11 - 441 Migraine and Other Primary Headache Disorders

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Migraine and Other

Primary Headache

Disorders The general approach to headache as a cardinal symptom is covered else where (Chap. 17); here, disorders in which headache and associated features occur in the absence of any exogenous cause are discussed. The most common are migraine, tension-type headache (TTH), and the trigeminal autonomic cephalalgias (TACs), notably cluster headache; the complete list is summarized in Table 441-1. ■ ■MIGRAINE Migraine, the second most common cause of headache, and the most common headache-related, and indeed neurologic, cause of disability in the world, afflicts ~15% of women and 6% of men over a 1-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 recur ring syndrome of headache associated with other symptoms of neu rologic dysfunction in varying admixtures (Table 441-2). A migraine attack has three phases: premonitory (prodrome), headache phase, and postdrome; each has distinct and sometimes disabling symptoms, which may overlap. About 20–25% of migraine patients have a fourth phase: aura. Migraine can often be recognized by its activators, referred to as triggers. PART 13 Neurologic Disorders Migraineurs are particularly sensitive to environmental and sen sory stimuli; migraine-prone patients do not habituate easily to sensory stimuli. This sensitivity is amplified in women during the menstrual cycle. Headache can be initiated or amplified by various triggers, including altered sleep patterns; hunger; let-down from stress; physical exertion; stormy weather or barometric pressure changes; hormonal fluctuations during menses; and alcohol or other chemical stimulation, such as with nitrates. Knowledge of a patient’s susceptibility to specific triggers can be useful in management strate gies involving lifestyle adjustments, although it is becoming recog nized that some apparent triggers, such as light sensitivity, may be part of the initial phase of the attack; i.e., the premonitory phase or prodrome. Pathogenesis The sensory sensitivity that is characteristic of migraine is probably due to dysfunction of monoaminergic and other sensory control systems located in the brainstem and

hypothalamus (Fig. 441-1). Activation of cells in the trigeminal nucleus results in the release of vasoactive neuropeptides, notably calcitonin gene–related pep tide (CGRP) and pituitary adenylate cyclase activating polypeptide (PACAP), at vascular terminals of the trigeminal nerve and within the trigeminal nucleus. CGRP receptor antagonists, gepants, have now been shown to be effective in the acute and preventive treat ment of migraine, and four monoclonal antibodies to CGRP, or its receptor, have been shown to be effective in migraine prevention, as has one PACAP monoclonal antibody in a phase 2 study. Centrally, the second-order trigeminal neurons cross the midline and project to ventrobasal and posterior nuclei of the thalamus for further process ing. 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 locus coeruleus and parabrachial nucleus in the pons and the rostro ventromedial medulla. Pharmacologic and other data point to the involvement of the neu rotransmitter 5-hydroxytryptamine (5-HT; also known as serotonin) in migraine. In the late 1950s, methysergide was suggested to antagonize certain peripheral actions of 5-HT and was introduced, based on its

anti-inflammatory properties, as a migraine preventive. The triptans were designed to stimulate selectively subpopulations of 5-HT recep tors; at least 14 different 5-HT receptors exist in humans. The triptans are potent agonists of 5-HT1B and 5-HT1D receptors, and some are active at the 5-HT1F receptor; the latter’s exclusive agonists are called ditans. Triptans arrest nerve signaling in the nociceptive pathways of the trigeminovascular system, at least in the trigeminal nucleus cauda lis and trigeminal sensory thalamus, in addition to promoting cranial vasoconstriction, whereas ditans, which are also effective in acute migraine, act only at neural targets. A range of other neural targets are currently under investigation for the acute and preventive management of migraine. Data also support a role for dopamine in the pathophysiology of migraine. Many migraine premonitory 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. Moreover, hypothalamic activation, anterior to that seen in cluster headache, has been shown in the premonitory (prodromal) phase of migraine using functional imaging, and this may hold a key to understanding some part of the role of dopamine in the disorder. Migraine genes identified by studying families with familial hemi plegic migraine (FHM) reveal involvement of ion channels, suggesting that alterations in membrane excitability can predispose to migraine aura. Mutations involving the Cav2.1 (P/Q)–type voltage-gated calcium channel CACNA1A gene are now known to cause FHM 1; this muta tion is responsible for about 50% of FHM cases. Mutations in the Na+- K+ ATPase ATP1A2 gene, designated FHM 2, are responsible for about 20% of FHMs. Mutations in the neuronal voltage-gated sodium chan nel SCN1A cause FHM 3. Functional neuroimaging has suggested that brainstem regions in migraine (Fig. 441-2) and the posterior hypotha lamic gray matter region close to the human circadian pacemaker cells of the suprachiasmatic nucleus in cluster headache (Fig. 441-3) are good candidates for specific involvement in these primary headache disorders. Diagnosis and Clinical Features Classic diagnostic criteria for migraine headache are listed in Table 441-3 and should be considered together with the extended features in Table 441-2. A high index of suspicion is required to diagnose migraine: the migraine aura, consist ing 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. It should be distinguished from the pan-field television static-like disturbance now recognized as visual snow. The first phase of a migraine attack for most patients is the premonitory (prodromal) phase consisting of some or all of the following: yawning, sleepiness, fatigue, cognitive dysfunction, mood change, neck discom fort, polyuria, and food cravings; this can last from a few hours to days. Typically, the headache phase follows with its associated features, such as nausea, photophobia, and phonophobia as well as allodynia or vertigo. When questioned, these typical migraine symptoms also emerge in the premonitory phase, and typical premonitory symptoms also continue into the headache phase. As the headache lessens, many patients enter a postdrome, most commonly feeling tired/weary, hav ing problems concentrating, and experiencing mild neck discomfort that can last for hours and sometimes up to a day. A headache diary can often be helpful in making the diagnosis and in assessing dis ability and the frequency of acute attacks. Patients with episodes of migraine on 8 or more days per month and with at least 15 total days of headache per month are considered to have chronic migraine (see “Chronic Daily Headache” in Chap. 17). Migraine must be differen tiated from TTH (discussed below), which is reported to be the most common primary headache disorder. Migraine has several forms that have been defined (Table 441-1): migraine with and without aura and chronic migraine are the most important. Migraine at its most

TABLE 441-1 Primary Headache Disorders, Modified from International Classification of Headache Disorders-III (Headache Classification Committee of the International Headache Society, 2018)

1. Migraine 1.1 Migraine without aura 1.2 Migraine with aura 1.2.1 Migraine with typical aura 1.2.1.1 Typical aura with headache 1.2.1.2 Typical aura without headache 1.2.2 Migraine with brainstem aura 1.2.3 Hemiplegic migraine 1.2.3.1 Familial hemiplegic migraine (FHM) 1.2.3.1.1 Familial hemiplegic migraine type 1 1.2.3.1.2 Familial hemiplegic migraine type 2 1.2.3.1.3 Familial hemiplegic migraine type 3 1.2.3.1.4 Familial hemiplegic migraine, other loci 1.2.3.2 Sporadic hemiplegic migraine 1.2.4 Retinal migraine 1.3 Chronic migraine 1.4 Complications of migraine 1.4.1 Status migrainosus 1.4.2 Persistent aura without infarction 1.4.3 Migrainous infarction 1.4.4 Migraine aura-triggered seizure 1.5 Probable migraine 1.5.1 Probable migraine without aura 1.5.2 Probable migraine with aura 1.6 Episodic syndromes that may be associated with migraine 1.6.1 Recurrent gastrointestinal disturbance 1.6.1.1 Cyclical vomiting syndrome 1.6.1.2 Abdominal migraine 1.6.2 Benign paroxysmal vertigo 1.6.3 Benign paroxysmal torticollis A 1.6.4 Infantile colic A 1.6.6 Vestibular migraine
2. Tension-type headache 2.1 Infrequent episodic tension-type headache 2.2 Frequent episodic tension-type headache 2.3 Chronic tension-type headache 2.4 Probable tension-type headache
3. Trigeminal autonomic cephalalgias 3.1 Cluster headache 3.1.1 Episodic cluster headache 3.1.2 Chronic cluster headache 3.2 Paroxysmal hemicrania 3.2.1 Episodic paroxysmal hemicrania 3.2.2 Chronic paroxysmal hemicrania 3.3 Short-lasting unilateral neuralgiform headache attacks 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) 3.3.1.1 Episodic SUNCT 3.3.1.2 Chronic SUNCT 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) 3.3.2.1 Episodic SUNA 3.3.2.2 Chronic SUNA 3.4 Hemicrania continua 3.5 Probable trigeminal autonomic cephalalgia

4. Other primary headache disorders 4.1 Primary cough headache 4.2 Primary exercise headache 4.3 Primary headache associated with sexual activity 4.4 Primary thunderclap headache 4.5 Cold-stimulus headache 4.5.1 Headache attributed to external application of a cold stimulus 4.5.2 Headache attributed to ingestion or inhalation of a cold stimulus 4.6 External-pressure headache 4.6.1 External-compression headache 4.6.2 External-traction headache 4.7 Primary stabbing headache 4.8 Nummular headache 4.9 Hypnic headache 4.10 New daily persistent headache (NDPH) Headache Classification Committee of the International Headache Society (IHS) 38(1), pp. 1-211. Copyright © 2018 by (International Headache Society) Reprinted by Permission of SAGE Publications.

CHAPTER 441 Migraine and Other Primary Headache Disorders

TABLE 441-2 Migraine Symptoms by Attack Phase Premonitory (prodromal)

- Neck discomfort
- Higher center • Cognitive impairment (brain “fog”) • Mood change • Fatigue
- Homeostatic • Yawning/sleepiness • Polyuria/polydipsia • Food cravings Aura
- Neurologic disturbance, such as scintillating scotoma Headache phase
- Pain
- Nausea/vomiting
- Sensory sensitivity PART 13 Neurologic Disorders • Photophobia • Phonophobia • Osmophobia • Allodynia • Vertigo Postdrome
- Tiredness
- Weariness
- Concentration impairment Source: Adapted from PJ Goadsby et al: Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev 97:553, 2017. Cortex Cortex Thalamus Thalamus Hypothalamus Hypothalamus Dura FIGURE 441-1 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.

basic level is headache with associated features, and TTH is headache that is featureless. Most patients with disabling headache probably have migraine. Patients with acephalgic migraine (typical aura without headache, 1.2.1.2 in Table 441-1) 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 diagno sis of migraine; the term vestibular migraine is often used in this setting (Table 441-1 A1.6.6). Migraine aura can have prominent brainstem symptoms, and the terms basilar artery and basilar-type migraine have now been replaced by migraine with brainstem aura (Table 441-1). TREATMENT Migraine Headache 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-touse tool (Fig. 441-4). Patient education is an important aspect of migraine

manage ment. Information for patients is available at websites such as the American Migraine Foundation (www.americanmigrainefounda tion.org) and the Migraine Trust (www.migrainetrust.org). It is helpful for patients to understand that migraine is an inherited tendency to headache; that migraine can be modified and con trolled by lifestyle adjustments and medications, but it cannot be eradicated; and that, except on some occasions in women on oral estrogens or contraceptives, migraine is not associated with serious or life-threatening illnesses. Quintothalamic tract Quintothalamic tract Dorsal raphe nucleus Dorsal raphe nucleus Locus coeruleus Locus coeruleus Superior salivatory nucleus Superior salivatory nucleus Magnus raphe nucleus Magnus raphe nucleus TCC Trigeminal ganglion Sphenopalatine ganglion

A B C D FIGURE 441-2 Positron emission tomography (PET) and arterial spin labelled activations in migraine. Hypothalamic, dorsal midbrain, and dorsolateral pontine activation are seen in triggered attacks in the premonitory phase before pain, whereas in migraine attacks, dorsolateral pontine activation persists, as it does in chronic migraine (not shown). The dorsolateral pontine 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 C and D are of patients with acute migraine headache on the right and left side, respectively. (Panel A from FH Maniyar et al: Brain activations in the premonitory phase of nitroglycerin-triggered migraine attacks. Brain 137:232, 2014. Panel B from unpublished data, Karsan and Goadsby. Panels C and D from SK Afridi et al: A PET study exploring the laterality of brainstem activation in migraine using glyceryl trinitrate. Brain 128:932, 2005.) A B FIGURE 441-3 A. Posterior hypothalamic gray matter region activation demonstrated by positron emission tomography in a patient with acute cluster headache. B. Highresolution T1-weighted magnetic resonance image obtained using voxel-based morphometry demonstrates increased gray matter activity, lateralized to the side of pain in a patient with cluster headache. (Panel A from A May et al: Hypothalamic activation in cluster headache attacks. Lancet 352:275, 1998. Panel B from A May et al: Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med 5:836, 1999.)

TABLE 441-3 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, Cephalalgia 38:1, 2018). NONPHARMACOLOGIC MANAGEMENT Migraine can often be managed to some degree by a variety of nonpharmacologic approaches. When patients can identify reli able triggers, their avoidance can be useful. A regulated lifestyle is helpful, including a healthy diet, regular exercise, regular sleep patterns, avoidance of excess caffeine and alcohol, and avoidance of acute changes in stress levels, being particularly wary of the letdown effect. The measures that benefit a given individual should be used routinely because they provide a simple, cost-effective approach to migraine management. Patients with migraine do not encounter more stress than headache-free individuals; overresponsiveness to changes in stress appears to be the issue. Because 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 con ditioning techniques such as biofeedback. For most patients seen in clinical practice, this approach is, at best, an adjunct to pharma cotherapy. Nonpharmacologic measures are unlikely to prevent all migraine attacks, and pharmacologic approaches are often needed. *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? ..... 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)? On how many days in the last 3 months did you not do household work because of your headaches? 3. ..... 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)? 5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? 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.) 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 © Innovative Medical Research 1997 FIGURE 441-4 The Migraine Disability Assessment Score (MIDAS) Questionnaire. (Courtesy of Dr. Richard Lipton.)

ACUTE ATTACK THERAPIES FOR MIGRAINE The mainstay of pharmacologic therapy is the judicious use of one or more of the many medicines that are effective in migraine (Table 441-4). 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 (pain relief) rate is 50–70%. Severe migraine attacks may require parenteral therapy. Most drugs effective in the treatment of migraine are members of one of five major pharmacologic classes: nonsteroidal antiinflammatory drugs; 5-HT1B/1D receptor agonists—triptans; CGRP receptor antagonists—gepants; 5-HT1F receptor agonists—ditans; and dopamine receptor antagonists. 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 or a different class of drug tried as first-line treatment. Repeat dosing of the same medicine at 2 h, while safe, is ineffective for triptans, and in contrast effective for gepants. Migraine therapy must be individualized; a standard approach for all patients is not possible. A therapeutic regimen may need to be refined until one is identified that provides the patient with rapid, complete, and con sistent relief with minimal side effects (Table 441-5). Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Both the sever ity and duration of a migraine attack can be reduced significantly by NSAIDs (Table 441-4). Indeed, many undiagnosed migraineurs self-treat with nonprescription NSAIDs. A general consensus is that NSAIDs are most effective when taken early in the migraine attack. However, the effectiveness of these agents in migraine is usu ally less than optimal in moderate or severe migraine attacks. The combination of acetaminophen (paracetamol), aspirin, and caffeine has been approved for use by the U.S. Food and Drug Administra tion (FDA)

for the treatment of mild to moderate migraine. The combination of aspirin and metoclopramide has been shown to be days days ..... days ..... days days .... days .....

TABLE 441-4 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 Diclofenac K Cambia 50 mg PO with water 5-HT1B/1D Receptor Agonists—Triptans Oral Ergotamine 1 mg, caffeine 100 mg Cafergot One or two tablets at onset, then one tablet q½h (max 6 per day, 10 per week) Naratriptan Amerge 2.5-mg tablet at onset Rizatriptan Maxalt 5–10-mg tablet at onset Maxalt-MLT Sumatriptan Imitrex 50–100-mg tablet at onset Frovatriptan Frova 2.5-mg tablet at onset Almotriptan Axert 12.5-mg tablet at onset Eletriptan Relpax 40 or 80 mg at onset Zolmitriptan Zomig 2.5-mg tablet at onset Zomig Rapimelt Nasal Dihydroergotamine Migranal Nasal Spray Trudhesa 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 One spray into each nostril Sumatriptan Imitrex Nasal Spray 5–20 mg intranasal spray as 4 sprays of 5 mg or a single 20 mg spray Zolmitriptan Zomig 5 mg intranasal spray as one spray 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 Alsuma Sumavel DosePro CGRP Receptor Antagonists—Gepants Oral Rimegepant Ubrogepant Nasal Zavegepant Nurtec Ubrelvy Zavzpret 10 mg intranasal, single spray to one nostril once in 24 h 5-HT1F Receptor Agonist—Ditans Oral Lasmiditan Reyvow 50, 100, or 200 mg PO Dopamine Receptor Antagonists Oral Metoclopramide Reglan,a generica 5–10 mg/d Prochlorperazine Compazine,a generica 1–25 mg/d Parenteral Chlorpromazine Generica 0.1 mg/kg IV at 2 mg/min; max 35 mg/d Metoclopramide Reglan,a generic 10 mg IV Prochlorperazine Compazine,a generica 10 mg IV Other Parenteral Opioids Other Neuromodulation Single-pulse transcranial magnetic stimulation (sTMS) Noninvasive vagus nerve stimulation (nVNS) Remote electrical neuromodulation (REN) Transcutaneous supraorbital nerve stimulation External concurrent occipital and trigeminal neurostimulation (eCOT-NS) Generica Savi Dual gammaCore Nerivio Cefaly Relivion aNot all drugs are specifically indicated by the U.S. Food and Drug Administration 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: 5-HT, 5-hydroxytryptamine; NSAIDs, nonsteroidal anti-inflammatory drugs; ODT, orally disintegrating tablets.

3, 4, or 6 mg SC at onset (may repeat once after 1 h for max of 2 doses in 24 h) 75 mg ODT PO 50 or 100 mg PO; a second dose may be taken 2 h after the first, if needed Multiple preparations and dosages; see Table 14-1 Two pulses at onset followed by two further pulses Two doses each of 120 s 30- to 45-min stimulation to the upper arm 60-min stimulation 30- to 60-min stimulation

TABLE 441-5 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 Rimegepant 75 mg Ubrogepant 50 or 100 mg Lasmiditan 50, 100, or 200 mg Slower effect/better tolerability Naratriptan 2.5 mg PO Frovatriptan 2.5 mg PO PART 13 Neurologic Disorders Infrequent headache Ergotamine/caffeine 1–2/100 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 Zavegepant 10 mg nasal spray Headache recurrence Ergotamine 2 mg (most effective PR/usually with caffeine) Naratriptan 2.5 mg PO Almotriptan 12.5 mg PO Eletriptan 40 mg Rimegepant 75 mg Ubrogepant 50 or 100 mg Tolerating acute treatments poorly Naratriptan 2.5 mg Almotriptan 12.5 mg Rimegepant 75 mg Ubrogepant 50, 100 mg Single-pulse transcranial magnetic stimulation Noninvasive vagus nerve stimulation Remote electrical neuromodulation Early vomiting Zolmitriptan 5 mg nasal spray Zavegepant 10 mg nasal spray Sumatriptan 25 mg PR Sumatriptan 6 mg SC Menses-related headache Prevention Ergotamine PO at night Estrogen patches Rimegepant 75 mg PO taken during the menses Treatment Triptans Dihydroergotamine nasal spray Very rapidly developing symptoms Zolmitriptan 5 mg nasal spray Zavegepant 10 mg nasal spray Sumatriptan 6 mg SC Dihydroergotamine 1 mg IM Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs. comparable to a single dose of oral sumatriptan. Important side effects of NSAIDs include dyspepsia and gastrointestinal irritation. 5-HT1B/1D RECEPTOR AGONISTS—TRIPTANS AND ERGOTS Oral Stimulation of 5-HT1B/1D receptors can stop an acute migraine attack. Ergotamine and dihydroergotamine are nonselective recep tor agonists, whereas the triptans are selective 5-HT1B/1D recep tor agonists. A variety of triptans—sumatriptan, almotriptan,

eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan— are available for the treatment of migraine. Each drug in the triptan class has similar pharmacologic proper ties, varying slightly in terms of clinical efficacy. Rizatriptan and eletriptan are, on a population basis, the most efficacious of the triptans. Sumatriptan and zolmitriptan have similar rates of effi cacy as well as time to onset, with an advantage of having multiple formulations, whereas almotriptan has a similar rate of efficacy to sumatriptan and is better tolerated, and frovatriptan and nara triptan are somewhat slower in onset and are also well tolerated. Clinical efficacy appears to be related more to the tmax (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 ones. Unfortunately, monotherapy with a selective oral 5-HT1B/1D receptor agonist does not result in rapid, consistent, and complete relief of migraine in all patients. Triptans are generally not effec tive in migraine with aura unless given after the aura is completed and the headache initiated. Side effects are common, although often mild and transient. Moreover, 5-HT1B/1D receptor agonists are contraindicated in individuals with a history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syn dromes. Recurrence of headache, within the usual time course of an attack, is another important limitation of triptan use and occurs at least occasionally in most patients. Evidence from randomized controlled trials shows that coadministration of a longer-acting NSAID, naproxen 500 mg, with sumatriptan will augment the ini tial effect of sumatriptan and, importantly, reduce rates of headache recurrence. Ergotamine preparations offer a nonselective means of stimulat ing 5-HT1 receptors. A nonnauseating dose of ergotamine should be sought because a dose that provokes nausea is too high and may intensify head pain. Oral (excluding sublingual) 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. Because the clinical studies demonstrating the efficacy of ergotamine in migraine predated the clinical trial methodolo gies

used with the triptans, it is difficult to assess the comparative efficacy of ergotamine versus the triptans. In general, with use of ergotamine there appears to be a much higher incidence of nausea than with triptans but less headache recurrence. Nasal Nasal formulations of dihydroergotamine, zolmitriptan, or sumatriptan can be useful in patients requiring a nonoral route of administration. 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 formu lations, their reported pain relief rate is only ~50–60%. Studies with a new inhalational formulation of dihydroergotamine indicate that its absorption problems can be overcome to produce rapid onset of action with good tolerability. Parenteral Administration of drugs by injection, such as dihydro ergotamine 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 intramuscular (IM) dosing, and 45 min after subcutaneous (SC) dosing. If an attack has not already peaked, SC or IM administration of 1 mg of dihydroergotamine is adequate for about 80–90% of patients. Sumatriptan, 3, 4, or 6 mg SC, depending on local availability, is effective in ~50–80% of patients and can now be administered by a needle-free device. CALCITONIN GENE-RELATED PEPTIDE (CGRP) RECEPTOR ANTAGONISTS—GEPANTS Gepants are small-molecule CGRP receptor antagonists that are effective in the acute treatment of migraine. Three are currently approved by the FDA: rimegepant, and ubrogepant are oral, and zavegepant is a nasal spray (Table 441-4). They are more likely to

render patients pain-free at 2 h and most bothersome symptom– free when compared with placebo in large phase 3 clinical trials. The most bothersome symptom is derived by asking patients to identify which symptom—of nausea, photophobia, or phonophobia—was most bothersome during the treated attack; success required that this symptom was eliminated at 2 h. Gepants are extremely well tolerated with only a small percentage of patients reporting trouble some side effects, such as mild nausea. 5-HT1F RECEPTOR AGONISTS—DITANS Lasmiditan, a highly selective, orally available, 5-HT1F receptor agonist, has been approved by the FDA for the acute treatment of migraine based on large phase 3 studies where it was superior to placebo (Table 441-4). Ditans have no vascular effects because the 5-HT1F receptor is located in the central and peripheral nervous system but not vasculature; the class thus unequivocally fills a gap in therapy for patients with cardiovascular and cerebrovascular disease. The major side effect is dizziness, occurring in ~15% of patients in clinical trials, and somnolence in 6%. Patients are advised not to drive for 8 h after treatment. DOPAMINE RECEPTOR ANTAGONISTS Oral Oral dopamine receptor antagonists can be considered as adjunctive therapy in migraine. Drug absorption is impaired dur ing 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 receptor antagonist, such as metoclopramide 10 mg, prochlorpera zine 10 mg, or domperidone 10 mg (not available in the United States), should be considered to enhance gastric absorption. In addition, dopamine receptor antagonists decrease nausea/vomiting and restore normal gastric motility. Parenteral Dopamine receptor antagonists (e.g., chlorpromazine, prochlorperazine, metoclopramide) by injection can also provide significant acute relief of migraine; they can be used in combination with parenteral 5-HT1B/1D receptor 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 OPTIONS FOR ACUTE MIGRAINE Oral For milder attacks of migraine, the combination of acet aminophen, aspirin, and caffeine is FDA approved (Table 441-4). Parenteral

Opioids are modestly effective in the acute treatment of migraine. For example, IV meperidine (50–100 mg) is given fre quently in the emergency department (ED). This regimen “works” in the sense that the pain of migraine is eliminated. Importantly, it is clear from a randomized controlled trial that prochlorperazine is superior to hydromorphone in the ED setting. However, opioids are clearly suboptimal for patients with recurrent headache. Opi oids do not treat the underlying headache mechanism; rather, they act to alter the pain sensation, and there is evidence their use may decrease the likelihood of a response to triptans in the future. More over, in patients taking oral opioids, such as oxycodone or hydro codone, habituation or addiction can greatly confuse the treatment of migraine. Opioid craving and/or withdrawal can aggravate and accentuate migraine. Therefore, it is recommended that opioid use in migraine be limited to patients with severe, but infrequent, head aches that are unresponsive to other pharmacologic approaches or who have contraindications to other therapies. Neuromodulation Single-pulse transcranial magnetic stimula tion (sTMS) is FDA cleared for the acute treatment of migraine. Two pulses can be applied at the onset of an attack, and this can be repeated. The use of sTMS is safe where there is no cranial metal implant and offers an option to patients seeking nonpharmaceuti cal approaches to treatment. Similarly, a noninvasive vagus nerve stimulator (nVNS) is FDA cleared for the treatment of migraine

attacks in adults. One to two 120-s doses may be applied for attack treatment. Remote electrical neuromodulation using a smartphone app that stimulates the upper arm for 30–45 min is also effective for treatment of acute migraine. Transcutaneous supraorbital nerve stimulation for 60 min and external concurrent occipital and tri geminal neurostimulation (eCOT-NS) for 30–60 min are both FDA cleared.

MEDICATION-OVERUSE HEADACHE Acute attack medications, particularly opioid or barbituratecontaining compound analgesics, have a propensity to aggravate headache frequency and induce a state of refractory daily or neardaily headache called medication-overuse headache. This condition is likely not a separate headache entity but a reaction of the patient’s underlying migraine biology 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” in Chap. 17). CHAPTER 441 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 patients with four or more migraine days a month. Significant side effects are associated with the use of many agents; furthermore, determination of dose can be difficult because the recommended doses have been derived for conditions other than migraine. The mechanism of action of older medicines 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.

Treatments that have the capacity to stabilize migraine are listed in Table 441-6. Most treatments must be taken daily, and there is usually a lag of 2–12 weeks before an effect is seen. The drugs that have been approved by the FDA for the preventive treatment of migraine include propranolol, timolol, sodium valproate, topi ramate, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, and atogepant. In addition, a number of other drugs appear to display preventive efficacy. This group includes amitripty line, candesartan, nortriptyline, flunarizine, phenelzine, and

cypro heptadine. Placebo-controlled trials of onabotulinum toxin type A in episodic migraine were negative, whereas, overall, placebocontrolled trials in chronic migraine were positive. The FDA has approved a range of neuromodulation approaches for the preventive treatment of migraine (Table 441-6). They offer a well-tolerated, effective option for patients. Phenelzine is a monoamine oxidase inhibitor (MAOI); therefore, tyramine-containing foods, decon gestants, and meperidine are contraindicated, and it is reserved for only very recalcitrant cases. Methysergide is now of historical interest only because it is no longer manufactured. Melatonin has been reported to be useful, with controlled trial evidence, but is not approved for this indication in the United States. The probability of success with any one of the antimigraine drugs is ~40–50%. Many patients are managed adequately with well-tolerated doses of candesartan, propranolol, amitriptyline, topiramate, or valproate. As data on fetal developmental issues have arisen, both topiramate and valproate are now considered less attractive for use in females during reproductive years. If these agents fail or produce unacceptable side effects, neuromodulation approaches can be used (Table 441-6). Once effective stabilization is achieved, the drug is continued for ~6–12 months and then slowly tapered, assuming the patient agrees, to assess the continued need. Many patients are able to discontinue medication and experience fewer and milder attacks for long periods. The advent of CGRP monoclonal antibodies and CGRP receptor antagonists has sig nificantly changed the landscape of preventive treatment; with the combination of efficacy that is often within the first month and excellent tolerability, expectations of outcomes have changed.

TABLE 441-6 Preventive Treatments in Migrainea DRUG DOSE SELECTED SIDE EFFECTS Beta blocker Propranolol Metoprolol 40–120 mg bid 25–100 mg bid Antidepressants Amitriptyline 10–75 mg at night Drowsiness Dosulepin 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. Venlafaxine 75–150 mg/d Anticonvulsants Topiramate 25–200 mg/d Paresthesias PART 13 Neurologic Disorders Valproate 400–600 mg bid Drowsiness Serotonergic drugs Pizotifenb 0.5–2 mg qd Weight gain CGRP pathway blockers Eptinezumab Erenumab Fremanezumab Galcanezumab 100 or 300 mg IV every 12 weeks 70 or 140 mg SC monthly 225 mg monthly or 675 mg q3 months, SC 240 mg loading then 120 mg monthly, SC Rimegepant Atogepant 75 mg every other day 10, 30, or 60 mg once daily Other classes Flunarizineb 5–15 mg qd Drowsiness Candesartan 4–24 mg daily Dizziness Memantine 5–20 mg daily Dizziness, tiredness Melatonin 3–12 mg nightly Drowsiness Neuromodulation Single-pulse transcranial magnetic stimulation (sTMS) Noninvasive vagus nerve stimulation (nVNS) Remote electrical neuromodulation (REN) Transcutaneous supraorbital nerve stimulation 4–24 pulses per day 120-s treatments 2–3 times daily 45 min every other day 20 min daily Chronic migraine Onabotulinum toxin type A 155 U Loss of brow furrow No convincing evidence from controlled trials Verapamil Controlled trials demonstrate no effect Nimodipine Clonidine Selective serotonin reuptake inhibitors: fluoxetine aCommonly used preventives are listed with typical doses and common side effects. Not all listed medicines are approved by the U.S. Food and Drug Administration; local regulations and guidelines should be consulted. bNot available in the United States.

Reduced energy Tiredness Postural symptoms Contraindicated in asthma Cognitive symptoms Weight loss Glaucoma Caution with nephrolithiasis Weight gain Tremor Hair loss Fetal abnormalities Hematologic or liver abnormalities Nasopharyngitis Nasopharyngitis, constipation

Injection site reactions Nasopharyngitis Nausea abdominal pain/dyspepsia Constipation, nausea Weight gain Depression Parkinsonism Lightheadedness Tingling Tinnitus Site discomfort, irritation or pain Muscle twitching Well-tolerated; some local sensory symptoms Local paresthesia

■ ■TENSION-TYPE HEADACHE Clinical Features The term tension-type headache 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 dif ferential 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 defi nition does not; this illustrates the difficulty in distinguishing these two clinical entities. In clinical practice, using the appendix definition to dichotomize patients on the basis of the presence of associated features (migraine) and the absence of associated features (TTH) is highly rec ommended. 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. TTH may be infrequent (episodic) or occur on 15 days or more a month (chronic). Pathophysiology The pathophysiology of TTH is incompletely understood. It seems likely that TTH is due to a primary disorder of central nervous system 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 TABLE 441-7 Clinical Features of the Trigeminal Autonomic Cephalalgias CLUSTER HEADACHE PAROXYSMAL HEMICRANIA SUNCT/SUNA Gender M > F F = M F ~ M Pain 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 1–20/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 featuresb Yes Yes Yes Alcohol trigger Yes No No Cutaneous triggers No No Yes Indomethacin effect — Yesc — Abortive treatment Sumatriptan injection or nasal spray Zolmitriptan nasal spray Oxygen nVNSc Preventive treatment Verapamil Galcanezumab Topiramate Melatonin Lithium Gabapentin aIf conjunctival injection and tearing are not present, consider SUNA. bNausea, photophobia, or phonophobia; photophobia and phonophobia are typically unilateral on the side of the pain. cNoninvasive vagus nerve stimulation is U.S. Food and Drug Administration approved in episodic cluster headache dIndicates complete response to indomethacin. Abbreviations: nVNS, non-invasive vagus nerve stimulation; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; SUNCT,

short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

considered to be a feature that distinguishes TTH from migraine, but there appear to be no differences in contraction between the two head ache types. In primary care, <10% of patients presenting with headache over 3 months or more without any neurologic symptoms or signs have tension-type headache; >90% have migraine.

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 apparent TTH when the patient also has migraine. For chronic TTH, amitriptyline is the only proven treat ment (Table 441-6); 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 were negative. CHAPTER 441 ■ ■TRIGEMINAL AUTONOMIC CEPHALALGIAS, INCLUDING CLUSTER HEADACHE The TACs describe a grouping of primary headache disorders including cluster headache, paroxysmal hemicrania (PH), SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)/SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms), and hemicrania continua (Table 441-1). TACs are characterized by relatively short-lasting attacks of head pain associated with lateralized cranial autonomic symptoms, such as lacrimation, conjunctival injection, aural fullness, or nasal con gestion (Table 441-7). 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.
Migraine and Other Primary Headache Disorders
No effective treatment Lidocaine (IV) Indomethacind Lamotrigine nVNS Topiramate

TACs must be differentiated from short-lasting headaches that do not have prominent cranial autonomic syndromes, notably trigeminal neuralgia (TN), 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 be considered, if clinically indicated, to undergo pituitary imaging and pituitary func tion tests because there is an excess of TAC presentations in clinical practice in patients with pituitary tumor–related headache, particularly prolactin and growth hormone secreting tumors.

Cluster Headache Cluster headache is a relatively rare form of primary headache, although nonetheless a common condition, with a population frequency of ~0.1%. The pain is deep, usually retroorbital, often excruciating in intensity, nonfluctuating, and explosive in qual ity. A core feature of cluster headache is periodicity. Usually 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 8–10 weeks a year; this is usually followed by a pain-free inter val that averages a little less than 1 year. Cluster headache is character ized as chronic when there is <3 months of sustained remission without treatment. Patients are generally perfectly well between episodes. Onset of attacks 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. PART 13 Neurologic Disorders Cluster

headache is associated with ipsilateral symptoms of cra nial parasympathetic autonomic activation: conjunctival injection or lacrimation, aural fullness, 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 more likely to be unilateral and on the same side of the pain, rather than bilateral, in contrast to migraine. This phenom enon of unilateral photophobia/phonophobia is characteristic of TACs. Cluster headache is likely to be a disorder involving central pacemaker neurons and neurons in the posterior hypothalamic region (Fig. 441-3). 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 rapid 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, thus ultra-high flow with a demand valve may be a better option for some patients. Sumatriptan 6 mg SC is rapid in onset and will usually shorten an attack to 10–15 min; where available, 3 or 4 mg SC can also be effec tive; 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. nVNS is FDA cleared for the acute treatment of attacks in episodic cluster headache using three 2-min stimulation cycles applied consecutively at the onset of headache on the side of pain; this may be repeated after 9 min. Oral sumatriptan is not effective for prevention or for acute treatment of cluster headache. PREVENTIVE TREATMENTS (TABLE 441-8) The choice of a preventive treatment in cluster headache depends in part on the length of the bout. Patients with long bouts or those

TABLE 441-8 Preventive Management of Cluster Headache SHORT-TERM PREVENTION LONG-TERM PREVENTION EPISODIC CLUSTER HEADACHE AND PROLONGED CHRONIC CLUSTER HEADACHE EPISODIC CLUSTER HEADACHE Prednisone 1 mg/kg up to 60 mg qd, tapering over 21 days Verapamil 160–960 mg/d Galcanezumab 300 mg SC Greater occipital nerve injection (local anesthetic and corticosteroids) Verapamil 160–960 mg/d nVNS 6–24 stimulations/d Melatonina 9–12 mg/d Topiramatea 100–400 mg/d Lithium 400–800 mg/d Abbreviations: nVNS, noninvasive vagus nerve stimulation. 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 can be very use ful. 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. Greater occipital nerve injection with lidocaine and corticosteroids has been shown to be effective in randomized controlled trials, with a benefit that lasts up to 6–8 weeks. The CGRP monoclonal antibody galcanezumab has been approved by the FDA for treatment of episodic cluster headache; it reduces attack frequency, is well tolerated, and is often an effec tive option. Most experts favor verapamil as the first-line preventive treat ment for patients with chronic cluster headache or with prolonged bouts. While verapamil compares favorably with lithium in practice, some patients require verapamil doses far in excess of those admin istered 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, leg swelling, or gingival hyperplasia 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 electrocardiogram (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 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. NEUROMODULATION THERAPY When medical therapies fail in chronic cluster headache, neuro modulation strategies can be used. Sphenopalatine ganglion (SPG) stimulation with an implanted battery-free stimulator has been shown in randomized controlled trials to be effective in aborting attacks and reducing their frequency over time. nVNS compares favorably with standard-of-care in open-label experience. Similarly, occipital nerve stimulation has been used open label and appears to be beneficial. Deep-brain stimulation of the region of the posterior hypothalamic gray matter is successful in about 50% of patients treated, although its risk-versus-benefit ratio makes it inappropriate before all other less invasive options have been explored. ■ ■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 cranial autonomic phenomena such as lacrima tion 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 >5 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-to-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. nVNS can be very effective in PH. Melatonin may be indomethacin-sparing in some patients. Verapamil, an effective treatment for cluster headache, does not appear to be useful for PH. In occasional patients, PH can coexist with TN (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, pituitary pathology, 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 cerebro spinal fluid (CSF) pressure should be suspected. It is important to note that indomethacin reduces CSF pressure. When a diagnosis of PH is considered, magnetic resonance imaging (MRI) is indicated to exclude a pituitary lesion. ■ ■SUNCT/SUNA SUNCT 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 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 under lying continuous head pain. Characteristics that lead to a suspected diagnosis of SUNCT are the cutaneous (or other) triggers 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/SUNA. The diagnosis of SUNCT/SUNA is often confused with TN, par ticularly in first-division TN (Chap. 452). Minimal or no cranial auto nomic 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 because the attacks are of such short duration. However, IV lido caine, 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. nVNS may be use ful. Occipital nerve stimulation is probably helpful in a subgroup of these patients. For intractable cases, short-term prevention with IV lidocaine can be effective.

■ ■HEMICRANIA CONTINUA The essential features of hemicrania continua are moderate and con tinuous unilateral pain associated with fluctuations of severe pain; complete resolution of pain with indomethacin; and exacerbations that may be associated with cranial autonomic features, including conjunc tival injection, lacrimation, and photophobia on the affected side. The age of onset ranges from 10 to 70 years; women are affected twice as often as men. The cause is unknown. CHAPTER 441 TREATMENT Hemicrania Continua Treatment consists of indomethacin; other NSAIDs appear to be of little or no benefit. The IM injection of 100 mg of indomethacin has been proposed as a diagnostic tool, and administration with a placebo injection in a blinded fashion can be very useful diagnosti cally. 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 2 weeks at the maximal dose may be necessary to assess whether a dose has a useful effect. Topiramate can be helpful in some patients. nVNS can be very useful in these patients. Melatonin can be useful as an indomethacin-sparing agent. Occipital nerve stimulation probably has a role in patients with hemicrania continua who are unable to tolerate indomethacin. Migraine and Other Primary Headache Disorders ■ ■OTHER PRIMARY HEADACHE DISORDERS Primary Cough Headache Primary cough (Valsalva maneuver) headache is a generalized headache that begins suddenly, lasts for seconds or several minutes, sometimes up to a few hours, and is pre cipitated 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); 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 complete cessation of their

attacks with lumbar puncture; 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 Exercise Headache Primary exercise 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 lasts <48 h, is bilateral, and is often throbbing at onset; migrainous features may develop in patients susceptible to migraine. The duration tends to be shorter in adolescents than in older adults. Primary exercise headache can be prevented by avoiding exces sive exertion, particularly in hot weather or at high altitude.

The mechanism of primary exercise 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. Because exercise can trigger headache in a number of seri ous underlying conditions (Chap. 17), these must be considered in patients with exercise headache. Pain from angina may be referred to the head, probably by central connections of vagal afferents, and may present as exercise headache (cardiac cephalgia). The link to exercise is the main clinical clue that headache is of cardiac origin. Pheochromo cytoma may occasionally cause exercise headache. Intracranial lesions and stenosis of the carotid arteries are other possible etiologies.

TREATMENT Primary Exercise Headache Exercise regimens should begin modestly and progress gradu ally to higher levels of intensity. Indomethacin at daily doses from 25–150 mg is generally effective in benign exertional headache. Indomethacin (50 mg), a gepant-rimegepant (75 mg orally) or ubrogepant (100 mg orally), ergotamine (1 mg orally), and dihy droergotamine (2 mg by nasal spray) are useful short-term pre ventive measures. PART 13 Neurologic Disorders Primary Headache Associated with Sexual Activity Three types of sex headache are reported: a dull bilateral 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. The latter arises from vigorous sexual activity and is a form of low CSF pressure headache and thus not a primary headache disorder (Chap. 17). Headaches developing at the time of orgasm are not always benign; 5–12% of cases of subarachnoid hemor rhage 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 appear on several occasions in succes sion 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. Most patients with sex headache do not have exercise or cough headache; this clinical paradox is generally a marker of primary sex headache. Migraine is probably more common in patients with sex headache. TREATMENT Primary Sex Headache Benign sex headaches recur irregularly and infrequently. Manage ment 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 40–200 mg/d. An alterna tive is the calcium channel–blocking agent diltiazem, 60 mg tid. Indomethacin (25–50 mg), a gepant-rimegepant (75 mg orally) or ubrogepant (100 mg orally), or frovatriptan (2.5 mg), taken 30–45 min prior to sexual activity can also be helpful. Primary Thunderclap Headache Sudden onset of severe head ache may occur in the absence of any known provocation. The differential diagnosis includes the sentinel bleed of an intracranial aneurysm, reversible cerebral vasoconstriction syndrome (RCVS), 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 pheochromo cytoma. Whether thunderclap headache can be the presentation of an unruptured cerebral aneurysm is uncertain; some experts believe

that RCVS is the cause of most or all cases of otherwise undiagnosed thunderclap headache. When neuroimaging studies and lumbar puncture exclude subarachnoid hemorrhage, patients with thunder clap headache usually do very well over the long term. In one study of patients whose computed tomography (CT) scans and CSF findings were negative, ~15% had recurrent episodes of thunderclap headache, and nearly half subsequently developed migraine or TTH. The first presentation of any sudden-onset severe headache should be diligently investigated with neuroimaging (CT or, when pos sible, MRI with MR angiography) and CSF examination. In the presence of posterior leukoencephalopathy, the differential diagnosis includes cerebral angiitis, posterior reversible encephalopathy syn drome (PRES), drug toxicity (cyclosporine, intrathecal methotrexate/ cytarabine, pseudoephedrine, or cocaine), posttransfusion effects, and postpartum angiopathy. Treatment with nimodipine may be helpful, although the vasoconstriction often resolves spontaneously. Cold-Stimulus Headache This refers to head pain triggered by application or ingestion/inhalation of something cold. It is brought on quickly and typically resolves within 10–30 min of the stimulus being removed. It is best recognized as “brain-freeze” headache or ice-cream headache when due to ingestion. Although cold may be uncomfortable at some level for many people, it is the reliable, severe, and somewhat prolonged nature of these pains that set them apart. The transient receptor potential cation subfamily M member 8 (TRPM8) channel, a known cold-temperature sensor, may be a mediator of this syndrome. Naproxen 500 mg taken 30 min prior to exposure can be helpful for this problem. External Pressure Headache External pressure from compres sion or traction on the head can produce a pain that may have some generalized component, although the pain is largely focused around the site of the pressure. It typically resolves within an hour of the stimu lus being removed. Examples of stimuli include helmets, swimming goggles, or very long ponytails. Treatment is to recognize the problem and remove the stimulus. 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 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). When present in adolescents, primary stabbing headache may be a presenting and very troublesome problem for the patient. 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 hemi crania continua. A key clinical feature is an irregular cadence compared to the regular cadence of the throbbing or pounding that characterizes migraine. 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. Nummular Headache Nummular headache is felt as a round or elliptical discomfort that is fixed in place, ranges in size from 1–6 cm, and may be continuous or intermittent. Uncommonly, it may be multifocal. It may be episodic but is more often continuous during exacerbations. Accompanying the pain there may be a local sensory disturbance, such as allodynia or hypesthesia. Local dermatologic or bony lesions need to be excluded by examination and investigation. This condition can be difficult to treat when present in isolation;

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