to 50 mg taken 30 to 60 minutes before exercise. Migraineurs with exertional headache may respond to migraine preventive medications. Primary exertional headache may resolve over time, often after 6 months.

The IHS criteria describe two types of primary headache precipitated by sexual activity in the absence of any intracranial disorder. Both are usually bilateral and may be prevented or eased by stopping sexual activity before orgasm. The preorgasmic type is a dull ache in the head or neck that intensifies as sexual excitement increases and is probably caused by muscle contraction. The orgasmic type is a sudden severe headache occurring at orgasm; the headache may remain severe for minutes to 4 hours and then fade to a milder headache lasting up to 48 hours. Forty percent of patients with the explosive type of headache also have exertional headache. A postural headache similar to a post–lumbar puncture headache can occur after sexual activity, presumably because of a dural tear and CSF leak triggered by the activity.

Sexual headache occurs more often when a person tries to have repeated orgasms in close succession. A personal or family history of migraine is common. SAH should be excluded, especially when patients present with their first sexual headache, because sexual activity is a precipitant of up to 12% of ruptured saccular aneurysms. Rarely, pheochromocytoma is a cause. Phosphodiesterase-5 inhibitors for erectile dysfunction can cause headaches in about 15% of users.

In some patients, primary orgasmic headaches can be prevented by weight loss, an exercise program, a more passive role during intercourse, variation in posture, and limitation of additional sexual activity on a single day. The headache may also be prevented by taking medication (e.g., indomethacin, ergotamine, or a triptan) 30 to 60 minutes before engaging in sexual activity. Patients with frequent sexual headaches may respond to migraine preventive medications, such as a beta blocker or verapamil.

HEADACHE IN IIH

IIH, also known as pseudotumor cerebri, is a disorder of unknown etiology, with an incidence of 1 to 2 per 100,000 population and an onset usually in persons between the ages of 11 and 58 (mean age 31 years). Ninety percent of

patients are young, obese women. Headache is present in 75% or more of patients, papilledema in 95%, a cranial nerve VI palsy in 25%, transient visual obscurations in 70%, visual loss in 30%, and roaring noises in 70%. The headaches, which are usually pulsatile, daily, and continuous, can be unilateral or bilateral, with a bifrontotemporal location being the most common. Nausea is present in about 60% of cases, and vomiting is present in 40%.

The diagnosis of IIH is one of exclusion because there are many other causes of papilledema [*see Table 11*]. Testing includes a scan of the brain. MRI is more sensitive than CT, and magnetic resonance venography will exclude cerebral venous thrombosis. If the brain scan is negative, a lumbar puncture should be done. The opening pressure is usually elevated and the CSF analysis is normal, except for a low CSF protein level in some cases.

Treatments include weight loss and diuretics to decrease CSF production.[71] Diuretics used in pseudotumor cerebri include acetazolamide, starting with a dosage of 500 mg twice daily and increasing to as much as 1 g twice daily, if necessary, and furosemide, starting at 20 mg twice daily and increasing to as much as 40 mg three times daily. Patients taking furosemide should also receive potassium supplementation. Migraine preventive medications can be useful for persistent headache. Topiramate is especially useful because weight loss is a side effect. Funduscopic examination, visual acuity, and visual fields should be closely monitored to help prevent visual loss. Corticosteroids can be used for emergency treatment of impending visual loss. Surgery may be considered for patients who do not respond to medical treatment and are experiencing progressive visual loss. Surgical options are optic nerve sheath fenestration and lumboperitoneal shunting.

Table 11 Etiologies of Papilledema and Headache[81]

Intracranial mass
Obstruction or deformity of the ventricular system
Cerebral venous thrombosis
Extracranial venous obstruction
Radical neck dissection
Cardiac failure
Chronic respiratory disease
Hypertensive encephalopathy
Preeclampsia and eclampsia
Meningitis/encephalitis
Meningeal carcinomatosis
Elevated CSF protein concentration
Guillain-Barré syndrome
Systemic lupus erythematosus
Spinal tumors, especially oligodendroglioma
Large arteriovenous malformations
Optic neuritis (usually unilateral)
Central retinal venous thrombosis (usually unilateral)
Lead toxicity (in children)
Lyme disease (in children)
Parameningeal infection (in children)
Head trauma
Medications
Vitamin A and derivatives (isotretinoin, etretinate)
Minocycline and tetracycline
Anabolic steroids
Steroid withdrawal
Nalidixic acid
Other medical conditions
Renal disease
Hypoparathyroidism
Hypercoagulable states

CSF = cerebrospinal fluid.

HEADACHE IN BRAIN TUMORS

Up to 70% of persons with brain tumors report headaches.[72] The headaches are usually similar to tension-type headaches but can mimic migraine and cluster headaches. The headaches are usually bilateral but can be unilateral. The neurologic examination can be normal. Suspicion of a brain tumor should be raised when a patient has new-onset or progressive headaches or headaches associated with other problems, such as a seizure, confusion, prolonged nausea and vomiting, hemiparesis, or other focal findings. Headaches that are worst on arising in the morning account for less than 20% of brain tumor headaches.

HEADACHE IN PARANASAL SINUSITIS

Acute sinusitis lasts from 1 day to 4 weeks, and subacute sinusitis lasts from 4 to 12 weeks. Nasal congestion, purulent nasal drainage, and facial tenderness and pain are common. Fever is present in 50% of patients. Anosmia, pain on mastication, and halitosis may also be present. Maxillary sinusitis usually causes pain in the cheek, gums, and maxillary teeth; less often, it causes pain in the periorbital, supraorbital, or temporal areas. The pain decreases when the patient is supine and increases when the head is upright. The maxillary sinus is tender to palpation. Frontal sinusitis causes severe frontal headaches with tenderness to percussion or palpation over the frontal sinus. The pain is less when the head is upright and worse when the patient is supine. Complications include brain abscess, meningitis, subdural or epidural abscess, osteomyelitis, subperiosteal abscess, orbital edema, orbital cellulitis, and orbital abscess.[73]

The headache of sphenoid sinusitis, which accounts for 3% of all cases of acute sinusitis and is usually associated with pansinusitis, may be frontal, occipital, or temporal (alone or in combination) and periorbital. The pain is less when the person is upright and increases when the person is supine, standing, walking, bending, or coughing. Nausea and vomiting are common. Photophobia and eye tearing may be present. Nasal discharge and drainage are present in 30% of cases, and fever occurs in more than 50%. Sphenoid sinusitis may be misdiagnosed as migraine, meningitis, trigeminal neuralgia, or brain tumor. Complications include bacterial meningitis, cavernous sinus thrombosis, subdural abscess, cortical vein thrombosis, ophthalmoplegia, and pituitary insufficiency. A parameningeal focus may cause an aseptic meningitis.

Ethmoid sinusitis produces pain in the periorbital, retroorbital, temporal, or inner canthal area or between the eyes and is usually associated with rhinitis. Coughing, straining, or lying supine can worsen the pain, whereas keeping the head upright lessens it. Complications include meningitis, orbital cellulitis, cavernous sinus thrombosis, and cortical vein thrombosis.

Chronic sinusitis has a duration longer than 12 weeks and can produce a usually low-grade and diffuse headache often

accompanied by nasal obstruction, congestion, and fullness. The symptoms often increase during the day.

Plain sinus radiographs can be used to diagnose acute maxillary or frontal sinusitis but are often inadequate for ethmoid or sphenoid disease. CT of the sinuses in the coronal plane is highly sensitive for the detection of nasal and paranasal sinus disease. However, a routine CT scan of the head may inadequately cover these areas. An MRI of the brain routinely visualizes the paranasal sinuses. Radiographic evidence of sinusitis is present as an incidental finding in 40% of adults without symptoms.

Treatment of paranasal sinusitis is discussed in detail elsewhere [*see 7:XIX Bacterial Infections of the Upper Respiratory Tract*].

HYPERTENSION

Although mild or moderate hypertension does not usually cause headache, severe hypertension from the following conditions can cause headache: acute pressor response to exogenous agents, pheochromocytoma, malignant hypertension, and preeclampsia and eclampsia. Headaches from severe hypertension are usually bioccipital and throbbing but can be generalized or involve frontal throbbing. The headache is often present on awakening in the morning. The diastolic blood pressure is usually elevated to 120 mm Hg or higher. Hypertensive encephalopathy can present as headache, nausea, and vomiting, which may be associated with visual symptoms. Papilledema, focal neurologic deficits, seizures, and decreased levels of consciousness may be present.

A sudden severe headache can reflect an acute pressor response caused when patients receiving monoamine oxidase inhibitors ingest wine or foods with a high tyramine level. Illicit drugs with sympathomimetic actions, such as cocaine, methamphetamine, and methylenedioxymethamphetamine (ecstasy), can also cause acute hypertension and stroke [*see 8:I Management of Poisoning and Drug Overdose*].

HEADACHES AND HEMODIALYSIS

The headaches associated with hemodialysis (HD) are typically bilateral and throbbing, of moderate to severe intensity, in the frontotemporal or occipital regions, or generalized and usually last less than 4 hours. The headache typically occurs between the third and fourth hour after the beginning of the HD session in about 7% of those undergoing chronic treatment.[74] Migraineurs may experience attacks during or following HD, and 20% of patients without a previous history of headaches may experience them with HD.

There are few treatment studies for prevention with a suggestion for use of angiotensin-converting enzyme inhibitors (such as lisinopril), magnesium supplementation, and sodium ramping in patients with hypotensive episodes and disequilibrium syndrome. Symptomatic treatment with acetaminophen is often used.

OCCIPITAL NEURALGIA

The term *occipital neuralgia* is in some ways a misnomer because the pain is not necessarily from the occipital nerve and does not usually have a neuralgic quality. Greater occipital neuralgia is a common type of posttraumatic headache but frequently is also seen in patients without injury. The aching, pressing, stabbing, or throbbing pain may be in a nuchal-occipital, parietal, temporal, frontal, periorbital, or retro-orbital distribution. Occasionally, a true neuralgia may be present, with paroxysmal shooting pain. The headache may last for minutes or hours to days and can be unilateral or bilateral. Lesser occipital neuralgia tends to be similar but with pain generally referred more laterally over the head.

The headache may result from an entrapment of the greater occipital nerve in the aponeurosis of the superior trapezius or semispinalis capitis muscle or may instead be referred pain without nerve compression from trigger points in these or other suboccipital muscles. Digital pressure over the greater occipital nerve at the midsuperior nuchal line (halfway between the posterior mastoid and the occipital protuberance) or just medial to the occipital artery reproduces the headache. However, pain referred from the C2–C3 facet joint or other area of the upper cervical spine, posterior fossa pathology, and temporal arteritis may produce a similar headache. Neuroimaging and blood work may be considered as clinically appropriate.

Occipital neuralgia may improve with local anesthetic nerve blocks (such as 3 cc of 1% lidocaine), which can be combined with an injectable corticosteroid (1% lidocaine combined with either triamcinolone 10 to 20 mg or betamethasone 2 to 4 mg for a total volume of 3 mL of injectate). Before giving the injection, the physician should perform aspiration to avoid inadvertent injection into the occipital or vertebral artery. NSAIDs and muscle relaxants may also be of benefit. If the patient has a true occipital neuralgia with paroxysmal lancinating pain, treatment with baclofen, carbamazepine, or gabapentin may help. Physical therapy and transcutaneous nerve stimulators may help some patients.

PRIMARY STABBING HEADACHE

Primary stabbing headache, previously known as ice-pick headache, ophthalmodynia periodica, and jabs and jolts syndrome, is defined by ICHD-2 as follows: head pain occurring as a single stab or a series of stabs that is exclusively or predominantly felt in the distribution of the first division of the trigeminal nerve (orbit, temple, and parietal area), lasts for up to a few seconds, and recurs with irregular frequency, ranging from one to many per day without accompanying symptoms not attributed to another disorder. The duration is 1 to 2 seconds in two thirds of patients and rarely up to 10 seconds, with attacks ranging from less than once to more than 50 times per day.[46] The pain can be felt in the occipital region and occasionally be multifocal and bilateral. The lifetime prevalence is up to 35% in the general population and is more common in women (3:1), migraineurs (about 40%), and those with cluster headaches (about 30%). The onset is usually after adolescence, although children can also be affected.

Although most cases are idiopathic, in those with new-onset symptoms, secondary causes have been reported, including ocular or cranial trauma, temporal arteritis, acute glaucoma, intracranial lesions (meningioma and pituitary tumors), and occurring at the onset of herpes zoster and shortly after a stroke. Trigeminal neuralgia involving the first ophthalmic division can be a consideration where

trigger zones and a response to carbamazepine may be present.

Patients with frequent attacks may respond to indomethacin (25 to 50 mg t.i.d.) or, if there is no response, melatonin (6 to 12 mg at bedtime), gabapentin (400 mg b.i.d.), and celecoxib.

EXPLODING HEAD SYNDROME

Episodes of exploding head syndrome, which occur on falling asleep or, less often, on awakening, awaken people from sleep with a sensation of a loud bang in the head, like an explosion.[75] Ten percent of cases are associated with the perception of a flash of light. Five percent of patients report a curious sensation as if they had stopped breathing and had to make a deliberate effort to breathe again. The episodes have a variable frequency and onset at any age, although the most common is middle age and older. The episodes take place in healthy individuals during any stage of sleep without evidence of epileptogenic discharges. The basis of this syndrome may be a delay in the reduction of activity in selected areas of the brainstem reticular formation as the patient passes from wakefulness to sleep. Symptoms typically resolve with time and with reassurance that the disorder is benign.

RED EAR SYNDROME

Red ear syndrome is characterized by episodic burning pain, usually in one ear lobe, associated with flushing or reddening of the ear with a duration of 5 minutes to 3 hours in children and adults.[76] In individuals, one ear, alternating ears, or occasionally both ears can be involved in attacks that can occur rarely or up to four per day. The redness can occur without pain. Frequent episodes might be reduced with preventive use of gabapentin, ibuprofen, amitriptyline, and propranolol.

The syndrome can be idiopathic or occur in association with migraine (during or between headache episodes), thalamic syndrome, atypical glossopharyngeal and trigeminal neuralgia, upper cervical spine pathology (cervical arachnoiditis, cervical spondylosis, traction injury, Chiari malformation, or herpes zoster of the upper cervical roots), and dysfunction of the temporomandibular joint.

BURNING MOUTH SYNDROME

Burning mouth syndrome is characterized by a burning, tingling, hot, scalded, or numb sensation in the oral cavity in patients who have a clinically normal oral mucosal examination.[75] Synonyms include glossodynia, glossopyrosis, glossalgia, stomatodynia, stomatopyrosis, sore tongue and mouth, burning tongue, oral or lingual paresthesia, and oral dysesthesia. This pain occurs most commonly on the anterior two thirds and tip of the tongue but also may occur on the upper alveolar region, palate, lips, and lower alveolar region. Less commonly, the buccal mucosa, floor of the mouth, and throat are affected. The pain may be constant or absent in the morning and progress during the day or be intermittent with symptom-free intervals. The prevalence in the general population is 3.7%, with a 7:1 female-to-male ratio, usually in a middle-aged and elderly population, with a mean age of 60 years. Thus, burning mouth syndrome is not an uncommon disorder but is one that may be uncommonly seen and recognized by neurologists.

The diagnosis is one of exclusion. Although approximately one third may have a psychiatric disorder, often depression, anxiety, or other causes should be considered. The following are causes: xerostomia or dry mouth, which can be the result of medications, such as tricyclic antidepressants, or systemic disease, such as Sjögren syndrome; nutritional deficiency, such as iron, vitamin B_{12}, zinc, or B-complex vitamins; a trigeminal small fiber neuropathy; allergic contact dermatitis resulting from food and oral preparation, which may be detected by patch testing; denture-related etiology; and parafunctional behavior, such as clenching or grinding the teeth, thrusting the tongue, or running the tongue along the teeth. Candidiasis may be a cause in up to 30% of cases and can be present with a normal examination; diabetes mellitus may be present in 5% of cases; and angiotensin-converting enzyme inhibitors (e.g., enalapril, captopril, and lisinopril) can be a cause.

If an underlying cause cannot be found and treated, treatments that might be tried include empiric anticandidal agents, B-complex vitamins, tricyclic antidepressants, gabapentin, oral clonazepam, and topical clonazepam (sucking a 1 mg tablet for 3 minutes and then spitting it out three times a day). Women who are postmenopausal might benefit from estrogen-progesterone replacement therapy.

The author is a consultant or a member of the speakers' bureaus of Eli Lilly, Glaxo-SmithKline, Merck & Co., Inc., Pfizer, Inc., UCB Pharma, Inc., and Teva Pharmaceuticals.

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