Chapter 80: Headache Disorders

Kimberly B. Tallian; Natalie T. Heinrich

UPDATE SUMMARY

Update Summary

August 8, 2023

The following sections and tables were updated:

- Updates to diclofenac and celecoxib in Table 80-3
- Addition of zavegepant nasal spray in Table 80-3 and section "CGRP Antagonists" ("gepants")
- Addition of rimegepant information in section "CGRP Antagonists" ("gepants")

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 55, Headache: Migraine and Tension-Type.

KEY CONCEPTS

KEY CONCEPTS

1. Acute migraine therapies should provide consistent, rapid relief, and enable the individual to resume normal activities at home, school, or work.
2. The selection of initial treatment is based on headache-related disability, symptom severity, and preference for the individual with migraine.
3. Strict adherence to maximum daily and weekly doses of anti-migraine medication is essential.
4. Preventive therapy should be considered for recurring migraine attacks that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective, contraindicated, or produce serious adverse effects; and uncommon migraine variants that cause profound disruption and/or risk of neurologic injury.
5. The selection of an agent for headache prophylaxis should be based on individual response, tolerability, convenience of the medication formulation, and coexisting conditions.
6. Each prophylactic medication should be given an adequate therapeutic trial (usually 6 months) to judge its maximal efficacy.
7. A general wellness program that considers headache triggers should be included in the management plan.
8. After an effective abortive agent and dose have been identified, subsequent treatments should begin with that same regimen.

BEYOND THE BOOK

BEYOND THE BOOK

Read the article by Vandenbussche N, Laterza D, Lisicki M, et al.[1]

Review other existing literature related to whether medication-overuse headache is a distinct entity. Summarize two key points on both the pro and con sides of the issue. Be prepared to discuss or debate in class. (Note to instructors: It would be a good opportunity to assign teams and have an in-class discussion or formal debate.)

INTRODUCTION

Headache is among the top five principal reasons adults 18 to 44 years of age visit US emergency departments and are one of the most common complaints encountered by healthcare practitioners.[2] They can be symptomatic of a distinct pathologic process or can occur without an underlying cause. In 2018, the International Headache Society (IHS) updated its classification system and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain.[3] The IHS classification provides more precise definitions and standardized nomenclature for both the primary (migraine, tension-type, and cluster headache) and secondary (symptomatic of organic disease) headache disorders. These criteria are designed to facilitate headache diagnosis in clinical practice, as well as being used for research. This chapter focuses on the management of primary headache disorders.

Most recurrent headaches result from a benign chronic primary headache disorder, with the most common being tension-type and migraine headache.[4] The peak prevalence for these headaches occurs during the most productive years of life (18-54 years of age).[5] Despite this and their associated disability, most headache sufferers do not obtain appropriate medical care for their headaches.[5,6] While most are benign, some headaches are symptomatic of a serious underlying medical condition, such as an infection, cerebral hemorrhage, or brain mass lesion. Therefore, a thorough evaluation of the headache history is essential to establish an accurate headache diagnosis and identify individuals who can benefit from these specific therapeutic options. In addition, advances in the field's understanding of the diagnosis and pathophysiologic mechanisms of the primary headache disorders, particularly migraine, have led to the development of medications that provide rapid relief from moderate to severe attacks.

MIGRAINE HEADACHE

Epidemiology

Approximately 20.7% of females and 9.7% of males in the United States experience one or more migraine headaches per year. While the prevalence of migraine varies by age and sex, the epidemiologic profile has remained stable over the past 8 years. Sex differences in migraine prevalence have been linked to menstruation, but these differences persist beyond menopause. Prevalence is highest in both males and females between the ages of 18 and 44 years and is inversely related to income and educational attainment. In the American Migraine Prevalence and Prevention Study, 93% of those with migraine reported some headache-related disability, and 54% were severely disabled or needed bed rest during an attack.[5,6] The economic burden of migraine is substantial as are the indirect costs from work-related disability and losses in productivity.[7,8] Several neurologic, psychiatric, and cardiovascular disorders, including stroke, epilepsy, major depression, sleep apnea, obesity, and anxiety, and other pain disorders, show increased comorbidity with migraine.[9,10] Whether this relationship is causal or representative of a common pathophysiologic mechanism is unknown.

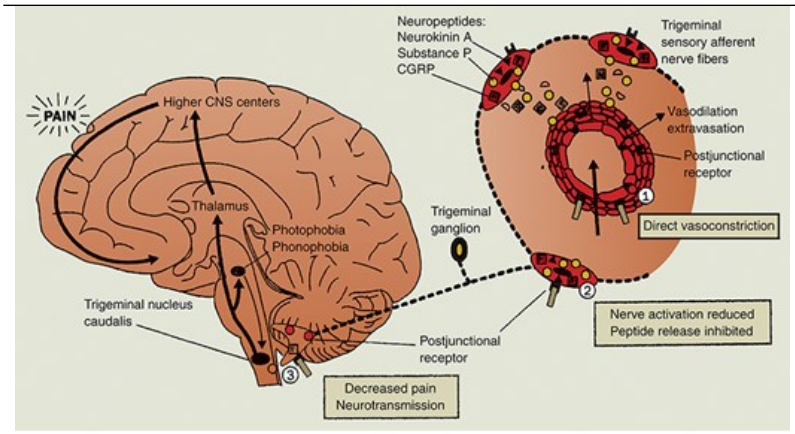
Etiology

The etiology of migraine is not entirely understood. Most clinicians now believe that the pathogenesis of migraine may be related to complex dysfunctions in neuronal and broad sensory processing.[3,9,10] However, earlier theories included hypotheses involving intracerebral arterial vasoconstriction, reactive extracranial vasodilation, in addition to neurovascular mechanisms.

The pain and symptoms of migraine are a combination of altered perceptions resulting from neural suppression and activation of subcortical structures and trigeminal systems. Migraine pain is believed to result from activity within the trigeminovascular system, a network of visceral afferent fibers that arises from the trigeminal ganglia and projects peripherally to innervate the pain-sensitive intracranial extracerebral blood vessels, dura mater, and large venous sinuses[11] (Fig. 80-1). These fibers also project centrally, terminating in the trigeminal nucleus caudalis in the brain stem and upper cervical spinal cord, and, thus, provide a pathway for nociceptive transmission from meningeal blood vessels into higher centers of the central nervous system (CNS). Activation of trigeminal sensory nerves triggers the release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), neurokinin A, and substance P, from perivascular axons. The released neuropeptides interact with dural blood vessels to promote vasodilation and dural plasma extravasation, resulting in neurogenic inflammation. Orthodromic conduction along trigeminovascular fibers transmits pain impulses to the trigeminal nucleus caudalis, where information is relayed further to higher cortical pain centers. Continued afferent input can result in sensitization of these central sensory neurons, producing a hyperalgesic state that responds to previously innocuous stimuli and maintains the headache.[10,11]

FIGURE 80-1

The pathophysiology of migraine headache. Vasodilation of intracranial extracerebral blood vessels (possibly the result of an imbalance in the brainstem) results in the activation of the perivascular trigeminal nerves that release vasoactive neuropeptides to promote neurogenic inflammation. Central pain transmission may activate other brainstem nuclei, resulting in associated symptoms (nausea, vomiting, photophobia, and phonophobia). The antimigraine effects of the 5-$HT_{1B/ID}$ receptor agonists are highlighted at areas 1, 2, and 3. (CGRP, calcitonin gene-related peptide.) *(Reprinted from Ferrari MD. Migraine.* Lancet. *1998 Apr 4;351(9108):1043-51.)*



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Aura occurs in a subgroup of individuals with migraines and other primary headache disorders. The neurologic changes of the aura parallel those that occur during cortical spreading depression, a neuronal event characterized by a wave of depressed electrical activity that advances across the brain cortex, causing inflammation and activation of the trigeminal nucleus caudalis. This neuronal event occurs at a rate consistent with the spread of aura symptoms.[3,10] It is not clear whether this cortical spreading depression and the aura are the substrate of pain or trigger the presentation of migraine.[10,12]

Pathophysiology

Genetic factors play an important role in susceptibility to migraine attacks. Studies in monozygotic twins suggest a 50% heritability of migraine with a multifactorial polygenic basis.[12] Although it is possible for any individual to experience a migraine attack, their abnormal recurrence can result in a diagnosis of migraine. Attack occurrence and frequency are governed by CNS sensitivity to migraine specific triggers or environmental factors. Individuals with migraine appear to have a lowered threshold of response to specific environmental circumstances resulting from genetic factors governing the balance of CNS excitation and inhibition at various levels. Thus, triggering factors modulate the genetic set point that predisposes to migraine headache.[10,12] The hyperresponsiveness of the individual's brain may be the result of an inherited abnormality in calcium and/or sodium channels and sodium/potassium pumps that regulate cortical excitability through serotonin (5-hydroxytryptamine [5-HT]) and other neurotransmitter releases. Increased levels of excitatory amino acids such as glutamate and/or alterations in extracellular levels of potassium also can affect the migraine threshold, resulting in the initiation and propagation of the phenomenon of cortical spreading depression.[12]

Serotonin (5-HT) is an important mediator of migraine headache and specific 5-HT receptor subfamilies are involved in the pathophysiology and treatment of migraine headache.[10,13] Acute antimigraine medications such as the ergot alkaloids and triptan derivatives are agonists of vascular and neuronal 5-HT_1 receptor subtypes, resulting in vasoconstriction of meningeal blood vessels, inhibition of vasoactive neuropeptide release and pain signal transmission.[13,14] Specifically, triptans bind nonspecifically to 5-$HT_{1B/D}$ receptors with variable 5-HT_{1F} receptor affinity, resulting in direct vascular vasoconstriction. In contrast, the ditans selectively bind to 5-HT_{1F} receptors without vasoconstrictive effects.[15] During a headache, CGRP is released by the trigeminal ganglion in response to vasoconstriction resulting in dilation and maintenance of cerebral blood flow.[16] By blocking CGRP release, migraine attacks can be either acutely aborted or prevented by antimigraine medications. Other medications used for migraine prophylaxis also modulate neurotransmitter systems[17] consistent with the current understanding of migraine pathophysiology and neurovascular disorders.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Migraine Headache

General

- Common, recurrent, severe headache

- Interferes with normal functioning
- Divided into two major subtypes
  - Migraine without aura
  - Migraine with aura

Symptoms

- Recurring episodes of throbbing head pain, frequently unilateral, lasting from 4 to 72 hours if left untreated
- Headaches can be severe and associated with nausea, vomiting, as well as sensitivity to light, sound, and/or movement, but not all symptoms are present in every attack
- Diagnostic alarms from evaluation include:
  - Acute onset of the “first” or “worst” headache ever
  - Accelerating pattern of headache following subacute onset
  - Onset of headache after age 50 years
  - Headache associated with systemic illness (eg, fever, nausea, vomiting, stiff neck, and rash)
  - Headache with focal neurologic symptoms or papilledema
  - New-onset headache in an individual with cancer or human immunodeficiency virus infection

Signs

- A stable pattern, absence of daily headache
- Positive family history for migraine
- Normal neurologic examination
- Food and menstruation may serve as triggers
- Improvement in headache with sleep
- Aura can signal the migraine headache but is not required for diagnosis

Laboratory Tests

- No one test can diagnose migraine headaches
- Possible tests to consider are:
  - Serum chemistries
  - Urine toxicology profiles
  - Thyroid function tests
  - Lyme disease studies
  - Complete blood count

- Antinuclear antibody titer
- Erythrocyte sedimentation rate
- Antiphospholipid antibody titer

Diagnostic Tests

- General medical and neurologic physical examination
- Vital signs (fever, hypertension)
- Funduscopy (papilledema, hemorrhage, and exudates)
- Palpation and auscultation of the head and neck (sinus tenderness, hardened or tender temporal arteries, trigger points, temporomandibular joint tenderness, bruits, nuchal rigidity, and cervical spine tenderness)
- Neurologic examination (identify abnormalities or deficits in mental status, cranial nerves, deep tendon reflexes, motor strength, coordination, gait, and cerebellar function)
- Consider neuroimaging studies in individuals with abnormal neurologic examination findings of unknown etiology and those with additional risk factors warranting imaging

The migraine attack is divided into several phases. *Premonitory symptoms* are experienced by up to 77% of those with migraine headaches in the hours or days before the onset of headache.[3,8] Premonitory symptoms vary widely among individuals with migraine but usually are consistent within an individual. Neurologic symptoms (eg, allodynia, phonophobia, photophobia, hyperosmia, and difficulty concentrating) are common, but psychological (eg, anxiety, depression, euphoria, irritability, drowsiness, fatigue, hyperactivity, and restlessness), autonomic (eg, polyuria, diarrhea, and constipation), and constitutional (eg, stiff neck, yawning, thirst, food cravings, and anorexia) symptoms also are reported.[3,8] The previously popular terms *prodrome* and *warning symptoms* should generally be avoided because these are often used mistakenly to include aura.[3]

The migraine *aura*, a complex of positive and negative focal neurologic symptoms that precedes or accompanies an attack, is experienced by approximately 25% of those with migraine headaches on some occasions.[3,10] The aura typically evolves over 5 minutes or longer and lasts less than 60 minutes. Headache usually occurs within the end 60 minutes of the aura; however, sometimes aura symptoms begin at the onset of headache or during the attack. The aura is most often visual and frequently affects half the visual field.[3] Visual auras vary in their complexity and can include both positive (scintillations, photopsia, teichopsia, or fortification spectrum) and negative (scotoma and hemianopsia) features. Sensory and motor aura symptoms, such as paresthesias or numbness involving the arms and face, dysphasia or aphasia, weakness, and hemiparesis, also are reported.[3,10]

Migraine *headache* pain is usually gradual in onset, peaking in intensity over a period of minutes to hours and lasting between 4 and 72 hours. Pain can occur anywhere in the face or head but most often involves the frontotemporal region. The headache is typically unilateral and throbbing or pulsating in nature; however, pain can be bilateral at onset or become generalized during the course of an attack.[3,10] Gastrointestinal (GI) symptoms almost invariably accompany the headache. During an attack, individuals with migraine frequently experience nausea and emesis sometimes occurs. Other systemic symptoms associated with the headache phase can include anorexia, food cravings, constipation, diarrhea, abdominal cramps, nasal stuffiness, blurred vision, diaphoresis, facial pallor, and localized facial, scalp, or periorbital edema. Sensory hyperacuity, manifested as photophobia, phonophobia, or osmophobia, is reported frequently. Because headache pain usually is aggravated by physical activity, most individuals with migraine headache seek a dark, quiet room for rest and relief. Impaired concentration, depression, irritability, fatigue, or anxiety often accompanies the headache. Once headache pain wanes, individuals may experience a postdrome or *resolution phase* characterized by feeling tired, exhausted, irritable, or listless. Impaired concentration may continue, as well as scalp tenderness or mood changes. Some individuals experience depression and malaise, whereas others can feel unusually refreshed or euphoric.[3,10,18]

Diagnosis of migraine can be refined based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs). Individuals with fewer than 15 MMDs or MHDs have episodic migraine, whereas chronic migraine is diagnosed in those with at least 15 MHDs for at least 3 months, of

which at least eight are MMDs.[3,19]

Although headaches have many potential causes, most are considered primary headache disorders. A comprehensive headache history is the most essential element in establishing the clinical diagnosis of migraine.[3,9] This history should include age at onset, attack frequency and timing, duration of attacks, precipitating or aggravating factors, ameliorating factors, description of neurologic symptoms, characteristics of the headache pain (quality, intensity, location, and radiation), associated signs and symptoms, treatment history, family and social history, and the impact of headaches on daily life.

Secondary headaches can be identified or excluded based on the headache history, as well as the results of general medical and neurologic examinations. Diagnostic and laboratory testing also can be warranted in the setting of suspicious headache features or an abnormal examination. Routine neuroimaging (computed tomography or magnetic resonance imaging) is generally not indicated in individuals with migraines and a normal neurologic examination but should be considered in individuals with an unexplained abnormal neurologic examination or an atypical headache history. Because migraine headaches usually begin by the second or third decade of life, those beginning after age 50 suggest an organic etiology such as a mass lesion, cerebrovascular disease, or temporal arteritis.[3,4,10] Table 80-1 lists the IHS diagnostic criteria for migraine with and without aura.[3]

TABLE 80-1

IHS Diagnostic Criteria for Migraine

Migraine without aura

At least five attacks

Headache attack lasts 4-72 hours (untreated or unsuccessfully treated)

Headache has at least two of the following characteristics:

- Unilateral location pulsating quality
- Moderate or severe intensity
- Aggravation by or avoidance of routine physical activity (ie, walking or climbing stairs)

During headache at least one of the following:

- Nausea, vomiting, or both
- Photophobia and phonophobia
- Not attributed to another disorder

Migraine with aura (classic migraine)

At least two attacks

Migraine aura fulfills criteria for typical aura, hemiplegic migraine, retinal migraine, or brainstem aura

Not attributed to another disorder

Typical aura

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

Homonymous or bilateral visual symptoms including positive features (eg, flickering lights, spot, lines) or negative features (eg, loss of vision) or unilateral sensory symptoms including positive features (eg, pins and needles) or negative features (ie, numbness), or any combination

At least two of the following:

- At least one symptom that develops gradually over a minimum of 5 minutes or different symptoms that occur in succession or both
- Each symptom lasts for at least 5 minutes and for no longer than 60 minutes
- Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 minutes

Adapted from Parisi P, Belcastro V, Verrotti A, et al. "Ictal epileptic headache" and the revised International Headache Classification (ICHD-3) published in Cephalalgia 2018, vol. 38(1) 1-211: Not just a matter of definition!

TREATMENT

Desired Outcome

1 Clinicians who care for individuals with migraine must appreciate the impact of this painful and debilitating disorder on the life of the individual, the individual's family, and the individual's employer. Treatment strategies must address both immediate and long-term goals. Acute migraine therapies should provide consistent, rapid relief and enable the individual to resume normal activities at home, school, or work. Recurrence of symptoms and treatment-related adverse effects should be minimal. Ideally, individuals should be able to manage their own headaches effectively without a medical visit. In addition, individuals should take an active role in the creation of a long-term formal management plan. An individualized approach to treatment can result in a reduction in attack frequency and severity; therefore, minimizing headache-related disability and emotional distress and improving the individual's quality of life. Goals of long-term and acute treatment of migraine are listed in Table 80-2.[14,19,20]

TABLE 80-2

Goals of Therapy in Migraine Management

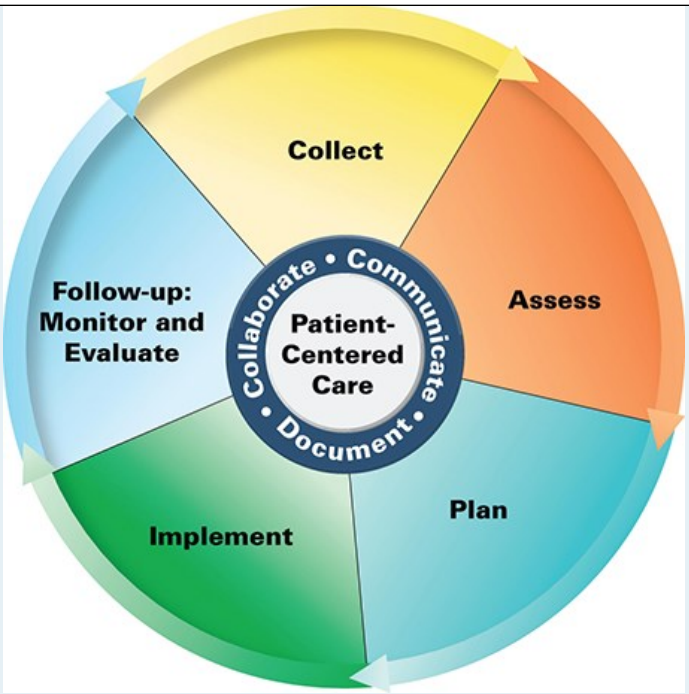
Goals of migraine prevention
Reduce migraine frequency, severity, and disability
Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
Improve quality of life
Prevent headache
Avoid escalation of headache medication use
Educate and enable individuals to manage their disease
Reduce headache-related distress and psychological symptoms
Goals of acute migraine treatment
Treat migraine attacks rapidly and consistently without recurrence
Restore the individual's ability to function
Minimize the use of backup and rescue medications[a]
Optimize self-care for overall management
Be cost-effective in overall management
Cause minimal or no adverse effects

[a]Rescue medications are defined as medications used at home when other treatments fail that permit the individual to get relief without a visit to the physician's office or emergency department.

Data from References 13, 19 and 20.

PATIENT CARE PROCESS

Patient Care Process for Headache Disorders



Collect

Subjective and Objective Data

- Presence of other symptoms
  - Nausea
  - Vomiting
  - Sensitivity to light, sound, and/or movement
- Identification of triggers or aura (Table 80-5)
- Patient characteristics (eg, age, sex, pregnant)
- Patient medical history (personal and family)
- Social history (smoking, diet, physical activity)
- Description of migraine/headache pain (including frequency and location)
- Presence of diagnostic alarms (see CLINICAL PRESENTATION)

Medication History

- Current use, dosage, and frequency of medications (especially over-the-counter aspirin/nonsteroidal anti-inflammatory drug [NSAID] use, herbal products, and dietary supplements) (Tables 80-3 and 80-4)

Diagnostic Tests

- Consider neuroimaging studies in individuals with abnormal neurologic examination findings of unknown etiology and in those with additional risk factors warranting imaging

- Physical Exam
- Neurological Exam
- Diagnostic abnormalities (Table 80-1)
  - Vital signs (fever, hypertension)
  - Funduscopy (papilledema, hemorrhage, and exudates)
  - Palpation and auscultation of the head and neck (sinus tenderness, hardened or tender temporal arteries, trigger points, temporomandibular joint tenderness, bruits, nuchal rigidity, and cervical spine tenderness)
  - Deficits in mental status, cranial nerves, deep tendon reflexes, motor strength, coordination, gait, and cerebellar function

Assess

Initial Assessment

- Type of headache, acute or chronic[3]
- Other contributing factors (eg, presence of anxiety, depression, or medication overuse)

Medication Assessment

- Evaluate the need for therapy
- Evaluate current therapy for appropriateness, response, adverse effects, and medication adherence
- Evaluate other therapy options (compare/contrast based on safety, efficacy, and cost/coverage by insurance)

Plan*

- Acute medication therapy regimen if needed (symptomatic or abortive)
- Establish individualized treatment plan for long term
  - Nonspecific agents for mild-to-moderate attacks
  - Reserve migraine-specific agents for more severe attacks
  - Use of prophylactic agents
- Identify goals of treatment and monitoring parameters (Tables 80-2 to 80-4)
- Patient education (avoidance of triggers, headache diary, and patient adherence)
- Referrals to other providers when appropriate (eg, secondary headache, psychiatry)

Implement*

- Provide patient education regarding all elements of treatment plan
- Patient education on the risk of medication, as well as caffeine overuse and limits
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up, sooner if an individual is unable to perform daily activities

Follow-up: Monitor and Evaluate*

- Strive for resolution of pain (Table 80-2)
- Aim for absence of adverse effects
- Reduce headache frequency, severity, and associated-disability
- Improve quality of life
- Optimize self-care and management

Collaborate with patients, caregiver(s), and other healthcare professionals.

General Approach to Treatment

Nonpharmacologic and pharmacologic interventions are available for migraine management; however, medication therapy is the treatment mainstay for most individuals. Pharmacotherapeutic management can be acute (ie, symptomatic or abortive) or preventive (ie, prophylactic). Therapy decisions should consider the individual's response to specific medications, their tolerability, and coexisting illnesses that limit treatment choices. Abortive or acute therapies can be migraine-specific (eg, ergots, triptans, and CGRP antagonists) or nonspecific (eg, analgesics, antiemetics, NSAIDs, and corticosteroids). Most effective at relieving pain and associated symptoms when administered at the onset of migraine[13,14,17,19–21] (Table 80-3). An initial treatment based on headache-related disability and symptom severity is the preferred treatment strategy.[13,21] Because attack severity varies in individuals, individuals may be advised to use nonspecific agents for mild-to-moderate headaches not causing disability, while reserving migraine-specific medications for more severe attacks. The gastric stasis or nausea and vomiting that accompany migraine may compromise the absorption and efficacy of orally administered medications. Pretreatment with antiemetic agents or use of non-oral formulations (eg, suppositories, nasal sprays, or injections) is advisable when nausea and vomiting are severe.[13,21]

TABLE 80-3

Dosing of Self-Administered Acute Migraine Therapies[a]

Medication	Dose	Maximum Dose/Comments
Analgesics		
Acetaminophen[a] (Tylenol)	500-1,000 mg every 4-6 hours as needed	Maximum daily dose is 4 g
Acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg[a] (Excedrin Migraine)	Two tablets every 6 hours as needed	Available over-the-counter as Excedrin Migraine
Nonsteroidal anti-inflammatory drugs		
Aspirin[a]	500-1,000 mg every 4-6 hours as needed	Maximum daily dose is 4 g
Ibuprofen[a] (Advil, Motrin)	400-800 mg every 4-6 hours as needed	Maximum daily dose is 3.2 g
Naproxen sodium[a] (Aleve, Anaprox)	220-550 mg every 8-12 hours as needed	Avoid doses greater than 1.375 g/day

Diclofenac potassium[a] (Cataflam)	50-100 mg every 8 hours as needed	Avoid doses greater than 150 mg/day
Diclofenac potassium power[a] (Cambia)	50 mg orally mixed in 1 to 2 ounces of water	Use the lowest effective dose for shortest duration
Ketorolac nasal (Sprix)	31.5 mg (one spray each nostril) every 6-8 hours as needed	Maximum daily dose is 126 mg/day × 5 days
Ketorolac IM[b]	30-60 mg every 6 hours as needed	Maximum daily dose is 120 mg/day × 5 days
Celecoxib solution (25mg/1ml)[a] (Elyxyb)	120 mg as needed	Maximum daily dose is 120 mg/day; use for the fewest days per month as necessary.
Ergotamine tartrate		
Oral tablet (1 mg) with caffeine 100 mg[b] (Cafergot)	2 mg at onset; can repeat 1-2 mg every 30 minutes as needed	Maximum dose is 6 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Sublingual tablet (2 mg) (Ergomar)	2 mg at onset; can repeat 2 mg every 30 minutes as needed	Maximum dose is 4 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Rectal suppository (2 mg) with caffeine 100 mg[b] (Cafergot, Migergot)	Insert half to one suppository at onset; can repeat after 1 hour if needed	Maximum dose is 4 mg/day or 10 mg/week; consider pretreatment with an antiemetic
Dihydroergotamine		
Injection 1 mg/mL (D.H.E. 45)[b]	0.25-1 mg (IM, IV, or subcutaneous) at onset; can repeat every hour as needed	Maximum dose is 3 mg/day or 6 mg/week
Nasal spray 4 mg/mL[a] (Migranal, Trudhesa)	One spray (0.5 mg) in each nostril at onset; can repeat sequence 15 minutes later (total dose is 2 mg or four sprays) (Migranal) 0.725 mg (one spray) in each nostril, may repeat once in 1 hour (Trudhesa)	Maximum dose is 3 mg/day or 6 mg/week; prime sprayer four times before using; do not tilt head back or inhale through nose while spraying; discard open ampules after 8 hours (Migranal) Two (four sprays)/day or three (six sprays)/week (Trudhesa)
Triptans		
Sumatriptan[a]		
Injection (Imitrex, Zembrace Symtouch)	1-6 mg subcutaneous at onset; can repeat after 1 hour if needed	Maximum daily dose is 12 mg
Oral tablets (Imitrex)	25, 50, 85, or 100 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 200 mg; combination product with naproxen, 85/500 mg
Nasal spray (Imitrex)	5 or 20 mg at onset; can repeat after 2 hours if	Maximum daily dose is 40 mg

	needed	
Nasal spray (Tosymra)	10 mg intranasally at onset; can repeat after 1 hour if needed	Maximum daily dose is 30 mg
Nasal powder (Onzetra Xsail)	22 mg (one 11-mg nosepiece in each nostril) at onset; can repeat after 2 hours if needed	Maximum daily dose is 44 mg (four nosepieces, 11 mg each)
Zolmitriptan[a]		
Oral tablets/ODT (Zomig, Zomig-ZMT)	1.25, 2.5, or 5 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg; do not divide ODT dosage form
Nasal spray (Zomig)	2.5 or 5 mg intranasally at onset; can repeat after 2 hours if needed	Maximum daily dose is 10 mg
Naratriptan[a] (Amerge)	1 or 2.5 mg at onset; can repeat after 4 hours if needed	Maximum daily dose is 5 mg
Rizatriptan[a] oral tablets/ODT (Maxalt, Maxalt-MLT)	5 or 10 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 30 mg; use 5 mg dose (15 mg/day maximum) in individuals on propranolol
Almotriptan[a] (Axert)	6.25 or 12.5 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 25 mg
Frovatriptan[a] (Frova)	2.5 or 5 mg at onset; can repeat in 2 hours if needed	Maximum daily dose is 7.5 mg
Eletriptan[a] (Relpax)	20 or 40 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 80 mg
Ditans		
Lasmiditan (Reyvow)	50, 100, or 200 mg at onset	Maximum of one dose per 24 hours; safety of treating more than four migraine attacks in a 30-day period has not been established
CGRP Antagonists		
Ubrogepant (Ubrelvy)	50 or 100 mg at onset; can repeat after 2 hours if needed	Maximum daily dose is 200 mg; safety of treating more than eight migraine attacks in a 30-day period has not been established
Rimegepant (Nurtec ODT)	75 mg at onset	Maximum of one dose per 24 hours; take on an empty stomach
Zavegepant nasal spray (Zavzpret)	10 mg intranasally at onset	Maximum daily dose is 10 mg; safety of treating more than 8 migraine attacks in a 30-day period has not been established
Anti-emetics/Miscellaneous		
Acetaminophen, Isometheptene, and	Two capsules to start followed by one capsule every hour until relief is obtained	Maximum five capsules/12 hours

Dichloralphenazone (generic Midrin)		
Metoclopramide[b] (Reglan)	10 mg every 4-6 mg hours as needed	Maximum daily dose is 40 mg (also available as ODT)
Metoclopramide[a] and Aspirin[a]	10 mg (metoclopramide) and 1,000 mg (aspirin) every 4-6 hours as needed	Maximum daily dose is 40 mg (metoclopramide) + 4 g (aspirin)
Prochlorperazine[b] (Compazine)	5-10 mg orally 3-4 times daily as needed or 25 mg via rectal suppository up to twice daily as needed	Maximum daily dose is 40 mg for oral and 50 mg for suppository
Promethazine (Phenergan)	25 mg oral or via rectal suppository every 4-6 hours as needed	Maximum daily dose is 100 mg

[a]Level A—established efficacy (≥2 Class I studies).

[b]Level B—probably effective (1 Class I or 2 Class II studies). IM, intramuscular; IV, intravenous; ODT, orally disintegrating tablet.

Data from References 13, 20, and 21.

3 The frequent or excessive use of acute migraine medications can also result in *medication-overuse headache* (or *rebound headache*), characterized by increased headache frequency and medication consumption.[3,22] This syndrome evolves as a self-sustaining headache-medication cycle in which the headache returns as the medication wears off, leading to more medication consumption for relief. The headache history often reflects the gradual onset of an atypical daily or near-daily headache with superimposed episodic migraine attacks. Medication overuse is one of the most common causes of chronic daily headache.[1,22,23] Agents most commonly implicated include simple and combination analgesics and opiates, and triptans.[1,22,23] Discontinuation of the offending agent leads to a gradual decrease in headache frequency and severity and a return of the original headache characteristics. Although detoxification can be accomplished on an outpatient basis, hospitalization may be necessary for refractory rebound headache and other withdrawal symptoms (eg, nausea, vomiting, asthenia, restlessness, and agitation).[22,23] Regulation of nociceptive systems and renewed responsiveness to therapy usually occur within 2 months of medication withdrawal.[3] Most experts recommend individuals limit triptan, ergotamine, and ditan use to fewer than 10 days per month, or 2 days per week. Exceptions include limiting aspirin, acetaminophen, and NSAIDs to 15 days or less per month.[3,7,24] Those with chronic migraine may be instructed to restrict all abortive therapy to fewer than 10 days per month. Additionally, they may be advised to limit the time period in which one or more medications are regularly taken to less than 3 months to avoid the development of medication-overuse headache. One exception to this recommendation is with the CGRP antagonists, which have not caused medication-overuse headache.[25]

4 5 6 Preventive migraine therapies are administered daily on a routine basis to reduce the frequency, severity, and duration of attacks and improve responsiveness to symptomatic migraine therapies[26,27] (Table 80-4). Preventive therapy should be considered in the setting of recurring migraine attacks that produce significant disability despite acute therapy; for frequent attacks occurring more than twice per week with the risk of developing medication-overuse headache; for symptomatic therapies that are ineffective or contraindicated, or produce serious adverse effects; or for uncommon migraine variants that cause profound disruption and/or risk of permanent neurologic injury (eg, hemiplegic migraine, basilar migraine, and migraine with prolonged aura); and individual preference to limit the number of attacks.[19,24] Preventive therapy may also be administered preemptively or intermittently when headaches recur in a predictable pattern (eg, exercise-induced migraine or menstrual migraine).[19] The various agents used for migraine prophylaxis are reviewed. Only propranolol, timolol, divalproex sodium, topiramate, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, eptinezumab-jjmr, atogepant, and rimegepant are currently FDA approved, although other agents have established or have probable efficacy for this indication.[28] Guidelines identify which agents might be effective, but the preference for one therapy over another is not advised due to lack of established results. Thus, the agent selection is based on adverse effect profiles and the individual's coexisting/comorbid

conditions.[19,26,27] A therapeutic trial of 2 to 3 months is necessary to achieve clinical benefit, but reductions in attack frequency can be evident by the first month with maximal benefits observed within 6 months.[17,19,26] Medication therapy should be initiated with low doses and gradually increased to therapeutic effect or intolerable adverse effects. Doses for migraine prophylaxis are often lower than those necessary for other indications.[19,27] Overuse of acute headache medications will interfere with preventative treatment effects.[3,19] Prophylactic treatment usually is continued for at least 6 to 12 months after the frequency and severity of headaches have diminished. After that time, based on discussions with the individual, gradual tapering or discontinuation may be reasonable.[17,24–26] Many individuals with migraine headache experience fewer and less severe attacks for lengthy periods following discontinuation of prophylactic medications or taper to a lower dose. Figures 80-2 and 80-3 identify treatment and management algorithms for migraine headache.

FIGURE 80-2

Mechanism of action of migraine medications. Nerve activity in the trigeminovascular pain pathway leads to the release of neuropeptides (ie, CGRP) and neurotransmitters (ie, serotonin and glutamate) that can hyperexcite neurons. CGRP release leads to activation of cyclic adenosine monophosphate (cAMP) signaling, which results in vasodilation of cerebrovascular smooth muscle, as well as pain signaling via Aδ fibers. Thus, injectable CGRP antagonists known as anti-CGRP antibodies bind to the CGRP receptor or CGRP ligand to block the effects of CGRP on vasodilation and neurogenic inflammation. Similarly, oral CGRP antagonists (“gepants”) also inhibit the action of CGRP at the receptor. Serotonin (or serotonin agonist) binding to 5-HT receptors can inhibit presynaptic vesicular release of CGRP and inhibit postsynaptic cAMP signaling cascades.

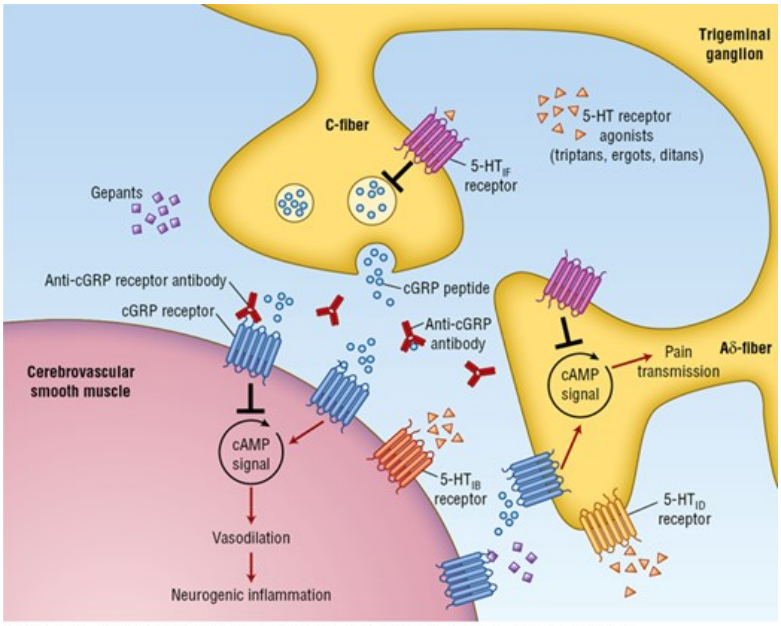


FIGURE 80-3

Treatment algorithm for migraine headaches.

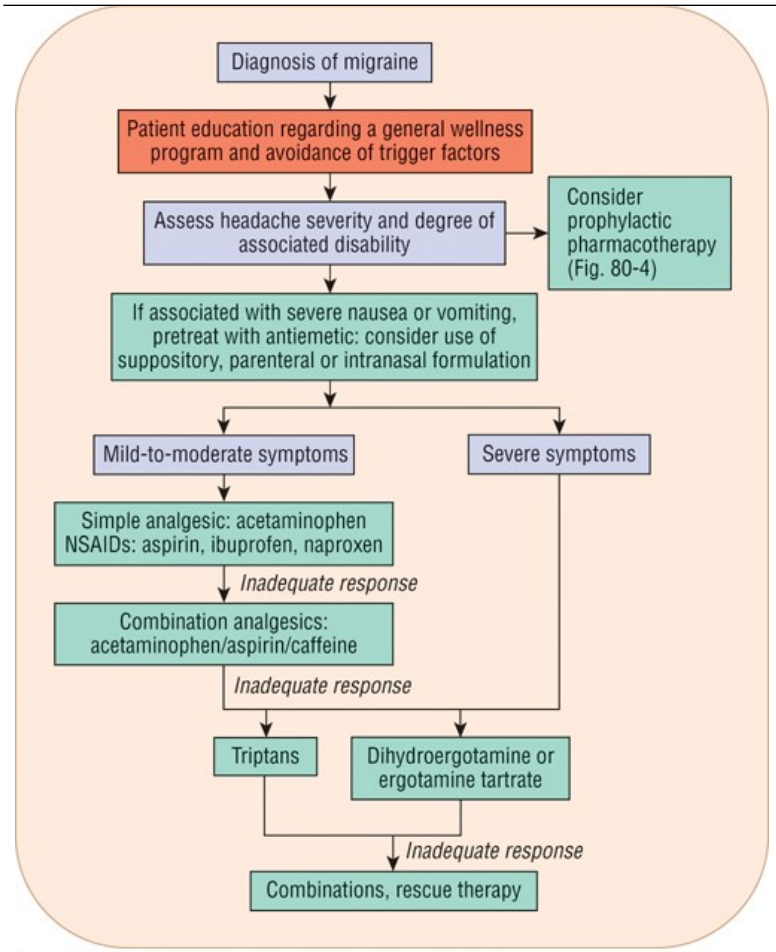


FIGURE 80-4

Treatment algorithm for prophylactic management of migraine headaches. (NSAID, nonsteroidal anti-inflammatory drug).

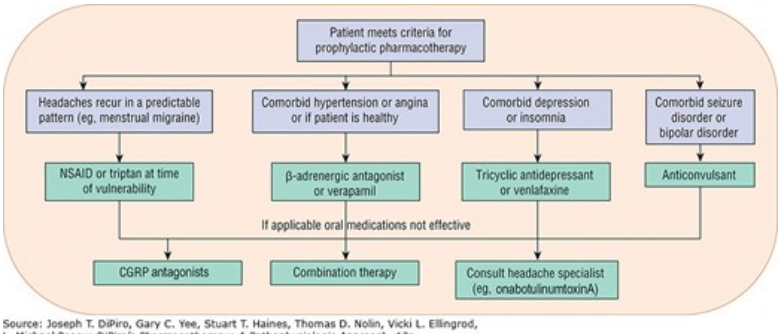


TABLE 80-4

Dosing of Prophylactic Migraine Therapies

Medication	Initial Dose	Usual Range	Comments
β-Adrenergic antagonists			

Atenolol[a] (Tenormin)	25-50 mg/day	50-200 mg/day	
Metoprolol[b] (Toprol, Toprol XL)	25-100 mg/day in divided doses	100-200 mg/day in divided doses	Dose short-acting two to four times a day and extended-release one to two times a day
Nadolol[a] (Corgard)	40-80 mg/day	80-240 mg/day	
Propranolol[b] (Inderal, Inderal LA)	40 mg/day in divided doses	40-160 mg/day in divided doses	Dose short-acting two to three times a day and extended-release one to two times a day
Timolol[b] (Blocadren)	20 mg/day in divided doses	20-60 mg/day in divided doses	
Antidepressants			
Amitriptyline[a] (Elavil)	10 mg at bedtime	20-50 mg at bedtime	
Venlafaxine[a] (Effexor, Effexor-XR)	37.5 mg/day	75-150 mg/day	Dose short-acting two times a day and extended-release once daily
Antiseizure Medications			
Topiramate[b] (Topamax)	12.5-25 mg/day	50-200 mg/day in divided doses or only at bedtime	Increase by 12.5-25 mg/week
Valproic acid/divalproex sodium[b] (Depakene, Depakote, Depakote ER)	250-500 mg/day in divided doses, or daily for extended release	500-1,500 mg/day	Dose short-acting two times a day and extended-release once daily; monitor levels if compliance is an issue
CGRP Antagonists (Anti-CGRP Antibodies)			
Erenumab-aooe (Aimovig)	70 mg subcutaneously monthly	70-140 mg subcutaneously every month	
Fremanezumab-vfrm (Ajovy)	225 mg subcutaneously monthly or 675 mg subcutaneously every 3 months	225 mg subcutaneously monthly or 675 mg subcutaneously every 3 months	
Galcanezumab-gnlm (Emgality)	240 mg subcutaneous loading dose, followed by 120 mg subcutaneously monthly	120 mg subcutaneously every month	
Eptinezumab-jjmr (Vyepti)	100 mg via IV infusion over 30 minutes every 3 months	100-300 mg IV infusion over 30 minutes every 3 months	
CGRP Antagonists ("gepants")			
Atogepant (Quilpta)	10 mg/day	60 mg/day	Taken with or without food

Rimegepant (Nurtec ODT)	75 mg every other day	75 mg/day	No titration required and taken on an empty stomach
Nonsteroidal anti-inflammatory drugs – *For prevention of menstrual migraine only*			
Ibuprofen[a] (Motrin)	200 mg/day in three to four divided doses	200-800 mg/day in three to four divided doses (maximum daily dose is 3,200 mg)	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Ketoprofen[a] (Orudis)	150 mg/day in divided doses	150 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Naproxen sodium[a] (Aleve, Anaprox)	550 mg/day in divided doses	550-1,100 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Triptans – *For prevention of menstrual migraine only*			
Frovatriptan[b] (Frova)	2.5 mg/day or 5 mg/day in divided doses; start 6 days prior to anticipated start of menstruation	5 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Naratriptan[a] (Amerge)	2 mg/day in divided doses; start 6 days prior to anticipated start of menstruation	2 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Zolmitriptan[a] (Zomig)	5-7.5 mg/day in divided doses; start 6 days prior to anticipated start of menstruation	5-7.5 mg/day in divided doses	Use intermittently only; daily or prolonged use may lead to medication-overuse headaches
Miscellaneous			
Histamine[a] (Histatrol)	1-10 ng 2 times/week	Same as initial dose	May cause transient itching and burning at injection site
Magnesium[a]	400 mg/day	800 mg/day in divided doses	May be more helpful in migraine with aura and menstrual migraine
MIG-99[a] (feverfew)	10-100 mg/day in divided doses	Same as initial dose	Withdrawal may be associated with increased headaches
Petasites[b]	100-150 mg/day in divided doses	150 mg/day in divided doses	Use only commercial preparations, plant is carcinogenic
Riboflavin[a]	400 mg/day in divided doses	400 mg/day in divided doses	Benefit only after 3 months

[a]Level B—probably effective (1 Class I or 2 Class II studies).

[b]Level A—established efficacy (≥2 Class I studies).

Data from References 26, 28, and 29.

Nonpharmacologic Therapy

7 Nonpharmacologic therapy of acute migraine headache is limited but can include application of ice to the head and periods of rest or sleep, usually in a dark, quiet environment. Preventative measures typically suggest individuals identify and avoid individual factors or triggers that consistently provoke migraine attacks, although some triggers are not modifiable[3,4,19,24,30] (Table 80-5). Changes in estrogen levels associated with menarche, menstruation, pregnancy, menopause, oral contraceptive use, and other hormone therapies can trigger, intensify, or alleviate migraine.[4,30] A headache diary that records the frequency, severity, and duration of attacks can facilitate identification of migraine triggers. In appropriate situations, some individuals may learn to cope with triggers after a process of controlled exposure and approach/confront strategies.[31] Individuals also can benefit from wellness programs that include regular sleep, exercise, and eating habits, smoking cessation, and limited caffeine intake. Behavioral interventions, such as acupuncture, relaxation therapy, biofeedback (often used in combination with relaxation therapy), neuromodulation devices that use currents or magnets to modulate or change brain activity such as Cefaly® and Nerivio®, and cognitive therapy, are preventive treatment options for individuals who prefer non-medication therapy or when symptomatic therapies are poorly tolerated, contraindicated, or ineffective.[19,30,32,33] A multimodal approach with non-pharmacologic interventions has Level A evidence for migraine management and should be recommended to individuals.

TABLE 80-5

Commonly Reported Triggers of Migraine

Food triggers
Alcohol
Caffeine (greater than 200 mg/day)/caffeine withdrawal
Chocolate
Fermented and pickled foods
Monosodium glutamate (eg, in Chinese food, seasoned salt, and instant foods)
Nitrate-containing foods (eg, processed meats)
Saccharin/aspartame (eg, diet foods or diet sodas)
Tyramine-containing foods
Environmental triggers
Glare or flickering lights
High altitude
Loud noises
Strong smells and fumes
Tobacco smoke
Weather changes*
Behavioral–physiologic triggers
Excess or insufficient sleep
Fatigue
Menstruation, menopause*
Sexual activity
Skipped meals/fasting*
Strenuous physical activity (eg, prolonged overexertion)
Stress or poststress*

*Not easily modified triggers.

Data from References 10, 30, and 34.

Pharmacologic Therapy

Abortive Treatments

Analgesics and NSAIDs

Simple analgesics and NSAIDs are effective medications for managing many migraine attacks (see Table 80-3). They offer a reasonable first-line choice for mild-to-moderate migraine attacks or severe attacks that have been responsive to similar NSAIDs or nonopiate analgesics in the past. Of the NSAIDs, aspirin, diclofenac, ibuprofen, naproxen sodium, celecoxib, and the combination of acetaminophen plus aspirin and caffeine have established efficacy in controlled clinical trials.[13,20,21,35] Oral acetaminophen alone also has efficacy for non-incapacitating migraine attacks.[20] The comparable efficacy of NSAIDs and triptans in acute migraine is known, although comparisons with other therapeutic classes are limited. Baseline headache intensity does not predict aspirin or other NSAID therapy success or failure.[3,36] No studies have compared the relative efficacy of different NSAIDs.[13,21]

NSAIDs prevent neurogenically mediated inflammation in the trigeminovascular system through the inhibition of prostaglandin synthesis. Metoclopramide can speed the absorption of analgesics and alleviate migraine-related nausea and vomiting.[37] Moreover, when metoclopramide is combined with aspirin, the combination has similar efficacy to sumatriptan and is an alternative for individuals where triptans are contraindicated.[13,14] Suppository analgesic preparations are an option when nausea and vomiting are severe.[21] Acute NSAID therapy is associated with GI (eg, dyspepsia, nausea, vomiting, and diarrhea) and CNS (eg, somnolence, dizziness) adverse effects. These agents should be avoided or used cautiously in individuals with previous ulcer disease, renal disease, severe cardiovascular disease, or hypersensitivity to aspirin.[13,21]

The nonprescription combination of acetaminophen, aspirin, and caffeine was approved for migraine treatment in the United States given its efficacy in relieving pain and associated symptoms.[20,21] Aspirin and acetaminophen are also available in prescription combination products containing a short-acting barbiturate (butalbital) or narcotic (codeine). While butalbital or butalbital-containing products are possibly effective for acute migraine, these analgesics or narcotics should be limited due to overuse, medication-overuse headache, and withdrawal concerns.[20–22] Frequent consumption of aspirin or acetaminophen alone can result in medication-overuse headache, and combination analgesics appear to pose a greater risk.[22]

Triptans

The 5-HT receptor agonists, or triptans, represented a significant advancement in migraine pharmacotherapy. The first member of this class, sumatriptan, and the second-generation agents zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan are selective agonists of the 5-HT_{1B} and 5-HT_{1D} receptors. With these agents, relief from migraine headache results from three key actions: (1) normalization of dilated intracranial arteries through enhanced vasoconstriction, (2) inhibition of vasoactive peptide release from perivascular trigeminal neurons, and (3) inhibition of transmission through second-order neurons ascending to the thalamus.[13,21] The triptans all have established efficacy and are appropriate first-line therapy for mild to severe migraine. They are also used for rescue therapy when nonspecific medications are ineffective.[20,21]

Sumatriptan, the most extensively studied acute therapy, is available for subcutaneous, oral, and intranasal administration. Subcutaneous sumatriptan is consistently superior to placebo in alleviating migraine headache and associated symptoms, with relief reported in 70% of individuals at 2 hours.[20] It also has a more rapid onset of action when compared with the oral formulation and is packaged as an autoinjector device for self-administration. Intranasal sumatriptan provides a faster onset of effect than the oral formulation and produces similar response rates in placebo-controlled studies.[13,21]

Triptan selection is based on headache characteristics, convenience of dosing, and the individual's preference. At all marketed doses, oral triptans are effective and generally well tolerated[21] and differ in their pharmacokinetic and pharmacodynamic profiles (Table 80-6). In general, they can be divided into those with a faster onset and higher efficacy and those with a slower onset and lower efficacy. A meta-analysis summarizes the efficacy and tolerability of the oral triptans across published and unpublished studies. Using 100 mg of sumatriptan as the reference dose and based on 2-hour response rates, most of the triptans show similar therapeutic gains at manufacturer recommended doses. Exceptions to this were frovatriptan and naratriptan with lower efficacy. These agents also have the longest half-lives, the slowest onset of action, and less headache recurrence, making them

more suitable for individuals who have migraine attacks with slow onset and longer duration. Faster-acting triptans are more efficacious when a rapid onset is necessary. Subcutaneous, intranasal, or orally dissolving tablets may be useful in individuals with prominent early nausea or vomiting or those who have difficulty in swallowing tablets. Most individuals prefer oral formulations even though oral absorption can be delayed during attacks.[13,21]

TABLE 80-6

Pharmacokinetic Characteristics of Triptans

Medication	Half-Life (hours)	Time to Maximal Concentration (t_{max})	Bioavailability (%)	Elimination
Almotriptan	3-4	1.4-3.8 hours	80	MAO-A, CYP3A4, CYP2D6
Eletriptan	4-5	1-2 hours	50	CYP3A4
Frovatriptan	25	2-4 hours	24-30	Mostly unchanged, CYP1A2
Naratriptan	5-6	2-3 hours	63-74	Largely unchanged, CYP450 (various isoenzymes); primary sulfa medication
Rizatriptan	2-3		45	MAO-A
Oral tablets		1-1.2 hours		
Disintegrating		1.6-2.5 hours		
Sumatriptan	2			MAO-A; primary sulfa medication
Subcutaneous injection		12-15 minutes	97	
Oral tablets		2.5 hours	14	
Nasal spray		10 minutes	17	
Nasal powder		45 minutes		
Patch		1.1 hours	45	
Zolmitriptan	3		40-48	CYP1A2, MAO-A
Oral		2 hours		
Disintegrating		3.3 hours		
Nasal		4 hours		

CYP, cytochrome P450; MAO-A, monoamine oxidase type A.

Data from References 13, 14, and 37–40.

Triptan clinical response can vary considerably among individuals and responses cannot be predicted. If one triptan fails, an individual can be switched successfully to another.[13,14] After an effective agent and dose are identified, subsequent treatments with that same regimen should begin. Combination therapy may improve response rates and diminish migraine recurrence. A proprietary single tablet formulation of sumatriptan 85 mg plus naproxen 500 mg was more effective in clinical trials for headache relief and sustained pain-free response than either agent as monotherapy.[20,21]

Triptan adverse effects are common but are usually mild to moderate in nature, of short duration, and common among the class; including paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence. Local adverse effects are reported with the subcutaneous (minor injection site reactions) and intranasal (taste perversion, nasal discomfort) routes. Up to 25% of individuals report "triptan sensations," including tightness, pressure, heaviness, or pain in the chest, neck, or throat. The mechanism of these symptoms is unknown, but a cardiac source seems unlikely in most individuals; however, all triptans are partial agonists of human 5-HT coronary artery receptors in vitro, resulting in a small but significant vasoconstrictor response. Other adverse cardiac events are rare, with only isolated cases of myocardial infarction and coronary vasospasm with ischemia reported. The triptans are contraindicated in individuals with a history of ischemic heart disease (eg, angina pectoris, Prinzmetal's angina, or previous myocardial infarction), uncontrolled hypertension, and cerebrovascular disease. Individuals at risk for unrecognized coronary artery disease should use triptans with caution. Postmenopausal females, males older than 40 years of age, and individuals with uncontrolled risk factors should receive a cardiovascular assessment prior to triptan use and have initial doses administered under medical supervision. These agents are also contraindicated in individuals with hemiplegic and basilar migraine and should not be used routinely in pregnancy.[1,21]

The triptans should not be given within 24 hours of the ergotamine derivatives. Administration of sumatriptan, rizatriptan, and zolmitriptan within 2 weeks of therapy with monoamine oxidase inhibitors is not recommended. Eletriptan should not be administered with cytochrome P4503A4 (CYP3A4) inhibitors such as macrolide antibiotics, antifungals, and some antiviral therapies. Concomitant therapy with the selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) (eg, duloxetine, venlafaxine, and mirtazapine) has been reported to cause serotonin syndrome based on several case reports. This interaction has been doubted as triptans are serotonin 1B and 1D agonists, whereas serotonin syndrome is hypothesized to involve 2A and 1A receptors.[41] Regulatory agencies, including the FDA, caution against concurrent administration, although it appears the likelihood of CNS adverse events is extremely low. The potential risk of these combinations should be carefully considered and discussed with the individual.[13,14,21] Frequent use of the triptans has been associated with the development of medication-overuse headache.[7,22]

Ergot Alkaloids and Derivatives

Ergotamine tartrate and dihydroergotamine can treat moderate-to-severe migraine attacks (see Table 80-4). These medications are nonselective 5-HT_1 receptor agonists that constrict intracranial blood vessels, centrally inhibit the trigeminovascular system, and prevent neurogenic inflammation development.[13,14] These agents also have agonist activity at dopaminergic receptors. Venous and arterial constriction occur with therapeutic doses, but ergotamine tartrate exerts more potent arterial effects than dihydroergotamine.[13,21]

The oral and rectal preparations of ergotamine tartrate containing caffeine, to enhance absorption and potentiate analgesia, are probably effective.[20] The dosage should be strictly titrated to establish an effective subnauseating dose for future attacks. The efficacy of ergotamine alone in migraine is inconsistent, despite its clinical use for decades.[13,21]

Dihydroergotamine is probably effective and available for intranasal and parenteral administration by the IM, subcutaneous and IV routes.[14,20,21] Parenteral dihydroergotamine was previously used as an inpatient or emergency department treatment for moderate-to-severe migraine or intractable headache, but individuals can be trained to self-administer either IM or subcutaneously. Clinical studies support the nasal spray and pulmonary inhaler (still in development) as effective.[14,20]

Nausea and vomiting resulting from chemoreceptor trigger zone stimulation are among the most common ergotamine derivative adverse effects. Pretreatment with an antiemetic agent should be considered with ergotamine and IV dihydroergotamine therapy. Other common adverse effects include abdominal pain, weakness, fatigue, paresthesias, muscle pain, diarrhea, and chest tightness. Rarely, symptoms of severe peripheral ischemia (ergotism), including cold, numb, painful extremities, continuous paresthesias, diminished peripheral pulses, and claudication, can result from their vasoconstrictor effects. Gangrenous extremities, myocardial infarction, hepatic necrosis, and bowel and brain ischemia have also been reported; however, dihydroergotamine is rarely associated with such adverse effects. Triptans and ergot derivatives should not be used within 24 hours of each other,[13,21] and they are contraindicated in individuals with renal or hepatic failure; coronary, cerebral, or peripheral vascular disease; uncontrolled

hypertension; and sepsis; or in individuals who are pregnant or nursing. Dihydroergotamine does not appear to cause rebound headache, but dosage restrictions for ergotamine tartrate should be strictly observed to prevent this complication.[21]

Antiemetics

Adjunctive antiemetic therapy is useful for the nausea and vomiting accompanying migraine headaches and the medications used to treat attacks (eg, ergotamine tartrate). A single antiemetic dose, such as metoclopramide or prochlorperazine, administered 15 to 30 minutes before migraine oral abortive treatment is often sufficient. Suppository preparations are available when nausea and vomiting are particularly prominent. Metoclopramide is also useful to reverse gastroparesis and improve absorption from the GI tract during severe attacks.[13]

In addition to antiemetic effects, dopamine antagonists have also been used successfully as monotherapy to treat intractable headaches (see Table 80-4). Prochlorperazine administered IV, IM, or rectal routes and IV metoclopramide provide more effective pain relief than placebo. Chlorpromazine and droperidol also provide migraine headache relief when administered parenterally at doses of 0.1 mg/kg and 2.75 to 8.25 mg, respectively. Their precise mechanism of action is unknown; however, they offer an alternative to the narcotic analgesics for refractory migraine treatment. Drowsiness and dizziness were reported occasionally, and extrapyramidal adverse effects were reported infrequently in migraine trials. Most of these medications have a risk for QT prolongation and torsades de pointes.[13,20,21]

Ditans

Lasmiditan is in a new class of abortive migraine medications known as “ditans.” Unlike the triptan mechanism of agonists at 5-HT_{1B} and 5-HT_{1D}, lasmiditan is a highly selective 5-HT_{1F} agonist whereby vasoconstrictive activity is minimized.[41] Ditans act by blocking both neurogenic inflammation in the dura and stimulation of the trigeminal nucleus caudalis. In clinical trials, all doses of lasmiditan were significantly superior to placebo both for headache-free days and improvement in most bothersome symptoms (eg, nausea, phonophobia, or photophobia) 2 hours post-dose, for individuals with three to eight migraine attacks per month.[42,43] Common adverse effects reported in 2% of individuals or more were dizziness, paresthesia, sedation, and nausea/vomiting. Lasmiditan is associated with significant driving impairment where sleepiness has been reported after each dose. This adverse effect has prompted specific labeling warnings and precautions regarding not driving a motor vehicle or operating heavy machinery for at least 8 hours following each dose.

CGRP Antagonists (“gepants”)

Three small-molecule CGRP antagonists, ubrogepant, rimegepant, and zayegepant which are also known as “gepants,” have been FDA approved for the acute treatment of migraine. During a migraine attack, CGRP levels rise resulting in vasodilation and neurogenic inflammation.[44,45] Thus, the blockade of CGRP receptors has become a breakthrough treatment for individuals with migraines. The clinical data regarding the efficacy of these medications is similar to triptans and lasmiditan, though they tend to have improved tolerability, and in contrast to triptans, the presence or history of cardiovascular disease is not a contraindication. Furthermore, medication overuse headache does not occur as a result of gepant use.[46]

The primary outcomes evaluated in clinical trials for these agents were pain freedom and reduction in most bothersome symptoms, two hours after dosing.[47–49] Using these outcomes, ubrogepant (50-mg and 100-mg doses), rimegepant (75-mg dose), and zayegepant (10-mg dose) have efficacy in pain freedom and freedom from most bothersome symptoms (photophobia, phonophobia, or nausea) at two hours. The incidence of adverse effects was very low (less than 5%) but included nausea for rimegepant and nausea, xerostomia, and somnolence for ubrogepant. Zavegepant adverse effects were also mild (less than 5%) for nausea, vomiting, and nasal irritation, but a higher rate of altered sense of taste (18%) was reported. Rimegepant is a relatively long-acting acute medication with a half-life of 11 hours, and thus, it is not recommended to repeat a dose within 24 hours. Ubrogepant has a shorter half-life of 5 to 7 hours, and the dose can be repeated two hours after the initial administration. Zavegepant has a half life of about 7 hours but should not be repeated within 24 hours. Rimegepant and ubrogepant have significant medication interactions, and concomitant use with strong CYP3A4 inhibitors, P-gp inhibitors, and BCRP inhibitors should be avoided; otherwise, dose adjustments may need to be made. Additionally, these agents should be avoided in severe renal or hepatic impairment and dose adjustments may need to be made in mild to moderate renal or hepatic impairment. Zavegepant carries some drug interactions with OATP1B3 inhibitors and intranasal decongestants and should also be avoided in severe renal or hepatic impairment.

Opiate Analgesics

There is inadequate evidence supporting narcotic analgesic use (ie, parenteral butorphanol, meperidine, methadone, and tramadol or oral codeine) in the treatment of acute migraine. However, oral codeine or tramadol combinations with acetaminophen are probably effective and butorphanol nasal spray has established efficacy.[20] Opiates have no vasopressor or anti-inflammatory effects and can cause central sensitization, increasing the risk of medication-overuse headache and interfering with the efficacy of other treatments even with intermittent use.[13,20,22] These agents should generally be reserved for individuals with moderate-to-severe infrequent headaches in whom conventional therapies are contraindicated, or as "rescue medication" after individuals have failed to respond to conventional therapies. Opioid therapy should be supervised closely because of the risk of sedation and the potential for unhealthy use.[13,21]

Miscellaneous Nonspecific Medications

Corticosteroids can be considered rescue therapy for status migrainous (a severe, continuous migraine that can last up to 1 week) or to reduce migraine recurrence. Intravenous (IV) dexamethasone at a 4- to 16-mg dose has been used as an adjunct to abortive therapy, although evidence is incomplete.[20,21] IV valproate 400 to 1,000 mg also plays a role in moderate or severe intensity headaches, although data to support this is limited. When used the majority of individuals report improvement after one dose. Lastly, magnesium sulfate 1,000 to 2,000 mg IV (in migraine with aura) and generic isometheptene combinations are probably effective. A more defined role for these agents in migraine management must be established.[20]

Prophylactic Pharmacologic Therapy

Antiseizure Medications

Antiseizure medications have emerged as important therapeutic options for migraine prophylaxis with valproate, divalproex, and topiramate all having established efficacy.[25] The beneficial effects of these agents are likely due to multiple mechanisms of action, including enhancement of γ-aminobutyric acid–mediated inhibition, modulation of the excitatory neurotransmitter glutamate, and inhibition of sodium and calcium ion channel activity. Antiseizure medications are particularly useful in individuals with migraine and comorbid seizures, anxiety disorder, or bipolar illness.[19,26,50,51] The use of sodium valproate and divalproex sodium (a 1:1 molar combination of valproate sodium and valproic acid) is effective based on multiple placebo-controlled studies. In most headache prophylaxis trials, there were no significant differences in treatment-emergent adverse effects between these agents and placebo. Nausea and vomiting are the most common early adverse effects but are self-limited and appear to be less common with divalproex sodium and gradual dose titration. Alopecia, tremor, asthenia, somnolence, and weight gain are also complaints.[19,25] The extended-release formulation of divalproex sodium is administered once daily and is better tolerated than the enteric-coated formulation. Hepatotoxicity is the most serious adverse effect associated with valproate, but the risk appears to be low in individuals with migraine headache (eg, individuals older than 10 years of age who are receiving monotherapy and have no underlying metabolic or neurologic disorder). Baseline liver function tests should be obtained, but routine follow-up is not necessary for asymptomatic adults on monotherapy. Regular follow-up is needed for dosage adjustments and adverse effect monitoring. Valproate when used for migraine prophylaxis, is contraindicated in pregnant individuals due to potential teratogenicity and for individuals with a history of pancreatitis or chronic liver disease.[19,25]

Topiramate is the most extensively studied antiseizure medication for migraine prophylaxis. Its efficacy shows improvements in health-related quality of life such as daily work, home, and social activities.. To minimize adverse effects, topiramate should be initiated at a low dose and slowly titrated upward. The benefits of topiramate are observed as early as 2 weeks after therapy initiation, with significant reductions in migraine frequency within the first month. Approximately half of the individuals treated to target doses are responders, defined as a 50% or greater reduction in mean headache frequency. Treatment-emergent adverse events include paresthesia, fatigue, anorexia, diarrhea, weight loss, hypesthesia, difficulty with memory, language problems, taste perversion, and nausea. Paresthesia, the most common adverse event, occurs in about half of the individuals at target doses. Weight loss, occurring in 9% to 12% of individuals, is a unique adverse effect, as weight gain is a common reason to discontinue other preventive medications. Topiramate should be used with caution or avoided in individuals with a history of kidney stones or cognitive impairment.[19,25]

Carbamazepine is possibly effective for migraine prophylaxis and gabapentin has modest impact.[52] Lamotrigine is classified as possibly or probably ineffective.[26]

Additional information regarding all antiseizure medications can be found in Chapter 75, "Epilepsy."

Antidepressants

The beneficial effects of antidepressants in migraine are independent of their antidepressant activity and may be related to downregulation of central 5-HT_2 receptors resulting in increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor actions.[10] The tricyclic antidepressant (TCA) amitriptyline and SNRI venlafaxine have demonstrated efficacy in placebo-controlled and comparative studies and are classified as probably effective for migraine prophylaxis (see Table 80-4).[19,26] Use of other antidepressants is based primarily on clinical and anecdotal experience. There is neither support nor refusal regarding the efficacy of other antidepressants, such as protriptyline, fluoxetine, or fluvoxamine, for migraine prophylaxis.[26]

Anticholinergic adverse effects are common with the TCAs and limit their use in individuals with benign prostatic hyperplasia and glaucoma. Evening doses are preferred because of associated sedation. Increased appetite and weight gain can also occur. Orthostatic hypotension and slowed atrioventricular conduction are also occasionally reported.[19,26] Venlafaxine's most common adverse effects are nausea, vomiting, and drowsiness. Again, the potential risk of 5-HT syndrome should be considered in individuals using SSRIs or SNRIs along with a triptan.[21,26] Additional information about the adverse effects of antidepressants can be found in Chapter 88.

β-Adrenergic Antagonists

β-Adrenergic antagonists are among the most widely used medications for migraine prophylaxis. Metoprolol, propranolol, and timolol have established efficacy and reduce the frequency of attacks by half in more than 50% of individuals.[19,26] Atenolol and nadolol are probably effective, while nebivolol and pindolol are possibly effective (see Table 80-5).[25] Because the individual agent's relative efficacy has not been established, β-blocker selection can be based on β-selectivity, formulation, and tolerability. β-blockers may raise the migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical or subcortical pathways, although their precise mechanism is unknown. Although not first-line treatment for hypertension, β-blockers may be useful along with other therapy in individuals with comorbid hypertension or angina. Adverse effects can include drowsiness, fatigue, sleep disturbances, vivid dreams, memory disturbance, depression, impotence, bradycardia, and hypotension. The β-blockers should be used with caution in individuals with congestive heart failure, peripheral vascular disease, atrioventricular conduction disturbances, asthma, depression, and diabetes.[19,26]

CGRP Antagonists (Anti-CGRP Antibodies)

Inhibition of the CGRP receptor is the newest target in the prophylaxis of migraine.[10,19,46,50] Several anti-CGRP receptor monoclonal antibodies have been FDA approved in recent years such as erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and eptinezumab-jjmr. While erenumab targets the CGRP receptor, the others target the CGRP ligand. These biologic agents have efficacy, safety, and tolerability for the prevention of episodic and chronic migraine.[18] Erenumab, fremanezumab, and galcanezumab are all administered as monthly subcutaneous injections and fremanezumab has a quarterly (every 3 months) dosing option. Eptinezumab is a quarterly IV infusion. The lack of hepatic metabolism or renal clearance for these agents avoids medication interactions with this medication class. Injection site reactions are the most common adverse event for all of the subcutaneous agents. For erenumab worsening of pre-existing hypertension can occur within 7 days of initiation and constipation has been reported in less than 5% of users. For eptinezumab, nasopharyngitis is reported in less than 10% of individuals and hypersensitivity is reported in less than 3%. The cost of these biological medications is higher than the oral preventive medications, and it is recommended that they are reserved for individuals who have been unable to tolerate or who did not respond to at least two of the preventive oral medications with highest level of evidence (topiramate, divalproex/valproate sodium, beta blockers, tricyclic antidepressants, or venlafaxine/duloxetine).

CGRP Antagonists ("gepants")

Unlike the large-molecule, injectable, preventative monoclonal antibodies, the "gepants" are small-molecule agents that block the ability of CGRP to bind to the CGRP docking station, which prevents prolonged migraine attacks. There are two "gepants," atogepant and rimegepant, that are FDA approved for preventative treatment of migraine in adults. Rimegepant has been approved for episodic migraine headaches and atogepant has been approved for episodic and preventive treatment of chronic migraine

Atogepant (placebo, 10 mg daily, 30 mg daily, 60 mg daily) was evaluated in two, 12-week, multicenter, randomized, placebo-controlled trials for

episodic migraine headache prevention.[53,54] Overall, the difference in the reduction of migraine days ranged from 0.7 to 1.1 days per month with atogepant (for all doses) versus placebo. Atogepant (placebo, 60 mg daily) was also evaluated in a 12-week multicenter, randomized, placebo-controlled study for chronic migraine headache prevention.[55] Overall, the difference in the reduction of migraine days was 1.8 days per month with atogepant versus placebo. Fatigue, nausea, and constipation appeared to increase at the higher doses, but still occurred at a rate of less than 10%, even with the 60 mg daily dose of atogepant. No liver abnormalities above the placebo rate were seen.[54] Like rimegepant and ubrogepant, atogepant has significant medication interactions, and concomitant use with strong CYP3A4 inhibitors, strong as well as moderate CYP3A4 inducers, and OATP inhibitors should be avoided; otherwise, dose adjustments may be needed. Additionally, atogepant should be avoided in severe renal or hepatic impairment. Rimegepant (75 mg every other day) was used in the prevention of episodic migraine headache for over 12 weeks in a multicenter, randomized, placebo-controlled study. Overall, the difference in the reduction of migraine days was 0.8 days per month with rimegepant versus placebo.[56] Two percent of adverse medication effects associated with rimegepant included nasopharyngitis, nausea, urinary tract infection, and upper respiratory tract infection were mild to moderate in severity. Adverse rimegepant effects include reversible alanine aminotransferase or aspartate aminotransferase greater than three times the upper limit of normal, reversible asymptomatic elevation of aminotransferases with alanine aminotransferase greater than 10 times the upper limit of normal, and hereditary liver disorder related where bilirubin levels greater than two times the upper limit of normal.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are modestly effective for reducing the frequency, severity, and duration of migraine attacks, but potential GI and renal toxicity limit the daily or prolonged use of these agents. Consequently, NSAIDs have been used intermittently to prevent headaches recurring in a predictable pattern, such as menstrual migraine. NSAID administration in the perimenstrual period can be beneficial in females with true menstrual migraine. They should be initiated up to 1 week prior to the expected onset of headache and continued for no more than 10 days.[27] If long-term NSAID therapy is initiated, renal function and occult blood loss should be monitored. The evidence for efficacy is strongest for naproxen and weakest for aspirin.[26,57]

Triptans

Triptans are also useful for the prevention of menstrual migraine. Frovatriptan has established efficacy, while naratriptan and zolmitriptan are probably effective. These agents are usually started 1 or 2 days before the expected onset of headache and continued during the period of vulnerability.[26,57] Regulatory authorities are currently deliberating a separate indication for pure menstrual migraine.[26]

Miscellaneous Prophylactic Agents

At least two placebo-controlled studies show that petasites, an extract from the butterbur plant *Petasites hybridus*, is an effective preventive treatment for migraine.[19,29] There is a probable efficacy of riboflavin (vitamin B2) 400 mg daily in migraine prophylaxis, based on double-blind, placebo-controlled study. Riboflavin is well tolerated and associated with a 50% or greater improvement in attack frequency in most individuals. However, these benefits were only significant after 3 months.[19,29] The relatively stable extract of feverfew (*Tanacetum parthenium*), MIG-99, is the most studied herbal preparation for migraine prevention and it reduces migraine frequency by almost two attacks per month and is classified as probably effective.[19,29] As CNS levels of magnesium are significantly low during migraine attacks, magnesium supplementation may be particularly effective for prevention of menstrual migraine.[31] The evaluation of various formulations of magnesium has yielded mixed results, but there is probable efficacy.[19,29] Subcutaneous histamine has been compared with placebo, sodium valproate, and topiramate, with favorable results indicating probable efficacy in improving headache frequency, duration, and intensity. Transient burning and itching at the injection site were the only reported adverse effects with histamine administration.[29]

Other agents are also possibly effective for migraine prevention.[26,29] The angiotensin-converting enzyme inhibitor lisinopril and the angiotensin II receptor blocker candesartan provided effective migraine prophylaxis in recent clinical trials.[19,25] Clonidine and guanfacine also have possible efficacy, although adverse effects limit their use.[26] Coenzyme Q10 was effective for migraine prevention and well-tolerated in a small, randomized, double-blind, controlled study.[19,29] Cyproheptadine (4 mg/day) was as effective as propranolol (80 mg/day) in reducing migraine frequency, duration, and severity, while the combination was more effective in attack frequency reduction.[26,29]

The calcium channel blockers, primarily verapamil, have been widely used for preventive treatment, although the results of their use is inadequate or conflicting.[19,26] Extensive clinical experience and verapamil's ease of use suggest a possible role in migraine prevention. Adverse effects include constipation, hypotension, bradycardia, atrioventricular block, and exacerbation of congestive heart failure.[26]

Localized injections of botulinum toxin type A have been used for various conditions and pain syndromes, including chronic migraines. This agent is FDA approved for individuals who have 15 or more headache days per month lasting 4 or more hours daily. The American Academy of Neurology concludes that a 6-week trial of botulinum toxin is effective as a second-line agent after inadequate response or adverse effects to at least two of the following agents: topiramate, divalproex sodium/valproate sodium, beta-blocker, tricyclic antidepressant, or SNRI.[19]

TENSION-TYPE HEADACHE

Epidemiology

Tension-type headache is the most common type of primary headache, with an estimated 1-year prevalence of 38% to 86%.[4,58] It peaks in the fourth decade of life and is higher among females; however, the incidence decreases with age.[31] Although most individuals with tension-type headaches experience some degree of functional impairment during their attacks, few seek medical attention, likely because they have intermittent attacks. These headaches are classified as either episodic (infrequent or frequent) or chronic based on the frequency and duration of the attacks.[3] Infrequent episodic tension-type headache (defined as fewer than one episode per month) is experienced by 64% of sufferers, while 22% have a frequent episodic tension-type headache for about 1-14 days per month). The prevalence of chronic tension-type headache (defined as 15 or more days/month, perhaps without recognizable episodes) is estimated at 0.9% to 2.2%.[3,58] Risk factors associated with a poor outcome include coexisting migraine, depression, anxiety, poor stress management, and the presence of chronic tension-type headache.[59]

Pathophysiology

Although tension-type headache is the most common type of headache, it is the least studied primary headache disorder, and there is limited understanding of key pathophysiologic concepts.[3,58] Migraine and tension-type headaches represent a continuum of headache severity with similarities in mechanisms and pathophysiology. However, tension-type headache has been recognized as a distinct disorder.[3,58] The mechanism of pain in chronic tension-type headache is thought to originate from myofascial factors and peripheral sensitization of nociceptors. Central mechanisms also are involved, with heightened sensitivity of CNS pain pathways.[58] Mental stress, nonphysiologic motor stress, a local myofascial release of irritants, or a combination of these may be the initiating stimulus. Following activation of supraspinal pain perception structures, a self-limiting headache results in most individuals owing to central modulation of the incoming peripheral stimuli. Chronic tension-type headache can evolve from episodic headaches in predisposed individuals due to changes in central circuits and nociceptive processing along the brain stem reflex pathway and subsequent CNS sensitization.[58] Other pathophysiologic mechanisms also contribute to the development of tension-type headache.

Clinical Presentation

Premonitory symptoms and aura are absent with this headache, and the pain usually is mild to moderate in intensity. It is often is described as bilateral dull, nonpulsatile tightness, or pressure classically described as having a "hatband" pattern.[3,58] Associated symptoms generally are absent, but mild photophobia or phonophobia may be reported. The disability associated with tension-type headache is typically minor compared to migraine headaches, and routine physical activity does not affect severity.[3,52] Palpation of the pericranial or cervical muscles can reveal tender spots or localized nodules in some individuals.[3]

Treatment

Desired Outcomes

While pain relief and prevention of further headaches are the main desired outcomes of treatment, the vast majority of episodic tension-type headache sufferers self-medicate with nonprescription medications and do not consult a healthcare professional. Although pharmacologic and nonpharmacologic treatments are available, simple analgesics and NSAIDs are the mainstay of acute therapy. Most agents used for tension-type

headache have not been studied in controlled clinical trials.[60]

Nonpharmacologic Therapy

Psychophysiologic therapy and physical therapy have been used in their management. Behavioral treatments can consist of cognitive-behavioral therapy (ie, stress management), relaxation training, and biofeedback.[59] These therapies (alone or in combination with pharmacotherapy) can result in a 33% to 64% reduction in headache activity. Relaxation training combined with biofeedback is more effective than other behavioral therapy options.[59] The effect of physical therapeutic options, such as heat or cold packs, ultrasound, electrical nerve stimulation, stretching, exercise, massage, acupuncture, manipulations, ergonomic instruction, and trigger point injections or occipital nerve blocks, is somewhat inconsistent. However, individuals may benefit from selected modalities in reducing the frequency of tension-type headache or during an acute episode.[59,60]

Pharmacologic Therapy

Simple analgesics (alone or in combination with caffeine) and NSAIDs are effective for the acute treatment of most mild-to-moderate tension-type headaches. Acetaminophen, aspirin, diclofenac, ibuprofen, naproxen, ketoprofen, and ketorolac have efficacy in placebo-controlled and comparative studies.[60] Failure of nonprescription agents can warrant therapy with prescription medications. The combination of aspirin or acetaminophen with butalbital or, rarely, codeine can be effective options in selected individuals; however, use of butalbital and codeine combinations should be avoided when possible owing to the high potential for overuse and unhealthy use.

Acute medications should be taken for episodic tension-type headache no more than 10 days a month for butalbital-containing or combination analgesics, or 15 days a month for NSAIDs. This practice helps prevent the development of medication-overuse or chronic tension-type headache.[60] The efficacy of muscle relaxants in episodic tension-type headache management is not known.[3,60] Preventive treatment is appropriate for most individuals with chronic tension-type headache and should be considered in those whose episodic headache occur more than twice per week, last more than 3 to 4 hours, or their severity results in medication overuse or substantial disability.[59]

Preventive treatment for tension-type headaches is similar to migraine headaches. The TCAs are prescribed most often for prophylaxis, but other medications can also be selected after considering comorbid medical conditions and medication adverse effect profiles. In general, the SSRIs are only effective in individuals with tension-type headache and depression, and limited studies support the mirtazapine and venlafaxine use in individuals with chronic tension-type headache without depression.[59] Topiramate, gabapentin, and tizanidine may have benefits in chronic tension-type headache; however, randomized clinical trials need to be done. Lidocaine trigger point injections may reduce headache frequency for frequent episodic or chronic tension-type headache. Injection of botulinum toxin into pericranial muscles has inconsistent efficacy in the prophylaxis, and because of this, it is of uncertain benefit.[59]

CLUSTER HEADACHE

Epidemiology

Cluster headache is the most severe of the primary headache disorders and is characterized by attacks of excruciating, unilateral head pain that occur in series lasting for weeks or months. These cluster periods are separated by remission periods, usually lasting months or years.[3,61] These headaches can be episodic or chronic[3] and are relatively uncommon among the primary headache disorders. However, the exact prevalence is uncertain. Estimates from pooled population studies show a lifetime prevalence of 124 per 100,000 or 0.12%.[61,62] The male-to-female ratio for cluster headache is approximately 4:1 with onset typically in the second to third decade of life. Up to 85% of individuals with cluster headaches are tobacco smokers or have a smoking history. Tobacco cessation, however, does not seem to improve the course of headaches. Recent genetic epidemiologic surveys support a predisposition for cluster headache in certain families.[61–63]

Pathophysiology

The etiologic and pathophysiologic mechanisms of these headaches are not entirely understood. Neuroimaging studies performed during acute attacks show activation of the ipsilateral hypothalamic gray area, implicating the hypothalamus as a modulator. The hypothalamus secondarily

activates trigeminal-autonomic reflexes, leading to the ipsilateral pain and cranial autonomic features characteristic of cluster headache.[61–63] The cyclic and circadian rhythmicity of attacks also implicates pathogenesis of hypothalamic dysfunction.[62,63] Cluster headache may result from inflammation of the nerves traversing the cavernous sinus resulting in injury to sympathetic fibers of the internal carotid artery.[62]

Clinical Presentation

One hallmark of cluster headaches is the circadian rhythm of painful attacks. Episodic cluster headaches are the most common cluster headache subtype, occurring in up to 90% of individuals.[62] These episodic attacks occur daily for a week to several months, followed by long pain-free intervals. Headache remission averages 2 years in length but can range from 2 months to 20 years in duration. Approximately 15% of individuals have chronic symptoms with attacks recurring for over 1 year without remission or with remission periods lasting less than 1month.[61,62]

Cluster headache attacks occur commonly at night and frequently in the spring and fall. These attacks occur suddenly and pain peaks quickly after onset. The pain is excruciating, penetrating, and of a boring (ie, deep, non-pulsating, behind the eye) intensity in orbital, supraorbital, and temporal unilateral locations. They generally lasts 15 to 180 minutes and are accompanied by cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal stuffiness, rhinorrhea, eyelid edema, facial sweating, and miosis/ptosis. Most sufferers also describe restlessness or agitation; however, all of these symptoms resolve when the headache ceases. While individuals with migraine retreat to a quiet, dark room, individuals with cluster headache generally sit and rock or pace about the room clutching their head. Auras are not present and during the cluster period, attacks occur from once every other day to eight times per day.[61,62] Specific diagnostic criteria for cluster headaches are provided within the IHS classification system.[3]

Treatment

Desired Outcomes

As in migraine, therapy for cluster headaches involves both abortive and prophylactic therapy with the overall desired outcomes being resolution or prevention of pain and disability. Abortive therapy is directed at managing the acute attack, whereas prophylactic therapies are started early in the cluster period in an attempt to induce remission. Individuals with chronic cluster headache can require prophylactic medications indefinitely.

Abortive Therapy

Oxygen

The standard acute treatment of cluster headache is inhalation of 100% oxygen by a nonbreather facial mask at a rate of at least 12 to 15 L/min, with effects usually starting 15 to 20 minutes after treatment.[63–66] Repeat or frequent administration over a short period of time should be avoided, as overuse may increase the frequency or merely delay rather than abort the attack in some individuals.[64,65] No adverse effects have been reported with the use of oxygen, but caution should be used for those who smoke or have chronic obstructive pulmonary disease.

Triptans

The quick onset of subcutaneous and intranasal triptans makes them safe and effective abortive agents for cluster headaches. Subcutaneous sumatriptan (6 mg) is the most effective agent, whereas nasal sprays, which are less effective than subcutaneous administration, may be better tolerated in some individuals. Adverse events reported with triptan use in individuals with cluster headache are similar to those seen in individuals with migraine. Orally administered triptans have limited use in cluster attacks because of their relatively slow onset of action; oral zolmitriptan (10 mg), however, was modestly effective in individuals with episodic cluster headache.[59]

Ergotamine Derivatives

All forms of ergotamine have been used in cluster headaches, although no controlled clinical trials support their use.[38,39] In clinical use, IV dihydroergotamine may be given as a bolus followed by repeated administration over several days to break the cycle of frequent attacks. In addition, ergotamine tartrate has provided effective relief from cluster headache attacks when administered sublingually.[64] Dosing guidelines are similar to

those for migraine headache therapy.

Prophylactic Therapy

Verapamil

The preferred first-line treatment for cluster headaches prevention is verapamil, a calcium channel blocker with antianginal and antiarrhythmic properties.[63,65,66] Its beneficial effects often appear within 2 to 3 weeks of therapy, starting with a dose of 240 mg/day, titrated to a target dose of 360 to 960 mg/day. Rarely, individuals with refractory cluster headaches require doses as high as 1,200 mg/day. In such individuals, an electrocardiogram should be obtained as the dose is increased, due to concerns for bradycardia or heart block.[64,66]

Galcanezumab

Galcanezumab is a monoclonal antibody that binds to the CGRP ligand that FDA approved for episodic cluster headache. It has a modest benefit in reducing the number of cluster headaches per week for one to three weeks for individuals with episodic cluster headaches in a randomized controlled trial. Galcanezumab is dosed subcutaneously (300 mg) at the onset of the cluster period, and then continued monthly until the end of the cluster period. It should be reserved for individuals with prior episodic cluster headache periods lasting longer than 1 month when first-line preventive medications are ineffective, poorly tolerated, or contraindicated. It was well tolerated with injection site reaction (less than 10%) being the most frequently reported adverse event.[67]

Lithium

Lithium carbonate is effective for episodic and chronic cluster headache attacks and can be used when other medications are ineffective or contraindicated. A positive response is seen in up to 78% of individuals with chronic cluster headache and in up to 63% of individuals with episodic cluster headache. The usual dose is 600 to 1,200 mg/day, with a suggested starting dose of 300 mg twice daily. Lithium levels should be monitored and maintained between 0.4 and 1.2 mEq/L (mmol/L).[64]

Major adverse effects include tremors, thyroid, and renal dysfunction, and rarely cardiac arrhythmias. Liver, thyroid, and renal function must be carefully monitored during therapy. Lithium should be administered with caution to individuals with significant renal or cardiovascular disease, dehydration, pregnancy, or concomitant diuretic or NSAID use.[64,66] Additional details regarding lithium administration can be found in Chapter 86, “Substance Use Disorders II: Alcohol Nicotine and Caffeine.”

Corticosteroids

Corticosteroids can be used effectively for inducing cluster headache remission, although clinical trial data are lacking.[64] Therapy is initiated as 60 to 100 mg/day prednisone for 5 days and then tapered by approximately 10 mg/day. Long-term use is generally not recommended to avoid steroid-induced complications, and headaches can recur when therapy is tapered or discontinued.[64,66]

Miscellaneous Agents

Other therapies used in the acute management of cluster headache include intranasal lidocaine and subcutaneous octreotide. There is limited support for the use of topiramate, divalproex sodium, melatonin, indomethacin, long-acting triptans, and intranasal capsaicin for cluster headache prevention.[64–66]

For individuals refractory to pharmacologic therapy, neurosurgical interventions to relieve debilitating chronic cluster headaches may be considered.[64] Neurostimulation has gained attention in the last several years, and vagal nerve stimulation and sphenopalatine stimulation have positive results in small clinical trials.[63,64,68]

EVALUATION OF THERAPEUTIC OUTCOMES

Pharmacologic treatment should occur with medications that have the highest level of efficacy and management should be individualized based on the

individual's clinical presentation and medical history, using the lowest effective doses titrated to clinical benefit and absence of adverse events. Avoid medications that increase headache frequency or severity. Nonpharmacologic or nonprescription treatments for headache management can be used either before or concurrently with other pharmacologic therapy. However, individuals may not know how to use these products optimally and often need instructions and dosing limits.

Analgesics and NSAIDs are considered the medications of choice for infrequent mild-to-moderate and severe attacks. The triptans or dihydroergotamine can be used if initial therapies prove ineffective or as first-line therapy in moderate-to-severe migraine headache. Abortive therapy should be instituted early in the course of the attack to optimize efficacy and minimize migraine-related pain and disability. Preventive therapy should be considered for recurring migraine attacks that produce significant disability or frequent attacks requiring symptomatic medication more than twice per week. Additionally, preventative therapy should be considered if symptomatic therapies that are ineffective or contraindicated or produce serious adverse effects and in the case of uncommon migraine variants that cause risk of neurologic injury. The efficacy of any prescribed prophylactic regimen should be periodically assessed for efficacy and adverse effects. Therapeutic interventions require an adequate trial to achieve clinical benefit, and maximal benefit may not be seen for 6 months or more. A prolonged headache-free interval could allow for gradual dosage reduction and discontinuation of therapy.

Monitor individuals for headache frequency, intensity, and duration, as well as any change in the headache pattern. To this end, they should be encouraged to keep a headache diary, documenting the frequency, severity, and duration of attacks and response to medication and potential trigger factors. Careful monitoring is essential to initiate the most appropriate pharmacotherapy, document therapeutic successes and failures, identify medication contraindications, and prevent or minimize adverse events. Individuals using acute therapies should be monitored for prescription and nonprescription medication use frequency to identify potential medication-overuse headache.

Although migraine is widely recognized as a disease that exacts an enormous toll on the sufferer, healthcare providers often do not recognize the degree and scope of functional impairment imposed on the individual. Approximately one out of every six healthcare visits for migraine occurs in the emergency department, although management in this setting is often suboptimal. The use of opioids for the acute migraine treatment in the emergency department is increasing, and the likelihood of unnecessary radiation exposure is greater.[6] Although most episodic migraine sufferers take medications for their headaches, only two-thirds of individuals who have been diagnosed consult with a healthcare provider regarding use of migraine-specific treatments. Just 11% of those eligible for medications to prevent migraines currently use them, although approximately 38% would benefit from prophylaxis.[15] Patient counseling is necessary to allow for proper medication use (eg, self-injection with sumatriptan), to encourage medication use early in the headache cycle, and enhance individual compliance. Strict adherence to dosing guidelines should be stressed to minimize potential toxicity. Patterns of abortive medication use should be documented to establish the need for prophylactic therapy. Prophylactic therapies also should be monitored closely (every 3-6 months until stable) for adverse reactions, abortive therapy needs, adequate dosing, and compliance. Since many individuals with migraine who receive inadequate care experience substantial levels of pain and disability, improvement in migraine diagnosis, care, and treatment potentially could result in lower direct and indirect disease costs. Consultation with other healthcare practitioners should be encouraged when changes in headache patterns or medication use occur.

CONCLUSION

Even though headache disorders result from neuronal dysfunction, the precise etiology and nature of the dysfunction are unknown. Serotonergic neurotransmission and the trigeminovascular system appear to play important roles. A careful individual workup, including patient history, physical examination, and appropriate laboratory tests, should identify most headache individuals with major disease. Various strategies can help manage migraine, tension-type, and cluster headaches to suppress acute attacks and prevent recurrences. Continuing research in existing and newly identified pathways will better define pathophysiologic mechanisms and aid the search for less toxic and more efficacious pharmacologic agents.

ABBREVIATIONS

5-HT	5-hydroxytryptamine
CGRP	calcitonin gene-related peptide
CNS	central nervous system
CYP	Cytochrome P450
FDA	Food and Drug Administration
GABA	γ-aminobutyric acid
GI	gastrointestinal
5-HT	serotonin, 5-hydroxytryptamine
IHS	International Headache Society
IM	intramuscular
IV	intravenous
MHD	monthly headache days
MMD	monthly migraine days
NSAIDs	nonsteroidal anti-inflammatory drugs
OATP	organic anion transporting polypeptides
ODT	orally disintegrating tablet
OTC	over the counter
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

REFERENCES

1. Vandenbussche N, Laterza D, Lisicki M, et al. Medication-overuse headache: A widely recognized entity amidst ongoing debate. *J Headache Pain*. 2018;19(1):50. [PubMed: 30003412]

2. Weiss AJ, Wier LM, Stocks C, Blanchard J. Overview of emergency department visits in the United States, 2011. Statistical Brief #174. June 2014. Agency for Health Care Policy and Research, Rockville, MD. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb174-Emergency-Department-Visits-Overview.pdf. Accessed August 9, 2015.

3. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd ed. *Cephalalgia.* 2018;38(1):1–211.

4. Wootton RJ, Wippold FJ, Whealy MA. Evaluation of headache in adults. *UpToDate*. 2020;21:1–23. Available at: www.uptodate.com. Accessed January 1, 2021.

5. Smitherman TA, Burch RC, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: A review of statistics from national surveillance studies. *Headache*. 2013;53:427–436. [PubMed: 23470015]

6. Burch RC, Rizzoli P, Loder E. The prevalence and burden of migraine and severe headache in the United States: Figures and trends from government health surveillance studies. *Headache*. 2018;58(4):496–505. [PubMed: 29527677]

7. Steiner TJ, Birbeck GL, Jensen RH, et al. Headache disorders are third cause of disability worldwide. *J Headache Pain*. 2015;16:58. [PubMed: 26109437]

8. Messali A, Sanderson J, Blumenfeld AM, et al. Direct and indirect costs of chronic and episodic migraine in the United States: A web-based survey. *Headache*. 2016;56:306–322. [PubMed: 26833083]

9. Charles A. Migraine. *N Engl J Med.* 2017;377:553–561. [PubMed: 28792865]

10. Cutrer FM. Pathophysiology, clinical manifestations, and diagnosis of migraine in adults. *UpToDate*. 2020;33:1–35. Available at: www.uptodate.com. Accessed January 1, 2021.

11. Ferrari MD. Migraine. *Lancet*. 1998;351:1043–1051. [PubMed: 9546526]

12. Silberstein SD, Dodick DW. Migraine genetics: Part II. *Headache*. 2013;53:1218–1229. [PubMed: 23919895]

13. Ong JJY, De Felice M. Migraine treatment: Current acute medications and their potential mechanisms of action. *Neurotherapeutics*. 2018;15:274–290. [PubMed: 29235068]

14. Da Silva AN, Tepper SJ. Acute treatment of migraines. *CNS Drugs*. 2012;10:823–839.

15. Oswald JC, Schuster NM. Lasmiditan for the treatment of acute migraine: A review and potential role in clinical practice. *J Pain Res.* 2018;11:2221–2227. [PubMed: 30323656]

16. Edvinsson L, Goadsby PJ. Discovery of CGRP in relation to migraine. *Cephalalgia.* 2019;39(3):331–332. [PubMed: 30827155]

17. Lipton RB, Silberstein SD. Episodic and chronic migraine headache: Breaking down barriers to optimal treatment and prevention. *Headache*. 2015;S2:103–122.

18. Bose P, Goadsby PJ. The migraine postdrome. *Curr Opin Neurol.* 2016;29:299–301. [PubMed: 26886356]

19. American Headache Society (AHS). AHS Consensus Statement: The AHS position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59:1–18.

20. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: The American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55:3–20. [PubMed: 25600718]

21. Smith JH. Acute treatment of migraine in adults. *UpToDate*. 2020;51:1–43. Available at: www.uptodate.com. Accessed October 18, 2021.

22. Garza I, Schwedt TJ. Medication overuse headache: Etiology, clinical features, and diagnosis. *UpToDate*. 2020;11:1–18. Available at:

www.uptodate.com. Accessed January 1, 2021.

23. Garza I, Schwedt TJ. Medication overuse headache: Treatment and prognosis. *UpToDate*. 2020;14:1–23. Available at: www.uptodate.com. Accessed October 18, 2021.

24. MacGregor EA. Migraine. *Ann Intern Med.* 2013;159:ITC51.

25. Navratilova E, Behravesh S, Oyarzo J, et al. Ubrogepant does not induce latent sensitization in a preclinical model of medication overuse headache. *Cephalalgia*. 2020;40(9):892–902. [PubMed: 32615788]

26. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacological treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337–1345. [PubMed: 22529202]

27. Rizzoli P. Preventive pharmacotherapy in migraine. *Headache*. 2014;54:364–369. [PubMed: 24261479]

28. American Headache Society Position Statement on Integrating New Migraine Treatment into Clinical Practice. *Headache*. 2019;59(1):1–18.

29. Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1346–1353. [PubMed: 22529203]

30. Marmura MJ. Triggers, projectors, and predictors in episodic migraine. *Curr Pain Headache Rep.* 2018;22(12):1–9. [PubMed: 29340793]

31. Martin PR. Behavioral management of the triggers of recurrent headache: A randomized controlled trial. *Behav Res Ther.* 2014;61:1–11. [PubMed: 25108482]

32. Schiapparelli P, Allais G, Castagnoli Gabellari I, et al. Non-pharmacological approach to migraine prophylaxis: part II. *Neurol Sci.* 2010;31(suppl 1):S137–S139. [PubMed: 20464605]

33. Puledda F, Shields K. Non-pharmacological approaches for migraine. *Neurotherapeutics*. 2018;15(2):336–345. [PubMed: 29616493]

34. Finkle AG, Yerry JA, Mann D. Dietary considerations in migraine management: Does a consistent diet improve migraine? *Curr Pain Headache Rep.* 2013;17(11):373. [PubMed: 24068338]

35. Lipton RB, Croop R, Stock DA, et al. 2023 Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial., Lancet Neurol, 22, 209-217, 10.1016/S1474-4422(22)00517-8

36. Lampl C, Voelker M, Steiner TJ. Aspirin is first-line treatment for migraine and episodic tension-type headache regardless of headache intensity. *Headache*. 2012;52:48–56. [PubMed: 21883198]

37. Kirthi V, Derry S, Moore RA et al. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev.* 2010;14(4):CD008041.

38. Triptans. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com. Accessed October 18, 2021.

39. Cortelli P, Allais G, Benedetto C. Overview of triptans in the treatment of acute migraine. *Eur Neurol Rev.* 2017:12(2):71–77.

40. Ansari H, Ziad S. Drug-drug interactions in headache medicine. *Headache*. 2016;56(7):1241–1248. [PubMed: 27350319]

41. Orlova Y, Rizzoli P, Loder E. Association of co-prescription of triptan antimigraine drug and selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurol.* 2018;75(5):566–572. [PubMed: 29482205]

42. Clemow DB, Johnson KW, Hochstetler HM, et al. Lasmiditan mechanism of action: review of a selective 5-HT1F agonist. *J Headache Pain*. 2020;21(71):1–13. [PubMed: 31898478]

43. Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. *Neurology*. 2018;19(24):e2222–e2232.

44. Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142(7):1894–1904. [PubMed: 31132795]

45. Deem M, Correnti E, Kamm P, et al. Blocking CGRP in migraine patients: A review of pros and cons. *J Headache Pain*. 2017;18(96):1–9. [PubMed: 28058534]

46. Tepper SJ. History and review of anti-calcitonin gene related peptide (CGRP) therapies: From translational research to treatment. *Headache*. 2018;58(Suppl 3):238–275. [PubMed: 30242830]

47. Lipton RB, Munjal S, Brand-Schieber E, et al. Efficacy, Tolerability, and Safety of DFN-15 (Celecoxib Oral Solution, 25 mg/mL) in the Acute Treatment of Episodic Migraine: A Randomized, Double-Blind, Placebo-Controlled Study. Headache 2020;60(1):58–70. 10.1111/head.13663 [PubMed: 31647577] .

48. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. N Engl J Med 2019;381(23):2230–2241. 10.1056/NEJMoa1813049 [PubMed: 31800988] .

49. Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet 2019;394(10200):737–745. 10.1016/S0140-6736(19)31606-X [PubMed: 31311674] .

50. Moreno-Ajona D, Chan C, Villar-Martinez MD, et al. Targeting CGRP and 5-HT1F receptors for the acute therapy of migraine: A literature review. *Headache*. 2019;59(Suppl 2):3–19. [PubMed: 31291016]

51. Minen MT, Begasse De Dhaem O, Kroon Van Diest A, et al. Migraine and its psychiatric comorbidities. *J Neurol Neurosurg Psychiatry*. 2016;87:741–749. [PubMed: 26733600]

52. Perloff MD, Berlin RK, Gillette M et al. Gabapentin in headache disorders: What is the evidence? *Pain Medicine*. 2016;17:162–171. [PubMed: 26398728]

53. Ailani J, Lipton RB, Goadsby PJ et al. Atogepant for the preventative treatment of migraine. *N Eng L Med.* 2021;385:695–706.

54. Schwedt TJ, Lipton RB, Ailani J et al. Time course of efficacy of atogepant for the preventative treatment of migraine: Results from the randomized, double-blind ADVANCE trial. *Cephalalgia*. 2021;0(0):1–9.

55. ozo-Rosich P P, Ailani J, Ashina M, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2023 10.1016/S0140-6736(23)01049-8 [PubMed: 37516125] .

56. Croop R, Lipton RB, Kudrow D et al. Oral rimegepant for preventative treatment of migraine: A phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(51):1–10. [PubMed: 33388095]

57. O'Neal MA. Estrogen-associated migraine, including menstrual migraine. *UpToDate*. 2020;26:1–24. Available at: www.uptodate.com. Accessed

October 18, 2021.

58. Taylor FR. Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis. *UpToDate*. 2020;14:1–25. Available at: www.uptodate.com. Accessed October 18, 2021.

59. Taylor FR. Tension-type headache in adults: Preventive treatment. *UpToDate*. 2020;15:1–19. Available at: www.uptodate.com. Accessed October 18, 2021.

60. Taylor FR. Tension-type headache in adults: Acute treatment. *UpToDate*. 2020;14:1–15. Available at: www.uptodate.com. Accessed October 18, 2021.

61. Nesbitt AD, Goadsy PJ. Cluster headache. *BMJ.* 2012;344:e2407. [PubMed: 22496300]

62. May A. Cluster headache: Epidemiology, clinical features, and diagnosis. *UpToDate*. 2020;11:1–17. Available at: www.uptodate.com. Accessed October 18, 2021.

63. Hoffman J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol.* 2018;17:75–83. [PubMed: 29174963]

64. May A. Cluster headache: Treatment and prognosis. *UpToDate*. 2020;31:1–24. Available at: www.uptodate.com. Accessed October 18, 2021.

65. Martelletti P. Cluster headache management and beyond. *Expert Opin Pharmacother.* 2015;16(10):1411–1415. [PubMed: 26027515]

66. Tfelt-Hansen PC, Jensen RH. Management of cluster headache. *CNS Drugs*. 2012;26(7):571–580. [PubMed: 22650381]

67. Goadsby PJ, Dodick DW, Leone M et al. Trial of galacanezumab in prevention of episode cluster headache. *N Engl J Med.* 2019;381(2):132–141. [PubMed: 31291515]

68. Wolter T, Kaube H. Neurostimulation for chronic cluster headache. *Ther Adv Neurol Disord.* 2012;5(3):175–180. [PubMed: 22590481]

SELF ASSESSMENT QUESTIONS

1. Which one of the following is NOT a type of primary headache disorder?

   A. Migraine

   B. Tension

   C. Cluster

   D. Vascular

2. Migraine pain is believed to result from activity in which one of the following systems?

   A. Perivascular

   B. Trigeminovascular

   C. Extravascular

   D. Tuberofundibular

3. The migraine aura is defined by which one of the following?

A. Positive focal neurologic symptoms that follow an attack

B. Negative focal neurologic symptoms that precede an attack

C. Positive and negative focal neurologic symptoms that follow an attack

D. Positive and negative focal neurologic symptoms that precede or accompany an attack

4. Migraine aura typically lasts:

A. Less than 20 minutes

B. Less than 60 minutes

C. More than 60 minutes

D. More than 120 minutes

5. Which one of the following is *not* part of International Headache Society diagnostic criteria for migraine without aura?

A. At least two attacks

B. Headache that lasts 4 to 72 hours (untreated or unsuccessfully treated)

C. At least two of the following characteristics: unilateral location, pulsating quality, moderate or severe intensity, aggravation by or avoidance of routine physical activity

D. During headache at least nausea, vomiting, or both or photophobia and phonophobia

6. Which one of the following drug or drug classes is *not* used in the acute treatment of migraine headaches?

A. Ergot alkaloids

B. Antidepressants

C. NSAIDs

D. Serotonin agonists

7. Individuals may benefit from adherence to a wellness program that may include all of the following *except*:

A. Regular exercise

B. Regular eating habits

C. Smoking cessation

D. Increasing caffeine intake

8. Medication-overuse headache is commonly implicated with the use of all of the following *except*:

A. Simple analgesics

B. CGRP antagonists

C. Opiates

D. Triptans

9. Which of the following is the most common adverse effect of the ergotamine derivatives?

   A. Painful extremities

   B. Peripheral ischemia

   C. Nausea and vomiting

   D. Continuous paresthesias

10. Which of the following preventive treatments for migraine is associated with weight loss?

   A. Propranolol

   B. Divalproex sodium

   C. Topiramate

   D. Amitriptyline

11. Which one of the following oral triptans has the longest half-life, but the slowest onset of action?

   A. Sumatriptan

   B. Eletriptan

   C. Naratriptan

   D. Frovatriptan

12. Which triptan has established efficacy in migraine prevention?

   A. Naratriptan

   B. Sumatriptan

   C. Frovatriptan

   D. Eletriptan

13. Which of the following would *not* be appropriate for migraine prophylaxis?

   A. Metoprolol

   B. Acebutolol

   C. Atenolol

   D. Propranolol

14. Which of the following medications does *not* target calcitonin gene-related peptide?

   A. Galcanezumab

   B. Ubrogepant

   C. Lasmiditan

   D. Eptinezumab

15. Which of the following vitamins has evidence to support efficacy in migraine prevention?

    A. Ascorbic acid

    B. Riboflavin

    C. Cyanocobalamin

    D. Pyridoxine

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** Vascular headache is an outdated term that is not considered a primary headache disorder. The other options listed are primary headache disorders. See "Etiology" section.

2. **B.** Migraine pain is associated with the trigeminovascular system that includes neurons in the trigeminal nerve and the cerebral blood vessels they innervate. See "Etiology" section under "Migraine."

3. **D.** Migraine aura may include positive and negative neurologic symptoms that occur *before* or *during* a migraine attack. See "Clinical Presentation" section under "Migraine."

4. **B.** Headache usually occurs within 60 minutes of the end of the aura. See "Clinical Presentation" section under "Migraine."

5. **A.** Minimum criteria include at least *five* attacks. See Table 80-1.

6. **B.** Antidepressants are not used for the acute treatment of migraine; they may be used for preventive therapy or for secondary psychological symptoms. See "Prophylactic Pharmacologic Therapy" section under "Migraine."

7. **D.** Caffeine is a stimulant that could potentially worsen or exacerbate migraine. Regular exercise, proper diet, and smoking cessation may be beneficial for individuals with migraines. See "Nonpharmacologic Therapy" section under "Migraine."

8. **B.** Agents most commonly implicated in medication-overuse headache include simple and combination analgesics, opiates, and triptans. CGRP antagonists have not been associated with medication-overuse. See "Abortive Treatments" section under "Migraine."

9. **C.** The use of ergotamine derivatives is most commonly associated with gastrointestinal adverse effects. These effects result from the stimulation of the chemoreceptor trigger zone. See "Ergotamine Derivatives" section.

10. **C.** Topiramate can lead to weight loss in approximately 10% of individuals, while some other prophylactic agents, especially divalproex, can cause weight gain. See "Antiseizure Medications" section.

11. **D.** Frovatriptan has a long half-life of 25 hours, and an onset action of up to 4 hours when compared to other agents in the same class. See Table 80-6.

12. **C.** Frovatriptan has established efficacy, particularly in the prevention of menstrual migraine. Naratriptan and zolmitriptan are probably effective. See "Triptans" section.

13. **B.** Acebutolol is a selective beta antagonist that would not be as likely to prevent migraine attacks. Metoprolol, atenolol, and propranolol would be more appropriate choices. See "β-Adrenergic Antagonists" section.

14. **C.** Lasmiditan is a 5-HT_{1F} receptor agonist, while galcanezumab and eptinezumab are CGRP monoclonal antibodies and ubrogepant is a CGRP antagonist. See "Pharmacologic Therapy" section.

15. **B.** Riboflavin has probable efficacy in migraine prophylaxis; however, the benefits of therapy became significant only after 3 months. See Table 80-4.