Harrison's Principles of Internal Medicine, 18e >

Chapter 14. Headache

Peter J. Goadsby; Neil H. Raskin

Headache: Introduction

Headache is among the most common reasons patients seek medical attention. Diagnosis and management is based on a careful clinical approach augmented by an understanding of the anatomy, physiology, and pharmacology of the nervous system pathways that mediate the various headache syndromes.

General Principles

A classification system developed by the International Headache Society characterizes headache as primary or secondary (**Table 14–1**). *Primary headaches* are those in which headache and its associated features are the disorder in itself, whereas *secondary headaches* are those caused by exogenous disorders. Primary headache often results in considerable disability and a decrease in the patient's quality of life. Mild secondary headache, such as that seen in association with upper respiratory tract infections, is common but rarely worrisome. Life-threatening headache is relatively uncommon, but vigilance is required in order to recognize and appropriately treat such patients.

Table 14-1 Common Causes of Headache

Primary Headache		**Secondary Headache**	
Type	**%**	**Type**	**%**
Tension-type	69	Systemic infection	63
Migraine	16	Head injury	4
Idiopathic stabbing	2	Vascular disorders	1
Exertional	1	Subarachnoid hemorrhage	<1
Cluster	0.1	Brain tumor	0.1

Source: After J Olesen et al: *The Headaches.* Philadelphia, Lippincott, Williams & Wilkins, 2005.

Anatomy and Physiology of Headache

Pain usually occurs when peripheral nociceptors are stimulated in response to tissue injury, visceral distension, or other factors (Chap. 11). In such situations, pain perception is a normal physiologic response mediated by a healthy nervous system. Pain can also result when pain-producing pathways of the peripheral or central nervous system (CNS) are damaged or activated inappropriately. Headache may originate from either or both

mechanisms. Relatively few cranial structures are pain-producing; these include the scalp, middle meningeal artery, dural sinuses, falx cerebri, and proximal segments of the large pial arteries. The ventricular ependyma, choroid plexus, pial veins, and much of the brain parenchyma are not pain-producing.

The key structures involved in primary headache appear to be

- the large intracranial vessels and dura mater and the peripheral terminals of the trigeminal nerve that innervate these structures
- the caudal portion of the trigeminal nucleus, which extends into the dorsal horns of the upper cervical spinal cord and receives input from the first and second cervical nerve roots (the trigeminocervical complex)
- rostral pain-processing regions, such as the ventroposteromedial thalamus and the cortex
- the pain-modulatory systems in the brain that modulate input from trigeminal nociceptors at all levels of the pain-processing pathways

The innervation of the large intracranial vessels and dura mater by the trigeminal nerve is known as the *trigeminovascular system*. Cranial autonomic symptoms, such as *lacrimation* and *nasal congestion*, are prominent in the trigeminal autonomic cephalalgias, including cluster headache and paroxysmal hemicrania, and may also be seen in migraine. These autonomic symptoms reflect activation of cranial parasympathetic pathways, and functional imaging studies indicate that vascular changes in migraine and cluster headache, when present, are similarly driven by these cranial autonomic systems. Migraine and other primary headache types are not “vascular headaches”; these disorders do not reliably manifest vascular changes, and treatment outcomes cannot be predicted by vascular effects. Migraine is a brain disorder, and best understood and managed as such.

Clinical Evaluation of Acute, New-Onset Headache

The patient who presents with a new, severe headache has a differential diagnosis that is quite different from the patient with recurrent headaches over many years. In new-onset and severe headache, the probability of finding a potentially serious cause is considerably greater than in recurrent headache. Patients with recent onset of pain require prompt evaluation and appropriate treatment. Serious causes to be considered include meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumor, and purulent sinusitis. When worrisome symptoms and signs are present (**Table 14–2**), rapid diagnosis and management is critical.

Table 14-2 Headache Symptoms that Suggest a Serious Underlying Disorder

“Worst” headache ever
First severe headache
Subacute worsening over days or weeks
Abnormal neurologic examination
Fever or unexplained systemic signs
Vomiting that precedes headache
Pain induced by bending, lifting, cough
Pain that disturbs sleep or presents immediately upon awakening
Known systemic illness

Onset after age 55
Pain associated with local tenderness, e.g., region of temporal artery

A complete neurologic examination is an essential first step in the evaluation. In most cases, patients with an abnormal examination or a history of recent-onset headache should be evaluated by a CT or MRI study. As an initial screening procedure for intracranial pathology in this setting, CT and MRI methods appear to be equally sensitive. In some circumstances, a lumbar puncture (LP) is also required, unless a benign etiology can be otherwise established. A general evaluation of acute headache might include the investigation of cardiovascular and renal status by blood pressure monitoring and urine examination; eyes by funduscopy, intraocular pressure measurement, and refraction; cranial arteries by palpation; and cervical spine by the effect of passive movement of the head and by imaging.

The psychological state of the patient should also be evaluated since a relationship exists between head pain and depression. Many patients in chronic daily pain cycles become depressed, although depression itself is rarely a cause of headache. Drugs with antidepressant actions are also effective in the prophylactic treatment of both tension-type headache and migraine.

Underlying recurrent headache disorders may be activated by pain that follows otologic or endodontic surgical procedures. Thus, pain about the head as the result of diseased tissue or trauma may reawaken an otherwise quiescent migrainous syndrome. Treatment of the headache is largely ineffective until the cause of the primary problem is addressed.

Serious underlying conditions that are associated with headache are described below. Brain tumor is a rare cause of headache and even less commonly a cause of severe pain. The vast majority of patients presenting with severe headache have a benign cause.

Secondary Headache

The management of secondary headache focuses on diagnosis and treatment of the underlying condition.

Meningitis

Acute, severe headache with stiff neck and fever suggests meningitis. Lumbar puncture is mandatory. Often there is striking accentuation of pain with eye movement. Meningitis can be easily mistaken for migraine in that the cardinal symptoms of pounding headache, photophobia, nausea, and vomiting are frequently present, perhaps reflecting the underlying biology of some of the patients.

Meningitis is discussed in Chaps. 381 and 382.

Intracranial Hemorrhage

Acute, severe headache with stiff neck but without fever suggests subarachnoid hemorrhage. A ruptured aneurysm, arteriovenous malformation, or intraparenchymal hemorrhage may also present with headache alone. Rarely, if the hemorrhage is small or below the foramen magnum, the head CT scan can be normal. Therefore, lumbar puncture may be required to diagnose definitively subarachnoid hemorrhage.

Intracranial hemorrhage is discussed in Chap. 275.

Brain Tumor

Approximately 30% of patients with brain tumors consider headache to be their chief complaint. The head pain is usually nondescript—an intermittent deep, dull aching of moderate intensity, which may worsen with exertion or change in position and may be associated with nausea and vomiting. This pattern of symptoms results from migraine far more often than from brain tumor. The headache of brain tumor disturbs sleep in about 10% of

patients. Vomiting that precedes the appearance of headache by weeks is highly characteristic of posterior fossa brain tumors. A history of amenorrhea or galactorrhea should lead one to question whether a prolactin-secreting pituitary adenoma (or the polycystic ovary syndrome) is the source of headache. Headache arising de novo in a patient with known malignancy suggests either cerebral metastases or carcinomatous meningitis, or both. Head pain appearing abruptly after bending, lifting, or coughing can be due to a posterior fossa mass, a Chiari malformation, or low CSF volume.

Brain tumors are discussed in Chap. 379.

Temporal Arteritis

(See also Chaps. 28 and 326) Temporal (giant cell) arteritis is an inflammatory disorder of arteries that frequently involves the extracranial carotid circulation. It is a common disorder of the elderly; its annual incidence is 77 per 100,000 individuals age 50 and older. The average age of onset is 70 years, and women account for 65% of cases. About half of patients with untreated temporal arteritis develop blindness due to involvement of the ophthalmic artery and its branches; indeed, the ischemic optic neuropathy induced by giant cell arteritis is the major cause of rapidly developing bilateral blindness in patients >60 years. Because treatment with glucocorticoids is effective in preventing this complication, prompt recognition of the disorder is important.

Typical presenting symptoms include headache, polymyalgia rheumatica (Chap. 326), jaw claudication, fever, and weight loss. Headache is the dominant symptom and often appears in association with malaise and muscle aches. Head pain may be unilateral or bilateral and is located temporally in 50% of patients but may involve any and all aspects of the cranium. Pain usually appears gradually over a few hours before peak intensity is reached; occasionally, it is explosive in onset. The quality of pain is only seldom throbbing; it is almost invariably described as dull and boring, with superimposed episodic stabbing pains similar to the sharp pains that appear in migraine. Most patients can recognize that the origin of their head pain is superficial, external to the skull, rather than originating deep within the cranium (the pain site for migraineurs). Scalp tenderness is present, often to a marked degree; brushing the hair or resting the head on a pillow may be impossible because of pain. Headache is usually worse at night and often aggravated by exposure to cold. Additional findings may include reddened, tender nodules or red streaking of the skin overlying the temporal arteries, and tenderness of the temporal or, less commonly, the occipital arteries.

The erythrocyte sedimentation rate (ESR) is often, though not always, elevated; a normal ESR does not exclude giant cell arteritis. A temporal artery biopsy followed by immediate treatment with prednisone 80 mg daily for the first 4–6 weeks should be initiated when clinical suspicion is high. The prevalence of migraine among the elderly is substantial, considerably higher than that of giant cell arteritis. Migraineurs often report amelioration of their headaches with prednisone; thus, caution must be used when interpreting the therapeutic response.

Glaucoma

Glaucoma may present with a prostrating headache associated with nausea and vomiting. The headache often starts with severe eye pain. On physical examination, the eye is often red with a fixed, moderately dilated pupil.

Glaucoma is discussed in Chap. 28.

Primary Headache Syndromes

Primary headaches are disorders in which headache and associated features occur in the absence of any exogenous cause (Table 14–1). The most common are migraine, tension-type headache, and cluster headache.

Migraine

Migraine, the second most common cause of headache, afflicts approximately 15% of women and 6% of men over a one year period. It is usually an episodic headache associated with certain features such as sensitivity to light, sound, or movement; nausea and vomiting often accompany the headache. A useful description of migraine

is a benign and recurring syndrome of headache associated with other symptoms of neurologic dysfunction in varying admixtures (**Table 14–3**). Migraine can often be recognized by its activators, referred to as *triggers*.

Table 14-3 Symptoms Accompanying Severe Migraine Attacks in 500 Patients

Symptom	Patients Affected, %
Nausea	87
Photophobia	82
Lightheadedness	72
Scalp tenderness	65
Vomiting	56
Visual disturbances	36
Paresthesias	33
Vertigo	33
Photopsia	26
Alteration of consciousness	18
Diarrhea	16
Fortification spectra	10
Syncope	10
Seizure	4
Confusional state	4

Source: From NH Raskin, *Headache*, 2nd ed. New York, Churchill Livingston, 1988; with permission.

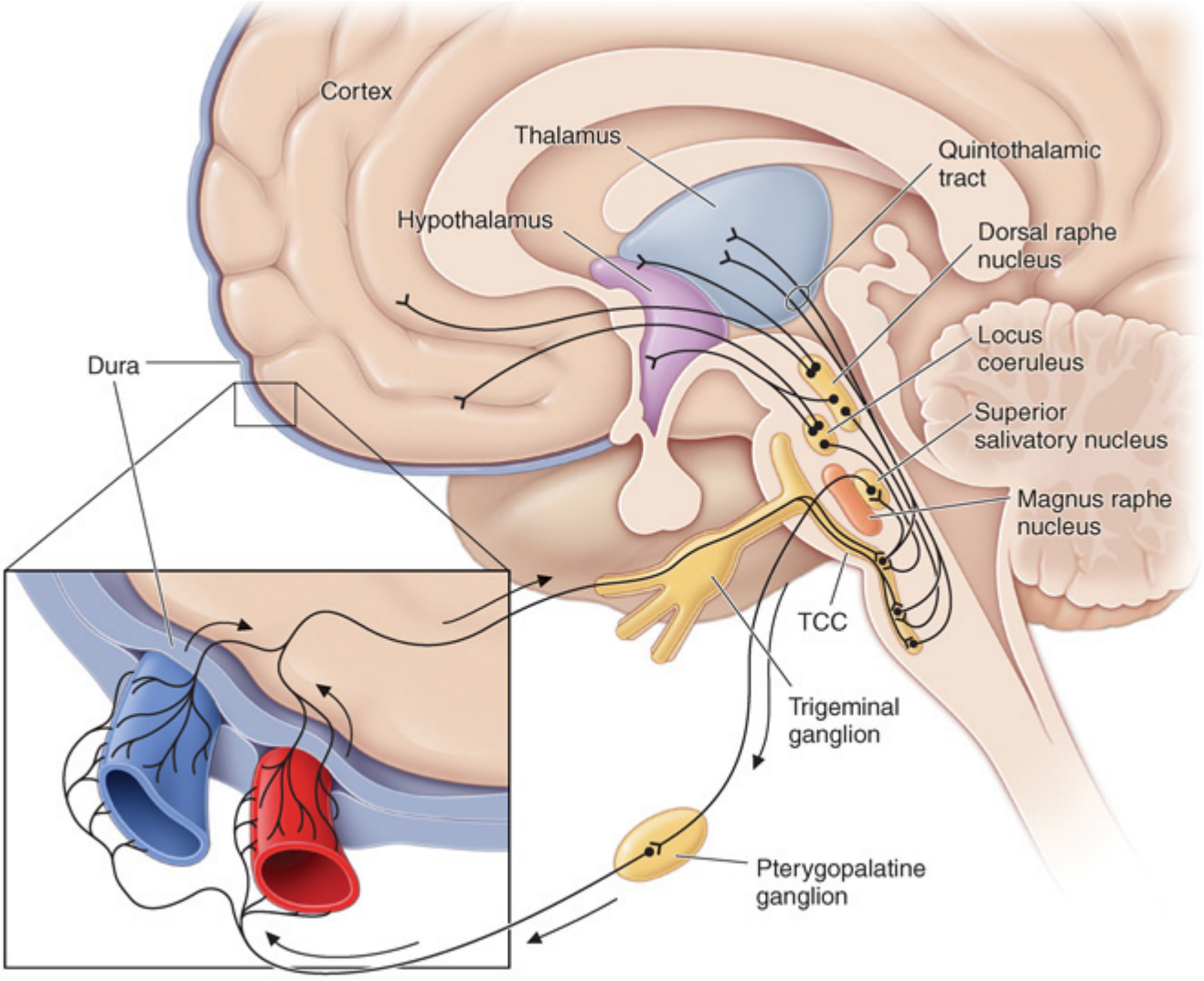
The brain of the migraineur is particularly sensitive to environmental and sensory stimuli; migraine-prone patients do not habituate easily to sensory stimuli. This sensitivity is amplified in females during the menstrual cycle. Headache can be initiated or amplified by various triggers, including glare, bright lights, sounds, or other afferent stimulation; hunger; excess stress; physical exertion; stormy weather or barometric pressure changes; hormonal

fluctuations during menses; lack of or excess sleep; and alcohol or other chemical stimulation. Knowledge of a patient's susceptibility to specific triggers can be useful in management strategies involving lifestyle adjustments.

Pathogenesis

The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic sensory control systems located in the brainstem and thalamus (**Fig. 14-1**).

FIGURE 14-1



Brainstem pathways that modulate sensory input. The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex (TCC). These neurons in turn project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

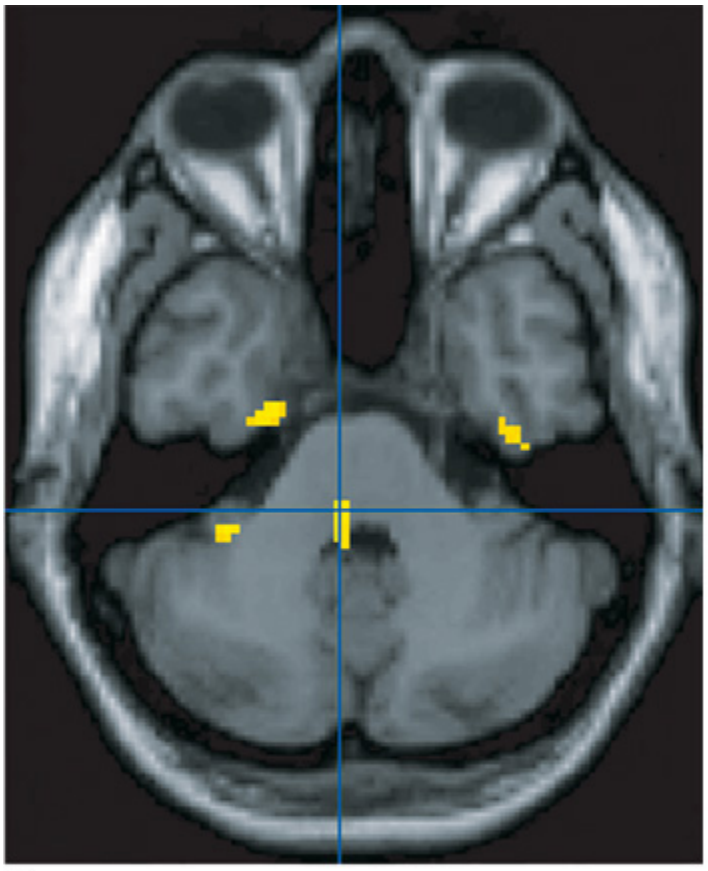
Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, particularly calcitonin gene–related peptide (CGRP), at vascular terminations of the trigeminal nerve and within the trigeminal nucleus. CGRP receptor antagonists have now been shown to be effective in the acute treatment of migraine. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further processing. Additionally, there are projections to the periaqueductal gray and hypothalamus, from which reciprocal descending systems have established antinociceptive effects. Other brainstem regions likely to be involved in descending modulation of trigeminal pain include the nucleus locus coeruleus in the pons and the rostroventromedial medulla.

Pharmacologic and other data point to the involvement of the neurotransmitter 5-hydroxytryptamine (5-HT; also known as serotonin) in migraine. Approximately 60 years ago, methysergide was found to antagonize certain peripheral actions of 5-HT and was introduced as the first drug capable of preventing migraine attacks. The triptans are designed to selectively stimulate subpopulations of 5-HT receptors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors and are less potent at the 5-HT_{1A} receptor. A growing body of data indicates that the antimigraine efficacy of the triptans relates to their ability to stimulate 5-$HT_{1B/1D}$ receptors, which are located on both blood vessels and nerve terminals. Separately, it has now been shown that selective 5-HT_{1F} receptor activation, which has a purely neural effect, can terminate acute migraine.

Data also support a role for dopamine in the pathophysiology of migraine. Most migraine symptoms can be induced by dopaminergic stimulation. Moreover, there is dopamine receptor hypersensitivity in migraineurs, as demonstrated by the induction of yawning, nausea, vomiting, hypotension, and other symptoms of a migraine attack by dopaminergic agonists at doses that do not affect nonmigraineurs. Dopamine receptor antagonists are effective therapeutic agents in migraine, especially when given parenterally or concurrently with other antimigraine agents.

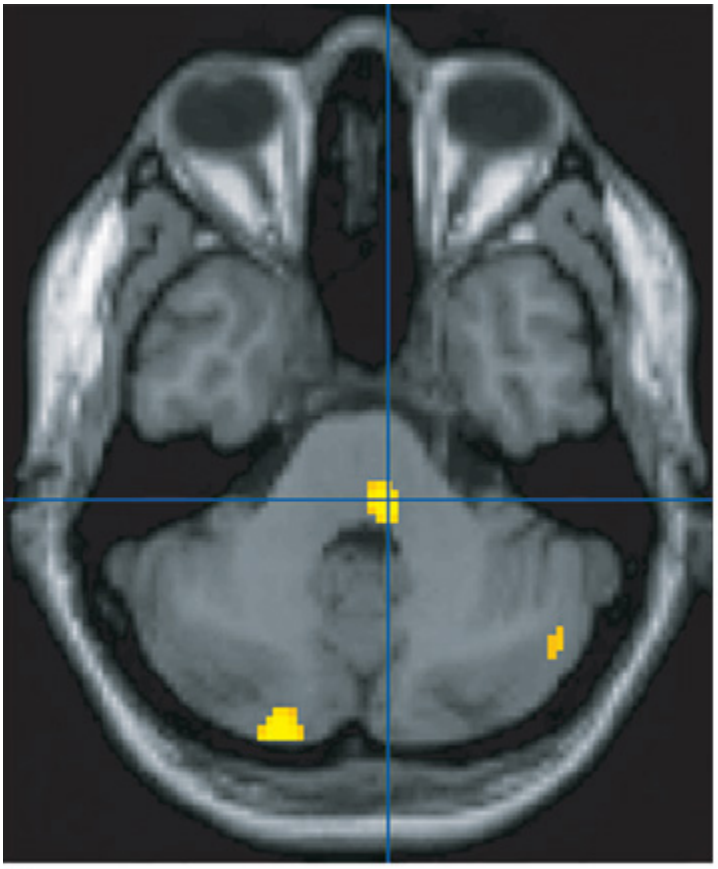
Migraine genes identified by studying families with familial hemiplegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in membrane excitability can predispose to migraine. Mutations involving the $Ca_V2.1$ (P/Q)–type voltage-gated calcium channel *CACNA1A* gene are now known to cause FHM 1; this mutation is responsible for about 50% of FHM. Mutations in the Na^+-K^+ATPase *ATP1A2* gene, designated FHM 2, are responsible for about 20% of FHM. Mutations in the neuronal voltage-gated sodium channel *SCN1A* cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine (**Fig. 14-2**) and the posterior hypothalamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache (**Fig. 14-3**) are good candidates for specific involvement in primary headache.

FIGURE 14-2



A

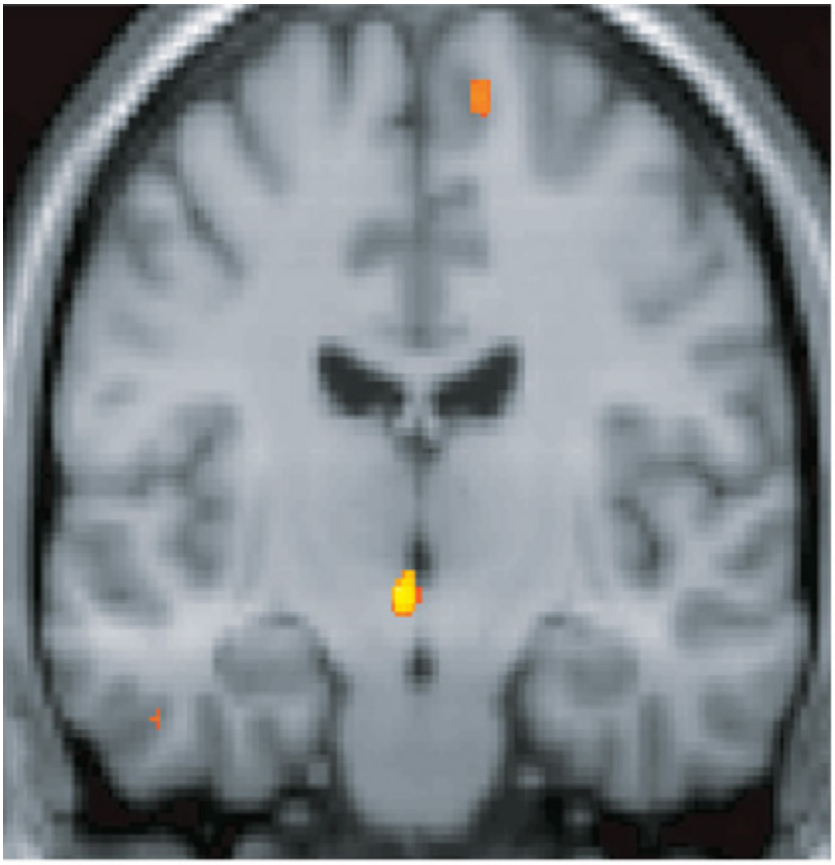
Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com



B

Positron emission tomography (PET) activation in migraine. In spontaneous attacks of episodic migraine there is activation of the region of the dorsolateral pons; an identical pattern is found in chronic migraine (not shown). This area, which includes the noradrenergic locus coeruleus, is fundamental to the expression of migraine. Moreover, lateralization of changes in this region of the brainstem correlates with lateralization of the head pain in hemicranial migraine; the scans shown in panels ***A*** and ***B*** are of patients with acute migraine headache on the right and left side, respectively. *(From S Afridi et al: Brain 128:932, 2005.)*

FIGURE 14-3



A

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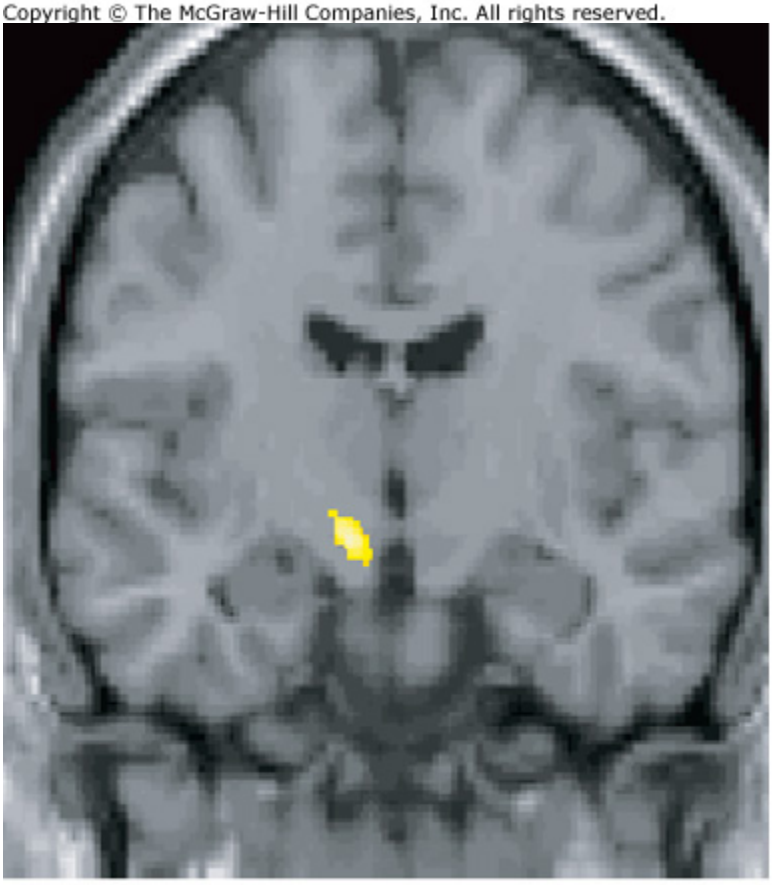


B

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Posterior hypothalamic gray matter activation on positron emission tomography (PET) in a patient with

acute cluster headache (***A***). *(From A May et al: Lancet 352:275, 1998.)* High-resolution T1 weighted MRI obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache (***B***). *(From A May et al: Nat Med 5:836, 1999.)*

Diagnosis and Clinical Features

Diagnostic criteria for migraine headache are listed in **Table 14–4**. A high index of suspicion is required to diagnose migraine: the migraine aura, consisting of visual disturbances with flashing lights or zigzag lines moving across the visual field or of other neurologic symptoms, is reported in only 20–25% of patients. A headache diary can often be helpful in making the diagnosis; this is also helpful in assessing disability and the frequency of treatment for acute attacks. Patients with episodes of migraine that occur daily or near-daily are considered to have chronic migraine (see "Chronic Daily Headache," below). Migraine must be differentiated from tension-type headache (discussed below), the most common primary headache syndrome seen in clinical practice. *Migraine at its most basic level is headache with associated features, and tension-type headache is headache that is featureless. Most patients with disabling headache probably have migraine.*

Table 14-4 Simplified Diagnostic Criteria for Migraine

Repeated attacks of headache lasting 4–72 h in patients with a normal physical examination, no other reasonable cause for the headache, and:	
At Least 2 of the Following Features:	**Plus at Least 1 of the Following Features:**
Unilateral pain	Nausea/vomiting
Throbbing pain	Photophobia and phonophobia
Aggravation by movement	
Moderate or severe intensity	

Source: Adapted from the International Headache Society Classification (Headache Classification Committee of the International Headache Society, 2004).

Patients with acephalgic migraine experience recurrent neurologic symptoms, often with nausea or vomiting, but with little or no headache. Vertigo can be prominent; it has been estimated that one-third of patients referred for vertigo or dizziness have a primary diagnosis of migraine.

Treatment: Migraine Headaches

Once a diagnosis of migraine has been established, it is important to assess the extent of a patient's disease and disability. The Migraine Disability Assessment Score (MIDAS) is a well-validated, easy-to-use tool (**Fig. 14-4**).

FIGURE 14-4

***MIDAS Questionnaire**

INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ____ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches *(do not include days you counted in question 1 where you missed work or school)*? ..... ____ days
3. On how many days in the last 3 months did you **not** do household work because of your headaches? ..... ____ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches *(do not include days you counted in question 3 where you did not do household work)*? ..... ____ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... ____ days

A. On how many days in the last 3 months did you have a headache? *(If a headache lasted more than one day, count each day.)* ..... ____ days

B. On a scale of 0–10, on average how painful were these headaches? *(Where 0 = no pain at all, and 10 = pain as bad as it can be.)* ..... ____

*Migraine Disability Assessment Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: > 20

Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

MIDAS Questionnaire.

Patient education is an important aspect of migraine management. Information for patients is available at *www.achenet.org*, the website of the American Council for Headache Education (ACHE). It is helpful for patients to understand that migraine is an inherited tendency to headache; that migraine can be modified and controlled by lifestyle adjustments and medications, but it cannot be eradicated; and that, except in some occasions in women on oral estrogens or contraceptives, migraine is not associated with serious or life-threatening illnesses.

Nonpharmacologic Management

Migraine can often be managed to some degree by a variety of nonpharmacologic approaches. Most patients benefit by the identification and avoidance of specific headache triggers. A regulated lifestyle is helpful, including a healthful diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance of acute changes in stress levels.

The measures that benefit a given individual should be used routinely since they provide a simple, cost-effective approach to migraine management. Patients with migraine do not encounter more stress than headache-free individuals; overresponsiveness to stress appears to be the issue. Since the stresses of everyday living cannot be eliminated, lessening one's response to stress by various techniques is helpful for many patients. These may include yoga, transcendental meditation, hypnosis, and conditioning techniques such as biofeedback. For most patients, this approach is, at best, an adjunct to pharmacotherapy. Nonpharmacologic measures are unlikely to prevent all migraine attacks. If these measures fail to prevent an attack, pharmacologic approaches are then needed to abort an attack.

Acute Attack Therapies for Migraine

The mainstay of pharmacologic therapy is the judicious use of one or more of the many drugs that are effective in

migraine (**Table 14–5**). The selection of the optimal regimen for a given patient depends on a number of factors, the most important of which is the severity of the attack. Mild migraine attacks can usually be managed by oral agents; the average efficacy rate is 50–70%. Severe migraine attacks may require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of three major pharmacologic classes: anti-inflammatory agents, 5-$HT_{1B/1D}$ receptor agonists, and dopamine receptor antagonists.

Table 14-5 Treatment of Acute Migraine

Drug	Trade Name	Dosage
Simple Analgesics		
Acetaminophen, aspirin, caffeine	Excedrin Migraine	Two tablets or caplets q6h (max 8 per day)
NSAIDs		
Naproxen	Aleve, Anaprox, generic	220–550 mg PO bid
Ibuprofen	Advil, Motrin, Nuprin, generic	400 mg PO q3–4h
Tolfenamic acid	Clotam Rapid	200 mg PO. May repeat ×1 after 1–2 h
5-HT_1 Agonists		
Oral		
Ergotamine	Ergomar	One 2 mg sublingual tablet at onset and q$^1/_2$h (max 3 per day, 5 per week)
Ergotamine 1 mg, caffeine 100 mg	Ercaf, Wigraine	One or two tablets at onset, then one tablet q$^1/_2$h (max 6 per day, 10 per week)
Naratriptan	Amerge	2.5 mg tablet at onset; may repeat once after 4 h
Rizatriptan	Maxalt	5–10 mg tablet at onset; may repeat after 2 h (max 30 mg/d)
	Maxalt-MLT	
Sumatriptan	Imitrex	50–100 mg tablet at onset; may repeat after 2 h (max 200 mg/d)
Frovatriptan	Frova	2.5 mg tablet at onset, may repeat after 2 h (max 5 mg/d)
Almotriptan	Axert	12.5 mg tablet at onset, may repeat after 2 h (max 25 mg/d)

Eletriptan	Relpax	40 or 80 mg
Zolmitriptan	Zomig Zomig Rapimelt	2.5 mg tablet at onset; may repeat after 2 h (max 10 mg/d)
Nasal		
Dihydroergotamine	Migranal Nasal Spray	Prior to nasal spray, the pump must be primed 4 times; 1 spray (0.5 mg) is administered, followed in 15 min by a second spray
Sumatriptan	Imitrex Nasal Spray	5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray (may repeat once after 2 h, not to exceed a dose of 40 mg/d)
Zolmitriptan	Zomig	5 mg intranasal spray as one spray (may repeat once after 2 h, not to exceed a dose of 10 mg/d)
Parenteral		
Dihydroergotamine	DHE-45	1 mg IV, IM, or SC at onset and q1h (max 3 mg/d, 6 mg per week)
Sumatriptan	Imitrex Injection	6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h)
Dopamine Antagonists		
Oral		
Metoclopramide	Reglan,[a] generic[a]	5–10 mg/d
Prochlorperazine	Compazine,[a] generic[a]	1–25 mg/d
Parenteral		
Chlorpromazine	Generic[a]	0.1 mg/kg IV at 2 mg/min; max 35 mg/d
Metoclopramide	Reglan,[a] generic	10 mg IV
Prochlorperazine	Compazine,[a] generic[a]	10 mg IV
Other		
Oral		
Acetaminophen, 325 mg, *plus*	Midrin,	

dichloralphenazone, 100 mg, *plus* isometheptene, 65 mg	Duradrin, generic	Two capsules at onset followed by 1 capsule q1h (max 5 capsules)
Nasal		
Butorphanol	Stadol[a]	1 mg (1 spray in 1 nostril), may repeat if necessary in 1–2 h
Parenteral		
Narcotics	Generic[a]	Multiple preparations and dosages; see Table 11-1

[a]Not all drugs are specifically indicated by the FDA for migraine. Local regulations and guidelines should be consulted.

Note: Antiemetics (e.g., domperidone 10 mg or ondansetron 4 or 8 mg) or prokinetics (e.g., metoclopramide 10 mg) are sometimes useful adjuncts.

Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs; 5-HT, 5-hydroxytryptamine.

In general, an adequate dose of whichever agent is chosen should be used as soon as possible after the onset of an attack. If additional medication is required within 60 min because symptoms return or have not abated, the initial dose should be increased for subsequent attacks. Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be constantly refined until one is identified that provides the patient with rapid, complete, and consistent relief with minimal side effects **(Table 14–6)**.

Table 14-6 Clinical Stratification of Acute Specific Migraine Treatments

Clinical Situation	**Treatment Options**
Failed NSAIDS/analgesics	**First tier**
	Sumatriptan 50 mg or 100 mg PO
	Almotriptan 12.5 mg PO
	Rizatriptan 10 mg PO
	Eletriptan 40 mg PO
	Zolmitriptan 2.5 mg PO
	Slower effect/better tolerability
	Naratriptan 2.5 mg PO

	Frovatriptan 2.5 mg PO
	Infrequent headache
	Ergotamine 1–2 mg PO
	Dihydroergotamine nasal spray 2 mg
Early nausea or difficulties taking tablets	Zolmitriptan 5 mg nasal spray
	Sumatriptan 20 mg nasal spray
	Rizatriptan 10 mg MLT wafer
Headache recurrence	Ergotamine 2 mg (most effective PR/usually with caffeine)
	Naratriptan 2.5 mg PO
	Almotriptan 12.5 mg PO
	Eletriptan 40 mg
Tolerating acute treatments poorly	Naratriptan 2.5 mg
	Almotriptan 12.5 mg
Early vomiting	Zolmitriptan 5 mg nasal spray
	Sumatriptan 25 mg PR
	Sumatriptan 6 mg SC
Menses-related headache	**Prevention**
	Ergotamine PO at night
	Estrogen patches
	Treatment
	Triptans
	Dihydroergotamine nasal spray
Very rapidly developing symptoms	Zolmitriptan 5 mg nasal spray

	Sumatriptan 6 mg SC
	Dihydroergotamine 1 mg IM

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Both the severity and duration of a migraine attack can be reduced significantly by nonsteroidal anti-inflammatory agents **(Table 14–5)**. Indeed, many undiagnosed migraineurs are self-treated with nonprescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of anti-inflammatory agents in migraine is usually less than optimal in moderate or severe migraine attacks. The combination of acetaminophen, aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administration (FDA) for the treatment of mild to moderate migraine. The combination of aspirin and metoclopramide has been shown to be comparable to a single dose of sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation.

5-HT$_1$ Receptor Agonists

ORAL

Stimulation of 5-HT$_{1B/1D}$ receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective receptor agonists, while the triptans are selective 5-HT$_{1B/1D}$ receptor agonists. A variety of triptans, 5-HT$_{1B/1D}$ receptor agonists—naratriptan, rizatriptan, eletriptan, sumatriptan, zolmitriptan, almotriptan, and frovatriptan—are now available for the treatment of migraine.

Each drug in the triptan class has similar pharmacologic properties but varies slightly in terms of clinical efficacy. Rizatriptan and eletriptan are the most efficacious of the triptans currently available in the United States. Sumatriptan and zolmitriptan have similar rates of efficacy as well as time to onset, with an advantage of having multiple formulations, whereas almotriptan, frovatriptan, and naratriptan are somewhat slower in onset and are better tolerated. Clinical efficacy appears to be related more to the t_{max} (time to peak plasma level) than to the potency, half-life, or bioavailability. This observation is consistent with a large body of data indicating that faster-acting analgesics are more effective than slower-acting agents.

Unfortunately, monotherapy with a selective oral 5-HT$_{1B/1D}$ agonist does not result in rapid, consistent, and complete relief of migraine in all patients. Triptans are not effective in migraine with aura unless given after the aura is completed and the headache initiated. Side effects are common though often mild and transient. Moreover, 5-HT$_{1B/1D}$ agonists are contraindicated in individuals with a history of cardiovascular and cerebrovascular disease. Recurrence of headache is another important limitation of triptan use and occurs at least occasionally in most patients. Evidence from randomized controlled trials show that coadministration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the initial effect of sumatriptan and, importantly, reduce rates of headache recurrence.

Ergotamine preparations offer a nonselective means of stimulating 5-HT$_1$ receptors. A nonnauseating dose of ergotamine should be sought since a dose that provokes nausea is too high and may intensify head pain. Except for a sublingual formulation of ergotamine, oral formulations of ergotamine also contain 100 mg caffeine (theoretically to enhance ergotamine absorption and possibly to add additional analgesic activity). The average oral ergotamine dose for a migraine attack is 2 mg. Since the clinical studies demonstrating the efficacy of ergotamine in migraine predated the clinical trial methodologies used with the triptans, it is difficult to assess the clinical efficacy of ergotamine versus the triptans. In general, ergotamine appears to have a much higher incidence of nausea than triptans, but less headache recurrence.

NASAL

The fastest-acting nonparenteral antimigraine therapies that can be self-administered include nasal formulations of dihydroergotamine (Migranal), zolmitriptan (Zomig nasal), or sumatriptan. The nasal sprays result in substantial

blood levels within 30–60 min. Although in theory nasal sprays might provide faster and more effective relief of a migraine attack than oral formulations, their reported efficacy is only approximately 50–60%. Studies with an inhalational formulation of dihydroergotamine indicate that its absorption problems can be overcome to produce rapid onset of action with good tolerability.

PARENTERAL

Parenteral administration of drugs such as dihydroergotamine and sumatriptan is approved by the FDA for the rapid relief of a migraine attack. Peak plasma levels of dihydroergotamine are achieved 3 min after IV dosing, 30 min after IM dosing, and 45 min after SC dosing. If an attack has not already peaked, SC or IM administration of 1 mg dihydroergotamine suffices for about 80–90% of patients. Sumatriptan, 6 mg SC, is effective in ~70–80% of patients.

Dopamine Antagonists

ORAL

Oral dopamine antagonists should be considered as adjunctive therapy in migraine. Drug absorption is impaired during migraine because of reduced gastrointestinal motility. Delayed absorption occurs even in the absence of nausea and is related to the severity of the attack and not its duration. Therefore, when oral NSAIDs and/or triptan agents fail, the addition of a dopamine antagonist such as metoclopramide 10 mg should be considered to enhance gastric absorption. In addition, dopamine antagonists decrease nausea/vomiting and restore normal gastric motility.

PARENTERAL

Parenteral dopamine antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-$HT_{1B/1D}$ agonists. A common IV protocol used for the treatment of severe migraine is the administration over 2 min of a mixture of 5 mg of prochlorperazine and 0.5 mg of dihydroergotamine.

Other Medications for Acute Migraine

ORAL

The combination of acetaminophen, dichloralphenazone, and isometheptene, one to two capsules, has been classified by the FDA as “possibly” effective in the treatment of migraine. Since the clinical studies demonstrating the efficacy of this combination analgesic in migraine predated the clinical trial methodologies used with the triptans, it is difficult to compare the efficacy of this sympathomimetic compound to other agents.

NASAL

A nasal preparation of butorphanol is available for the treatment of acute pain. As with all narcotics, the use of nasal butorphanol should be limited to a select group of migraineurs, as described below.

PARENTERAL

Narcotics are effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given frequently in the emergency room. This regimen “works” in the sense that the pain of migraine is eliminated. However, this regimen is clearly suboptimal for patients with recurrent headache. Narcotics do not treat the underlying headache mechanism; rather, they act to alter the pain sensation. Moreover, in patients taking oral narcotics such as oxycodone or hydrocodone, narcotic addiction can greatly confuse the treatment of migraine. Narcotic craving and/or withdrawal can aggravate and accentuate migraine. Therefore, it is recommended that narcotic use in migraine be limited to patients with severe, but infrequent, headaches that are unresponsive to other pharmacologic approaches.

Medication-Overuse Headache

Acute attack medications, particularly codeine or barbiturate-containing compound analgesics, have a propensity to aggravate headache frequency and induce a state of refractory daily or near-daily headache called *medication-*

overuse headache. This condition is likely not a separate headache entity but a reaction of the migraine patient to a particular medicine. Migraine patients who have two or more headache days a week should be cautioned about frequent analgesic use (see "Chronic Daily Headache," below).

Preventive Treatments for Migraine

Patients with an increasing frequency of migraine attacks, or with attacks that are either unresponsive or poorly responsive to abortive treatments, are good candidates for preventive agents. In general, a preventive medication should be considered in the subset of patients with five or more attacks a month. Significant side effects are associated with the use of many of these agents; furthermore, determination of dose can be difficult since the recommended doses have been derived for conditions other than migraine. The mechanism of action of these drugs is unclear; it seems likely that the brain sensitivity that underlies migraine is modified. Patients are usually started on a low dose of a chosen treatment; the dose is then gradually increased, up to a reasonable maximum to achieve clinical benefit.

Drugs that have the capacity to stabilize migraine are listed in **Table 14–7**. Drugs must be taken daily, and there is usually a lag of at least 2–12 weeks before an effect is seen. The drugs that have been approved by the FDA for the prophylactic treatment of migraine include propranolol, timolol, sodium valproate, topiramate, and methysergide (not available in the United States). In addition, a number of other drugs appear to display prophylactic efficacy. This group includes amitriptyline, nortriptyline, flunarizine, phenelzine, gabapentin, and cyproheptadine. Placebo-controlled trials of onabotulinum toxin type A in episodic migraine were negative, while, overall, placebo-controlled trials in chronic migraine were positive. Phenelzine and methysergide are usually reserved for recalcitrant cases because of their serious potential side effects. Phenelzine is a monoamine oxidase inhibitor (MAOI); therefore, tyramine-containing foods, decongestants, and meperidine are contraindicated. Methysergide may cause retroperitoneal or cardiac valvular fibrosis when it is used for >6 months, and thus monitoring is required for patients using this drug; the risk of fibrosis is about 1:1500 and is likely to reverse after the drug is stopped.

Table 14-7 Preventive Treatments in Migraine[a]

Drug	Dose	Selected Side Effects
Pizotifen[b]	0.5–2 mg qd	Weight gain
		Drowsiness
Beta blocker		
Propranolol	40–120 mg bid	Reduced energy
		Tiredness
		Postural symptoms
		Contraindicated in asthma
Tricyclics		
	10–75	

Amitriptyline	mg at night	Drowsiness
Dothiepin	25–75 mg at night	
Nortriptyline	25–75 mg at night	***Note:*** Some patients may only need a total dose of 10 mg, although generally 1–1.5 mg/kg body weight is required
Anticonvulsants		
Topiramate	25–200 mg/d	Paresthesias
		Cognitive symptoms
		Weight loss
		Glaucoma
		Caution with nephrolithiasis
Valproate	400–600 mg bid	Drowsiness
		Weight gain
		Tremor
		Hair loss
		Fetal abnormalities
		Hematologic or liver abnormalities
Gabapentin	900–3600 mg qd	Dizziness
		Sedation
Serotonergic drugs		
	1–4 mg	

Methysergide	qd	Drowsiness
		Leg cramps
		Hair loss
		Retroperitoneal fibrosis (1-month drug holiday is required every 6 months)
Flunarizine[b]	5–15 mg qd	Drowsiness
		Weight gain
		Depression
		Parkinsonism
No convincing evidence from controlled trials		
Verapamil		
Controlled trials demonstrate *no effect*		
Nimodipine		
Clonidine		
SSRIs: fluoxetine		

[a]Commonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the FDA; local regulations and guidelines should be consulted.

[b]Not available in the United States.

The probability of success with any one of the antimigraine drugs is 50–75%. Many patients are managed adequately with low-dose amitriptyline, propranolol, topiramate, gabapentin, or valproate. If these agents fail or lead to unacceptable side effects, second-line agents such as methysergide or phenelzine can be used. Once

effective stabilization is achieved, the drug is continued for ~6 months and then slowly tapered to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods, suggesting that these drugs may alter the natural history of migraine.

Tension-Type Headache

Clinical Features

The term *tension-type headache* (TTH) is commonly used to describe a chronic head-pain syndrome characterized by bilateral tight, bandlike discomfort. The pain typically builds slowly, fluctuates in severity, and may persist more or less continuously for many days. The headache may be episodic or chronic (present >15 days per month).

A useful clinical approach is to diagnose TTH in patients whose headaches are completely without accompanying features such as nausea, vomiting, photophobia, phonophobia, osmophobia, throbbing, and aggravation with movement. Such an approach neatly separates migraine, which has one or more of these features and is the main differential diagnosis, from TTH. The International Headache Society's main definition of TTH allows an admixture of nausea, photophobia, or phonophobia in various combinations, although the appendix definition does not; this illustrates the difficulty in distinguishing these two clinical entities. In clinical practice, dichotomizing patients on the basis of the presence of associated features (migraine) and the absence of associated features (TTH) is highly recommended. Indeed patients whose headaches fit the TTH phenotype and who have migraine at other times, along with a family history of migraine, migrainous illnesses of childhood, or typical migraine triggers to their migraine attacks, may be biologically different from those who have TTH headache with none of the features.

Pathophysiology

The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of CNS pain modulation alone, unlike migraine, which involves a more generalized disturbance of sensory modulation. Data suggest a genetic contribution to TTH, but this may not be a valid finding: given the current diagnostic criteria, the studies undoubtedly included many migraine patients. The name *tension-type headache* implies that pain is a product of *nervous tension*, but there is no clear evidence for tension as an etiology. Muscle contraction has been considered to be a feature that distinguishes TTH from migraine, but there appear to be no differences in contraction between the two headache types.

Treatment: Tension-Type Headache

The pain of TTH can generally be managed with simple analgesics such as acetaminophen, aspirin, or NSAIDs. Behavioral approaches including relaxation can also be effective. Clinical studies have demonstrated that triptans in pure TTH are not helpful, although triptans are effective in TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treatment **(Table 14–7)**; other tricyclics, selective serotonin reuptake inhibitors, and the benzodiazepines have not been shown to be effective. There is no evidence for the efficacy of acupuncture. Placebo-controlled trials of onabotulinum toxin type A in chronic TTH have not shown benefit.

Trigeminal Autonomic Cephalalgias, Including Cluster Headache

The trigeminal autonomic cephalalgias (TACs) describe a grouping of primary headaches including cluster headache, paroxysmal hemicrania, and SUNCT (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing)/SUNA (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with cranial *a*utonomic symptoms). TACs are characterized by relatively short-lasting attacks of head pain associated with cranial autonomic symptoms, such as lacrimation, conjunctival injection, or nasal congestion (**Table 14–8**). Pain is usually severe and may occur more than once a day. Because of the associated nasal congestion or rhinorrhea, patients are often misdiagnosed with “sinus headache” and treated with decongestants, which are ineffective.

Table 14-8 Clinical Features of the Trigeminal Autonomic Cephalalgias

		Paroxysmal	**SUNCT**

	Cluster Headache	Hemicrania	
Gender Pain	M > F	F = M	F ˜ M
Type	Stabbing, boring	Throbbing, boring, stabbing	Burning, stabbing, sharp
Severity	Excruciating	Excruciating	Severe to excruciating
Site	Orbit, temple	Orbit, temple	Periorbital
Attack frequency	1/alternate day–8/d	1–40/d (>5/d for more than half the time)	3–200/d
Duration of attack	15–180 min	2–30 min	5–240 s
Autonomic features	Yes	Yes	Yes (prominent conjunctival injection and lacrimation)[a]
Migrainous features[b]	Yes	Yes	Yes
Alcohol trigger	Yes	No	No
Cutaneous triggers	No	No	Yes
Indomethacin effect	—	Yes[c]	—
Abortive treatment	Sumatriptan injection or nasal spray	No effective treatment	Lidocaine (IV)
	Oxygen		
Prophylactic treatment	Verapamil	Indomethacin	Lamotrigine Topiramate
	Methysergide		
	Lithium		Gabapentin

[a]If conjunctival injection and tearing not present, consider SUNA.

[b] Nausea, photophobia, or phonophobia; photophobia and phonophobia are typically unilateral on the side of the pain.

[c]Indicates complete response to indomethacin.

Abbreviation: SUNCT, *s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing.

TACs must be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia, primary stabbing headache, and hypnic headache. The cycling pattern and length, frequency, and timing of attacks are useful in classifying patients. Patients with TACs should undergo pituitary imaging and pituitary function tests as there is an excess of TAC presentations in patients with pituitary tumor–related headache.

Cluster Headache

Cluster headache is a rare form of primary headache with a population frequency of approximately 0.1%. The pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating, and explosive in quality. A core feature of cluster headache is periodicity. At least one of the daily attacks of pain recurs at about the same hour each day for the duration of a cluster bout. The typical cluster headache patient has daily bouts of one to two attacks of relatively short-duration unilateral pain for 8 to 10 weeks a year; this is usually followed by a pain-free interval that averages a little less than 1 year. Cluster headache is characterized as chronic when there is no significant period of sustained remission. Patients are generally perfectly well between episodes. Onset is nocturnal in about 50% of patients, and men are affected three times more often than women. Patients with cluster headache tend to move about during attacks, pacing, rocking, or rubbing their head for relief; some may even become aggressive during attacks. This is in sharp contrast to patients with migraine, who prefer to remain motionless during attacks.

Cluster headache is associated with ipsilateral symptoms of cranial parasympathetic autonomic activation: conjunctival injection or lacrimation, rhinorrhea or nasal congestion, or cranial sympathetic dysfunction such as ptosis. The sympathetic deficit is peripheral and likely to be due to parasympathetic activation with injury to ascending sympathetic fibers surrounding a dilated carotid artery as it passes into the cranial cavity. When present, photophobia and phonophobia are far more likely to be unilateral and on the same side of the pain, rather than bilateral, as is seen in migraine. This phenomenon of unilateral photophobia/phonophobia is characteristic of TACs. Cluster headache is likely to be a disorder involving central pacemaker neurons in the region of the posterior hypothalamus (Fig. 14-3).

Treatment: Cluster Headache

The most satisfactory treatment is the administration of drugs to prevent cluster attacks until the bout is over. However, treatment of acute attacks is required for all cluster headache patients at some time.

ACUTE ATTACK TREATMENT

Cluster headache attacks peak rapidly, and thus a treatment with quick onset is required. Many patients with acute cluster headache respond very well to oxygen inhalation. This should be given as 100% oxygen at 10–12 L/min for 15–20 min. It appears that high flow and high oxygen content are important. Sumatriptan 6 mg SC is

rapid in onset and will usually shorten an attack to 10–15 min; there is no evidence of tachyphylaxis. Sumatriptan (20 mg) and zolmitriptan (5 mg) nasal sprays are both effective in acute cluster headache, offering a useful option for patients who may not wish to self-inject daily. Oral sumatriptan is not effective for prevention or for acute treatment of cluster headache.

PREVENTIVE TREATMENTS

(**Table 14–9**) The choice of a preventive treatment in cluster headache depends in part on the length of the bout. Patients with long bouts or those with chronic cluster headache require medicines that are safe when taken for long periods. For patients with relatively short bouts, limited courses of oral glucocorticoids or methysergide (not available in the United States) can be very useful. A 10-day course of prednisone, beginning at 60 mg daily for 7 days and followed by a rapid taper, may interrupt the pain bout for many patients. When ergotamine (1–2 mg) is used, it is most effective when given 1–2 h before an expected attack. Patients who use ergotamine daily must be educated regarding the early symptoms of ergotism, which may include vomiting, numbness, tingling, pain, and cyanosis of the limbs; a weekly limit of 14 mg should be adhered to. Lithium (600–900 mg qd) appears to be particularly useful for the chronic form of the disorder.

Table 14-9 Preventive Management of Cluster Headache

Short-Term Prevention	**Long-Term Prevention**
Episodic Cluster Headache	**Episodic Cluster Headache & Prolonged Chronic Cluster Headache**
Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days	Verapamil 160–960 mg/d
	Lithium 400–800 mg/d
Methysergide 3–12 mg/d	Methysergide 3–12 mg/d
Verapamil 160–960 mg/d	Topiramate[a] 100–400 mg/d
Greater occipital nerve injection	Gabapentin[a] 1200–3600 mg/d
	Melatonin[a] 9–12 mg/d

[a] Unproven but of potential benefit.

Many experts favor verapamil as the first-line preventive treatment for patients with chronic cluster headache or prolonged bouts. While verapamil compares favorably with lithium in practice, some patients require verapamil doses far in excess of those administered for cardiac disorders. The initial dose range is 40–80 mg twice daily; effective doses may be as high as 960 mg/d. Side effects such as constipation and leg swelling can be problematic. Of paramount concern, however, is the cardiovascular safety of verapamil, particularly at high doses. Verapamil can cause heart block by slowing conduction in the atrioventricular node, a condition that can be monitored by following the PR interval on a standard ECG. Approximately 20% of patients treated with verapamil develop ECG abnormalities, which can be observed with doses as low as 240 mg/d; these abnormalities can worsen over time in patients on stable doses. A baseline ECG is recommended for all patients. The ECG is repeated 10 days after a dose change in those patients whose dose is being increased above 240 mg daily. Dose

increases are usually made in 80-mg increments. For patients on long-term verapamil, ECG monitoring every 6 months is advised.

NEUROSTIMULATION THERAPY

When medical therapies fail in chronic cluster headache, neurostimulation strategies can be employed. Deep-brain stimulation of the region of the posterior hypothalamic gray matter has proven successful in a substantial proportion of patients. Favorable results have also been reported with the less-invasive approach of occipital nerve stimulation.

Paroxysmal Hemicrania

Paroxysmal hemicrania (PH) is characterized by frequent unilateral, severe, short-lasting episodes of headache. Like cluster headache, the pain tends to be retroorbital but may be experienced all over the head and is associated with autonomic phenomena such as lacrimation and nasal congestion. Patients with remissions are said to have episodic PH, whereas those with the nonremitting form are said to have chronic PH. The essential features of PH are unilateral, very severe pain; short-lasting attacks (2–45 min); very frequent attacks (usually more than five a day); marked autonomic features ipsilateral to the pain; rapid course (<72 h); and excellent response to indomethacin. In contrast to cluster headache, which predominantly affects males, the male:female ratio in PH is close to 1:1.

Indomethacin (25–75 mg tid), which can completely suppress attacks of PH, is the treatment of choice. Although therapy may be complicated by indomethacin-induced gastrointestinal side effects, currently there are no consistently effective alternatives. Topiramate is helpful in some cases. Piroxicam has been used, although it is not as effective as indomethacin. Verapamil, an effective treatment for cluster headache, does not appear to be useful for PH. In occasional patients, PH can coexist with trigeminal neuralgia (PH-tic syndrome); similar to cluster-tic syndrome, each component may require separate treatment.

Secondary PH has been reported with lesions in the region of the sella turcica, including arteriovenous malformation, cavernous sinus meningioma, and epidermoid tumors. Secondary PH is more likely if the patient requires high doses (>200 mg/d) of indomethacin. In patients with apparent bilateral PH, raised CSF pressure should be suspected. It is important to note that indomethacin reduces CSF pressure. When a diagnosis of PH is considered, MRI is indicated to exclude a pituitary lesion.

Sunct/Suna

SUNCT (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing) is a rare primary headache syndrome characterized by severe, unilateral orbital or temporal pain that is stabbing or throbbing in quality. Diagnosis requires at least 20 attacks, lasting for 5–240 s; ipsilateral conjunctival injection and lacrimation should be present. In some patients conjunctival injection or lacrimation is missing, and the diagnosis of SUNA (*s*hort-lasting *u*nilateral *n*euralgiform headache attacks with cranial *a*utonomic symptoms) can be made.

Diagnosis

The pain of SUNCT/SUNA is unilateral and may be located anywhere in the head. Three basic patterns can be seen: single stabs, which are usually short-lived; groups of stabs; or a longer attack comprising many stabs between which the pain does not completely resolve, thus giving a “saw-tooth” phenomenon with attacks lasting many minutes. Each pattern may be seen in the context of an underlying continuous head pain. Characteristics that lead to a suspected diagnosis of SUNCT are the cutaneous (or other) triggerability of attacks, a lack of refractory period to triggering between attacks, and the lack of a response to indomethacin. Apart from trigeminal sensory disturbance, the neurologic examination is normal in primary SUNCT.

The diagnosis of SUNCT is often confused with trigeminal neuralgia (TN) particularly in first-division TN (Chap. 376). Minimal or no cranial autonomic symptoms and a clear refractory period to triggering indicate a diagnosis of TN.

Secondary (Symptomatic) Sunct

SUNCT can be seen with posterior fossa or pituitary lesions. All patients with SUNCT/SUNA should be evaluated with pituitary function tests and a brain MRI with pituitary views.

Treatment: Sunct/Suna

Abortive Therapy

Therapy of acute attacks is not a useful concept in SUNCT/SUNA since the attacks are of such short duration. However, IV lidocaine, which arrests the symptoms, can be used in hospitalized patients.

Preventive Therapy

Long-term prevention to minimize disability and hospitalization is the goal of treatment. The most effective treatment for prevention is lamotrigine, 200–400 mg/d. Topiramate and gabapentin may also be effective. Carbamazepine, 400–500 mg/d, has been reported by patients to offer modest benefit.

Surgical approaches such as microvascular decompression or destructive trigeminal procedures are seldom useful and often produce long-term complications. Greater occipital nerve injection has produced limited benefit in some patients. Occipital nerve stimulation is probably helpful in an important subgroup of these patients. Complete control with deep-brain stimulation of the posterior hypothalamic region was reported in a single patient. For intractable cases, short-term prevention with IV lidocaine can be effective, as can occipital nerve stimulation.

Chronic Daily Headache

The broad diagnosis of chronic daily headache (CDH) can be applied when a patient experiences headache on 15 days or more per month. CDH is not a single entity; it encompasses a number of different headache syndromes, including chronic TTH as well as headache secondary to trauma, inflammation, infection, medication overuse, and other causes (**Table 14–10**). Population-based estimates suggest that about 4% of adults have daily or near-daily headache. Daily headache may be primary or secondary, an important consideration in guiding management of this complaint.

Table 14-10 Classification of Chronic Daily Headache

Primary		
>4 h Daily	**<4 h Daily**	**Secondary**
Chronic migraine[a]	Chronic cluster headache[b]	Posttraumatic Head injury Iatrogenic Postinfectious
Chronic tension-type headache[a]	Chronic paroxysmal hemicrania	Inflammatory, such as Giant cell arteritis Sarcoidosis Behçet's syndrome
Hemicrania continua[a]	SUNCT/SUNA	Chronic CNS infection
New daily persistent headache[a]	Hypnic headache	Medication-overuse headache[a]

[a] May be complicated by analgesic overuse.

[b] Some patients may have headache >4 h/d.

Abbreviations: SUNA, *s*hort-lasting *u*nilateral *n*euralgiform headache *a*ttacks with cranial autonomic symptoms; SUNCT, *s*hort-lasting *u*nilateral *n*euralgiform headache attacks with *c*onjunctival injection and *t*earing.

Approach to the Patient: Chronic Daily Headache

The first step in the management of patients with CDH is to diagnose any underlying condition (Table 14–10). For patients with primary headaches, diagnosis of the headache type will guide therapy. Preventive treatments such as tricyclics, either amitriptyline or nortriptyline at doses up to 1 mg/kg, are very useful in patients with CDH arising from migraine or tension-type headache. Tricyclics are started in low doses (10–25 mg) daily and may be given 12 h before the expected time of awakening in order to avoid excess morning sleepiness. Anticonvulsants, such as topiramate, valproate, and gabapentin, are also useful in migraineurs. Flunarizine can also be very effective for some patients, as can methysergide or phenelzine.

Management of Medically Intractable Disabling Chronic Daily Headache

The management of medically intractable headache is difficult. At this time, the only promising approach is occipital nerve stimulation, which appears to modulate thalamic processing in migraine and has also shown promise in chronic cluster headache, SUNCT/SUNA, and hemicrania continua (see below).

Medication-Overuse Headache

Overuse of analgesic medication for headache can aggravate headache frequency and induce a state of refractory daily or near-daily headache called *medication-overuse headache*. A proportion of patients who stop taking analgesics will experience substantial improvement in the severity and frequency of their headache. However, even after cessation of analgesic use, many patients continue to have headache, although they may feel clinically improved in some way, especially if they have been using codeine or barbiturates regularly. The residual symptoms probably represent the underlying headache disorder.

MANAGEMENT OF MEDICATION OVERUSE: OUTPATIENTS

For patients who overuse medications, it is essential that analgesic use be reduced and eliminated. One approach is to reduce the medication dose by 10% every 1–2 weeks. Immediate cessation of analgesic use is possible for some patients, provided there is no contraindication. Both approaches are facilitated by the use of a medication diary maintained during the month or two before cessation; this helps to identify the scope of the problem. A small dose of an NSAID such as naproxen, 500 mg bid, if tolerated, will help relieve residual pain as analgesic use is reduced. NSAID overuse is not usually a problem for patients with daily headache when the dose is taken once or twice daily; however, overuse problems may develop with more frequent dosing schedules. Once the patient has substantially reduced analgesic use, a preventive medication should be introduced. It must be emphasized that *preventives generally do not work in the presence of analgesic overuse*. The most common cause of unresponsiveness to treatment is the use of a preventive when analgesics continue to be used regularly. For some patients, discontinuing analgesics is very difficult; often the best approach is to directly inform the patient that some degree of pain is inevitable during this initial period.

MANAGEMENT OF MEDICATION OVERUSE: INPATIENTS

Some patients will require hospitalization for detoxification. Such patients have typically failed efforts at outpatient

withdrawal or have a significant medical condition, such as diabetes mellitus, which would complicate withdrawal as an outpatient. Following admission to the hospital, acute medications are withdrawn completely on the first day, in the absence of a contraindication. Antiemetics and fluids are administered as required; clonidine is used for opiate withdrawal symptoms. For acute intolerable pain during the waking hours aspirin, 1 g IV (not approved in United States), is useful. IM chlorpromazine can be helpful at night; patients must be adequately hydrated. Three to five days into the admission as the effect of the withdrawn substance settles a course of IV dihydroergotamine (DHE) can be employed. DHE, administered every 8 h for 5 consecutive days, can induce a significant remission that allows a preventive treatment to be established. 5-HT_3 antagonists, such as ondansetron or granisetron, are often required with DHE to prevent significant nausea, and domperidone (not approved in the United States) orally or by suppository can be very helpful.

New Daily Persistent Headache

New daily persistent headache (NDPH) is a clinically distinct syndrome; its causes are listed in **Table 14–11**.

Table 14-11 Differential Diagnosis of New Daily Persistent Headache

Primary	Secondary
Migrainous-type	Subarachnoid hemorrhage
Featureless (tension-type)	Low CSF volume headache
	Raised CSF pressure headache
	Posttraumatic headache[a]
	Chronic meningitis

[a] Includes postinfectious forms.

CLINICAL PRESENTATION

The patient with NDPH presents with headache on most if not all days and the patient can clearly, and often vividly, recall the moment of onset. The headache usually begins abruptly, but onset may be more gradual; evolution over 3 days has been proposed as the upper limit for this syndrome. Patients typically recall the exact day and circumstances of the onset of headache; the new, persistent head pain does not remit. The first priority is to distinguish between a primary and a secondary cause of this syndrome. Subarachnoid hemorrhage is the most serious of the secondary causes and must be excluded either by history or appropriate investigation (Chap. 275).

SECONDARY NDPH

Low CSF Volume Headache

In these syndromes, head pain is positional: it begins when the patient sits or stands upright and resolves upon reclining. The pain, which is occipitofrontal, is usually a dull ache but may be throbbing. Patients with chronic low CSF volume headache typically present with a history of headache from one day to the next that is generally not present on waking but worsens during the day. Recumbency usually improves the headache within minutes, but it takes only minutes to an hour for the pain to return when the patient resumes an upright position.

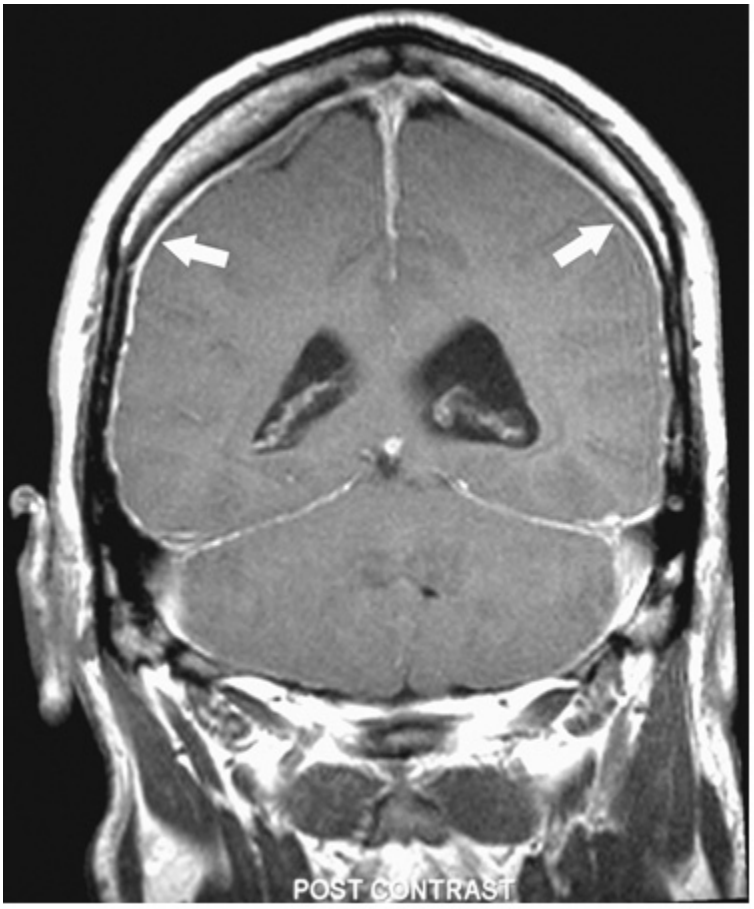
The most common cause of headache due to persistent low CSF volume is CSF leak following lumbar puncture (LP). Post-LP headache usually begins within 48 h but may be delayed for up to 12 days. Its incidence is between

10 and 30%. Beverages with caffeine may provide temporary relief. Besides LP, index events may include epidural injection or a vigorous Valsalva maneuver, such as from lifting, straining, coughing, clearing the eustachian tubes in an airplane, or multiple orgasms. Spontaneous CSF leaks are well recognized, and the diagnosis should be considered whenever the headache history is typical, even when there is no obvious index event. As time passes from the index event, the postural nature may become less apparent; cases in which the index event occurred several years before the eventual diagnosis have been recognized. Symptoms appear to result from low volume rather than low pressure: although low CSF pressures, typically 0–50 mmH_2O, are usually identified, a pressure as high as 140 mmH_2O has been noted with a documented leak.

Postural orthostatic tachycardia syndrome [POTS (Chap. 375)] can present with orthostatic headache similar to low CSF volume headache and is a diagnosis that needs consideration here.

When imaging is indicated to identify the source of a presumed leak, an MRI with gadolinium is the initial study of choice **(Fig. 14-5)**. A striking pattern of diffuse meningeal enhancement is so typical that in the appropriate clinical context the diagnosis is established. Chiari malformations may sometimes be noted on MRI; in such cases, surgery to decompress the posterior fossa usually worsens the headache. Spinal MRI with T2 weighting may reveal a leak and spinal MRI may demonstrate spinal meningeal cysts whose role in these syndromes is yet to be elucidated. The source of CSF leakage may be identified by spinal MRI, by CT, or increasingly with MR myelography, or with ^{111}In-DTPA CSF studies; in the absence of a directly identified site of leakage, early emptying of ^{111}In-DTPA tracer into the bladder or slow progress of tracer across the brain suggests a CSF leak.

FIGURE 14-5



Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low CSF volume headache.

Initial treatment for low CSF volume headache is bed rest. For patients with persistent pain, IV caffeine (500 mg in 500 mL saline administered over 2 h) can be very effective. An ECG to screen for arrhythmia should be

performed before administration. It is reasonable to administer at least two infusions of caffeine before embarking on additional tests to identify the source of the CSF leak. Since IV caffeine is safe and can be curative, it spares many patients the need for further investigations. If unsuccessful, an abdominal binder may be helpful. If a leak can be identified, an autologous blood patch is usually curative. A blood patch is also effective for post-LP headache; in this setting, the location is empirically determined to be the site of the LP. In patients with intractable pain, oral theophylline is a useful alternative; however, its effect is less rapid than caffeine.

Raised CSF Pressure Headache

Raised CSF pressure is well recognized as a cause of headache. Brain imaging can often reveal the cause, such as a space-occupying lesion. NDPH due to raised CSF pressure can be the presenting symptom for patients with idiopathicintracranial hypertension (pseudotumor cerebri) without visual problems, particularly when the fundi are normal. Persistently raised intracranial pressure can trigger chronic migraine. These patients typically present with a history of generalized headache that is present on waking and improves as the day goes on. It is generally worse with recumbency. Visual obscurations are frequent. The diagnosis is relatively straightforward when papilledema is present, but the possibility must be considered even in patients without funduscopic changes. Formal visual field testing should be performed even in the absence of overt ophthalmic involvement. Headache on rising in the morning or nocturnal headache is also characteristic of obstructive sleep apnea or poorly controlled hypertension.

Evaluation of patients suspected to have raised CSF pressure requires brain imaging. It is most efficient to obtain an MRI, including an MR venogram, as the initial study. If there are no contraindications, the CSF pressure should be measured by LP; this should be done when the patient is symptomatic so that both the pressure and the response to removal of 20–30 mL of CSF can be determined. An elevated opening pressure and improvement in headache following removal of CSF is diagnostic.

Initial treatment is with acetazolamide (250–500 mg bid); the headache may improve within weeks. If ineffective, topiramate is the next treatment of choice; it has many actions that may be useful in this setting, including carbonic anhydrase inhibition, weight loss, and neuronal membrane stabilization, likely mediated via effects on phosphorylation pathways. Severely disabled patients who do not respond to medical treatment require intracranial pressure monitoring and may require shunting.

Post-Traumatic Headache

A traumatic event can trigger a headache process that lasts for many months or years after the event. The term *trauma* is used in a very broad sense: headache can develop following an injury to the head, but it can also develop after an infectious episode, typically viral meningitis, a flulike illness, or a parasitic infection. Complaints of dizziness, vertigo, and impaired memory can accompany the headache. Symptoms may remit after several weeks or persist for months and even years after the injury. Typically the neurologic examination is normal and CT or MRI studies are unrevealing. Chronic subdural hematoma may on occasion mimic this disorder. In one series, one-third of patients with NDPH reported headache beginning after a transient flulike illness characterized by fever, neck stiffness, photophobia, and marked malaise. Evaluation reveals no apparent cause for the headache. There is no convincing evidence that persistent Epstein-Barr infection plays a role in this syndrome. A complicating factor is that many patients undergo LP during the acute illness; iatrogenic low CSF volume headache must be considered in these cases. Posttraumatic headache may also be seen after carotid dissection and subarachnoid hemorrhage, and following intracranial surgery. The underlying theme appears to be that a traumatic event involving the pain-producing meninges can trigger a headache process that lasts for many years.

Treatment is largely empirical. Tricyclic antidepressants, notably amitriptyline, and anticonvulsants such as topiramate, valproate, and gabapentin, have been used with reported benefit. The MAOI phenelzine may also be useful in carefully selected patients. The headache usually resolves within 3–5 years, but it can be quite disabling.

PRIMARY NDPH

Primary NDPH occurs in both males and females. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH (Table 14–11). Migrainous features are common and include

unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients. Some patients have a previous history of migraine; however, the proportion of NDPH sufferers with preexisting migraine is no greater than the frequency of migraine in the general population. At 24 months, ~86% of patients are headache-free. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (Table 14–7). Featureless NDPH is one of the primary headache forms most refractory to treatment. Standard preventive therapies can be offered but are often ineffective.

Other Primary Headaches

Hemicrania Continua

The essential features of hemicrania continua are moderate and continuous unilateral pain associated with fluctuations of severe pain; complete resolution of pain with indomethacin; and exacerbations that may be associated with autonomic features, including conjunctival injection, lacrimation, and photophobia on the affected side. The age of onset ranges from 11 to 58 years; women are affected twice as often as men. The cause is unknown.

Treatment: Hemicrania Continua

Treatment consists of indomethacin; other NSAIDs appear to be of little or no benefit. The IM injection of 100 mg indomethacin has been proposed as a diagnostic tool and administration with a placebo injection in a blinded fashion can be very useful diagnostically. Alternatively, a trial of oral indomethacin, starting with 25 mg tid, then 50 mg tid, and then 75 mg tid, can be given. Up to two weeks at the maximal dose may be necessary to assess whether a dose has a useful effect. Topiramate can be helpful in some patients. Occipital nerve stimulation may have a role in patients with hemicrania continua who are unable to tolerate indomethacin.

Primary Stabbing Headache

The essential features of primary stabbing headache are stabbing pain confined to the head or, rarely, the face, lasting from 1 to many seconds or minutes and occurring as a single stab or a series of stabs; absence of associated cranial autonomic features; absence of cutaneous triggering of attacks; and a pattern of recurrence at irregular intervals (hours to days). The pains have been variously described as “ice-pick pains” or “jabs and jolts.” They are more common in patients with other primary headaches, such as migraine, the TACs, and hemicrania continua.

Treatment: Primary Stabbing Headache

The response of primary stabbing headache to indomethacin (25–50 mg two to three times daily) is usually excellent. As a general rule, the symptoms wax and wane, and after a period of control on indomethacin, it is appropriate to withdraw treatment and observe the outcome.

Primary Cough Headache

Primary cough headache is a generalized headache that begins suddenly, lasts for several minutes, and is precipitated by coughing; it is preventable by avoiding coughing or other precipitating events, which can include sneezing, straining, laughing, or stooping. In all patients with this syndrome, serious etiologies must be excluded before a diagnosis of “benign” primary cough headache can be established. A Chiari malformation or any lesion causing obstruction of CSF pathways or displacing cerebral structures can be the cause of the head pain. Other conditions that can present with cough or exertional headache as the initial symptom include cerebral aneurysm, carotid stenosis, and vertebrobasilar disease. Benign cough headache can resemble benign exertional headache (below), but patients with the former condition are typically older.

Treatment: Primary Cough Headache

Indomethacin 25–50 mg two to three times daily is the treatment of choice. Some patients with cough headache obtain pain relief with LP; this is a simple option when compared to prolonged use of indomethacin, and it is

effective in about one-third of patients. The mechanism of this response is unclear.

Primary Exertional Headache

Primary exertional headache has features resembling both cough headache and migraine. It may be precipitated by any form of exercise; it often has the pulsatile quality of migraine. The pain, which can last from 5 min to 24 h, is bilateral and throbbing at onset; migrainous features may develop in patients susceptible to migraine. Primary exertional headache can be prevented by avoiding excessive exertion, particularly in hot weather or at high altitude.

The mechanism of primary exertional headache is unclear. Acute venous distension likely explains one syndrome, the acute onset of headache with straining and breath holding, as in weightlifter's headache. As exertion can result in headache in a number of serious underlying conditions, these must be considered in patients with exertional headache. Pain from angina may be referred to the head, probably by central connections of vagal afferents, and may present as exertional headache (cardiac cephalgia). The link to exercise is the main clinical clue that headache is of cardiac origin. Pheochromocytoma may occasionally cause exertional headache. Intracranial lesions and stenosis of the carotid arteries are other possible etiologies.

Treatment: Primary Exertional Headache

Exercise regimens should begin modestly and progress gradually to higher levels of intensity. Indomethacin at daily doses from 25 to 150 mg is generally effective in benign exertional headache. Indomethacin (50 mg), ergotamine (1 mg orally), dihydroergotamine (2 mg by nasal spray), or methysergide (1–2 mg orally given 30–45 min before exercise) are useful prophylactic measures.

Primary Sex Headache

Sex headache is precipitated by sexual excitement. The pain usually begins as a dull bilateral headache that suddenly becomes intense at orgasm. The headache can be prevented or eased by ceasing sexual activity before orgasm. Three types of sex headache are reported: a dull ache in the head and neck that intensifies as sexual excitement increases; a sudden, severe, explosive headache occurring at orgasm; and a postural headache developing after coitus that resembles the headache of low CSF pressure. The latter arises from vigorous sexual activity and is a form of low CSF pressure headache. Headaches developing at the time of orgasm are not always benign; 5–12% of cases of subarachnoid hemorrhage are precipitated by sexual intercourse. Sex headache is reported by men more often than women and may occur at any time during the years of sexual activity. It may develop on several occasions in succession and then not trouble the patient again, even without an obvious change in sexual activity. In patients who stop sexual activity when headache is first noticed, the pain may subside within a period of 5 min to 2 h. In about half of patients, sex headache will subside within 6 months. About half of patients with sex headache have a history of exertional headaches, but there is no excess of cough headache. Migraine is probably more common in patients with sex headache.

Treatment: Primary Sex Headache

Benign sex headaches recur irregularly and infrequently. Management can often be limited to reassurance and advice about ceasing sexual activity if a mild, warning headache develops. Propranolol can be used to prevent headache that recurs regularly or frequently, but the dosage required varies from 40 to 200 mg/d. An alternative is the calcium channel–blocking agent diltiazem, 60 mg tid. Ergotamine (1 mg) or indomethacin (25–50 mg) taken about 30–45 min prior to sexual activity can also be helpful.

Primary Thunderclap Headache

Sudden onset of severe headache may occur in the absence of any known provocation. The differential diagnosis includes the sentinel bleed of an intracranial aneurysm, cervicocephalic arterial dissection, and cerebral venous thrombosis. Headaches of explosive onset may also be caused by the ingestion of sympathomimetic drugs or of tyramine-containing foods in a patient who is taking MAOIs, or they may be a symptom of pheochromocytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is uncertain. When neuroimaging studies and LP exclude subarachnoid hemorrhage, patients with thunderclap headache usually do

very well over the long term. In one study of patients whose CT scans and CSF findings were negative, ~15% had recurrent episodes of thunderclap headache, and nearly half subsequently developed migraine or tension-type headache.

The first presentation of any sudden-onset severe headache should be vigorously investigated with neuroimaging (CT or, when possible, MRI with MR angiography) and CSF examination. Formal cerebral angiography should be reserved for those cases in which no primary diagnosis is forthcoming and for clinical situations that are particularly suggestive of intracranial aneurysm. Reversible segmental cerebral vasoconstriction may be seen in primary thunderclap headache without an intracranial aneurysm. In the presence of posterior leukoencephalopathy, the differential diagnosis includes cerebral angiitis, drug toxicity (cyclosporine, intrathecal methotrexate/cytarabine, pseudoephedrine, or cocaine), posttransfusion effects, and postpartum angiopathy. Treatment with nimodipine may be helpful, although by definition the vasoconstriction of primary thunderclap headache resolves spontaneously.

Hypnic Headache

This headache syndrome typically begins a few hours after sleep onset. The headaches last from 15 to 30 min and are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are female, and the onset is usually after age 60 years. Headaches are bilateral in most, but may be unilateral. Photophobia or phonophobia and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition.

Treatment: Hypnic Headache

Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). For those intolerant of lithium, verapamil (160 mg) or methysergide (1–4 mg at bedtime) may be alternative strategies. One to two cups of coffee or caffeine, 60 mg orally, at bedtime may be effective in approximately one-third of patients. Case reports suggest that flunarizine, 5 mg nightly, can be effective.

Further Readings

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Brainstem pathways that modulate sensory input. The key pathway for pain in migraine is the trigeminovascular input from the meningeal vessels, which passes through the trigeminal ganglion and synapses on second-order neurons in the trigeminocervical complex (TCC). These neurons in turn project in the quintothalamic tract and, after decussating in the brainstem, synapse on neurons in the thalamus. Important modulation of the trigeminovascular nociceptive input comes from the dorsal raphe nucleus, locus coeruleus, and nucleus raphe magnus.

Positron emission tomography (PET) activation in migraine. In spontaneous attacks of episodic migraine there is activation of the region of the dorsolateral pons; an identical pattern is found in chronic migraine (not shown). This area, which includes the noradrenergic locus coeruleus, is fundamental to the expression of migraine. Moreover, lateralization of changes in this region of the brainstem correlates with lateralization of the head pain in hemicranial migraine; the scans shown in panels ***A*** and ***B*** are of patients with acute migraine headache on the right and left side, respectively. *(From S Afridi et al: Brain 128:932, 2005.)*

Posterior hypothalamic gray matter activation on positron emission tomography (PET) in a patient with acute cluster headache (***A***). *(From A May et al: Lancet 352:275, 1998.)* High-resolution T1 weighted MRI obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache (***B***). *(From A May et al: Nat Med 5:836, 1999.)*

MIDAS Questionnaire.

Magnetic resonance image showing diffuse meningeal enhancement after gadolinium administration in a patient with low CSF volume headache.