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Headache

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Headache

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EDITOR'S PREFACE

No Longer a Headache: Accessing *Continuum* on the Go

This issue of *Continuum* is devoted to the diagnosis and management of headache and facial pain, symptoms that are common in our clinical practices and have profound effects on patients' quality of life. To achieve this goal, I am indebted to Dr Matthew S. Robbins for accepting my invitation to serve as guest editor of this issue and for enlisting outstanding and prominent experts in the field to guide us in the diagnosis and management of primary or secondary headache disorders.

The issue begins with two articles that serve as important introductions to the articles that follow. First, Dr David W. Dodick provides a very practical overview of his clinical approach to the diagnosis of patients with secondary and primary headache disorders. Next, Dr Ana Recober reviews the current thinking regarding the underlying pathophysiology of migraine and its various phases from prodrome to postdrome.

Dr Jessica Ailani reviews the many agents and approaches currently available in our armamentarium for the management of acute migraine attacks. Dr Rebecca Burch then discusses the many therapeutic strategies and options available for the prevention of migraine. Dr Stephanie J. Nahas next describes the diagnosis of and current management options for cluster headache and other trigeminal autonomic cephalalgias, stressing the severity of these syndromes and the great impact these painful disorders can have on our patients' lives.

Dr Jonathan H. Smith reviews the diagnosis and management of the variety of other primary headache disorders; recognition of the unique clinical characteristics of these disorders can lead the clinician to the most appropriate counseling and treatment options. Dr Carrie Robertson then discusses the diagnosis and current management strategies of the cranial neuralgias, including trigeminal and glossopharyngeal neuralgia and other neuralgias of the head and neck.

Dr Jelena M. Pavlović provides us with an extensive overview of the diagnosis and treatment of headache in women, with emphasis on the relation of headache to hormonal changes during the menstrual cycle, in pregnancy, and throughout life. Next, Dr Christina Szperka provides an approach to the unique aspects of history taking, diagnosis, management, and counseling of the most common headache disorders presenting in children and adolescents.

Dr Robbins then reviews the indications, evidence base, technical aspects, and safety considerations of various procedural therapies for headache disorders, particularly migraine and cluster headache. In the final review article of the issue, Dr Shuu-Jiun Wang discusses the variable clinical presentations (including headache and nonheadache symptoms), diagnostic testing, and current therapeutic strategies for patients who present with spontaneous intracranial hypotension.

In this issue's Medicolegal Issues article, Ms Rachel V. Rose and Dr Joseph S. Kass provide several real-life examples relevant to neurology to discuss the False Claims Act and its implications for neurologists.

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After reading the issue and taking the Postreading Self-Assessment and CME Test written by Drs Adam G. Kelly and Allison L. Weathers, readers may earn up to 20 *AMA PRA Category 1 Credits*™ toward self-assessment CME or, for Canadian participants, a maximum of 20 hours toward the Self-Assessment Program (Section 3) of the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Additional credit can be obtained by listening to *Continuum* Audio interviews associated with this and other *Continuum* issues, available to all subscribers, and completing tests on the *Continuum* Audio web platform or mobile app. *Continuum* Audio is also accredited by the Royal College of Physicians and Surgeons of Canada.

This issue is part of a pilot program of *Continuum* issues read aloud. Different from *Continuum* Audio, these are recordings read verbatim from the print articles by Dr Michael Kentris, a neurologist at Bon Secours Mercy Health in Youngstown, Ohio. The audio files are available to all *Continuum* subscribers in the AAN's Online Learning Center at continpub.com/CME. I encourage you to listen and submit the survey with your feedback on this pilot, which has been extended to include this issue and the August 2021 issue.

...I am indebted to Dr Matthew S. Robbins...for enlisting outstanding and prominent experts in the field to guide us in the diagnosis and management of primary or secondary headache disorders.

We are also pleased to introduce the rollout of the new *Continuum* mobile experience at ContinuumJournal.com. Just follow the directions on the inside front cover in the "Beyond the Page" section of this issue to save *Continuum* to your phone's home screen. You will then be able to simply and easily navigate content from any *Continuum* issue on your mobile phone as well as read full-text articles and access tables and figures wherever you are and whenever you need it, including at the point of care.

My sincere thanks to Dr Robbins for his skillful and dedicated guest editorship and to all of the experienced and thoughtful experts who joined him in this issue. This issue so thoroughly covers so many practical aspects of the diagnosis and management of both the common and uncommon disorders that may present as headaches and whose effective treatment can have such an important impact on improving our patients' quality of life.

—STEVEN L. LEWIS, MD, FAAN
EDITOR-IN-CHIEF

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Diagnosing Secondary and Primary Headache Disorders

By David W. Dodick, MD, FAAN, FAHS

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ABSTRACT

PURPOSE OF REVIEW: This article provides a systematic diagnostic approach to the patient with headache.

RECENT FINDINGS: The vast majority of patients presenting with headache in clinical practice have a primary headache disorder. The most common primary headache disorder in clinical practice is overwhelmingly migraine. Unfortunately, a substantial proportion of patients with migraine do not receive an accurate diagnosis. In addition, the clinical features of migraine overlap with secondary causes of headache, making a careful history and deliberative evaluation for warning symptoms or signs of a secondary headache disorder of paramount importance.

SUMMARY: The approach to the patient with headache requires knowledge of the diagnostic criteria for primary headache disorders, recognition of the importance of a systematic evaluation for red flags associated with secondary headache disorders, and awareness of the pearls and pitfalls encountered in the diagnostic evaluation of a patient with headache.

INTRODUCTION

Headache is the most common symptom neurologists are asked to evaluate. Because headache is a ubiquitous symptom in the general population, is a common and often cardinal manifestation of a myriad of diseases, and may be a disease unto itself, a disciplined and systematic diagnostic approach is required. The challenge is made more difficult because primary headache disorders are highly prevalent; therefore, it is common for patients with a secondary cause of headache to also have a long-standing history of a primary headache disorder. Worldwide, almost 3 billion people have a headache disorder; of those, approximately 1.89 billion have tension-type headache and 1.04 billion have migraine. For tension-type headache, the global age-standardized prevalence is 30.8% for women and 21% for men, whereas the prevalence rates for migraine are 19% for women and 10% for men.[1] In addition, serious secondary causes of headache invariably present with clinical features that are consistent with or indistinguishable from the most common primary headache disorders. Therefore, a standardized approach to identifying warning signals in all patients is necessary, whether evaluating a

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patient with headache for the first time or assessing a change in headache pattern in an established patient with a primary headache disorder.

SECONDARY HEADACHE DISORDERS

A plethora of systemic, neurologic, and vascular disorders may present with headache as a prominent or predominant feature. Although about 2% of those with headache may have a secondary cause for headache, up to 18% of patients presenting with headache to tertiary care centers may harbor an underlying secondary cause.[2] The index of suspicion for a secondary cause of headache can be effectively raised by identifying historical and examination red flags. The acronym $SNOOP_4$ ("snoop for" red flags) may be useful as a memory aid to ensure that warning signals for sinister causes of headache that are associated with serious morbidity and mortality are not overlooked (TABLE 1-1).[3] Recently, this acronym was expanded (to $SNOOP_{10}$) to include other non–life-threatening conditions, such as medication-overuse headache and posttraumatic headache.[2]

Warning Signals to Raise Suspicion of Secondary Causes of Headache Using the Mnemonic $SNOOP_4$[a] TABLE 1-1

Letter	Warning signal	Features	Differential diagnosis
S	Systemic symptoms	Fever, night sweats, chills, weight loss, jaw claudication	Metastases, giant cell arteritis, infection (central nervous system, systemic)
	Secondary diseases	Cancer, immunosuppression, chronic infection (human immunodeficiency virus [HIV], tuberculosis)	
N	Neurologic symptoms/signs	Confusion, focal neurologic symptoms/signs, diplopia, transient visual obscurations, pulsatile tinnitus	Mass lesion, structural lesion, stroke, hydrocephalus
O	Onset	Thunderclap	Reversible cerebral vasoconstriction syndrome (RCVS), stroke, subarachnoid hemorrhage, cerebral venous sinus thrombosis, arterial dissection, pituitary apoplexy, idiopathic intracranial hypertension
O	Older (age >50 years)	New onset, persistent/progressive headache	Mass lesion, giant cell arteritis
P1	Positional	Orthostatic, recumbent, or worsens with change in position	Low intracranial pressure (CSF leak), mass lesion, cerebral venous sinus thrombosis, sinus pathology
P2	Prior history	New onset or change to persistent/daily headache	Mass lesion, infection (central nervous system/systemic)
P3	Pregnancy/postpartum	New onset during pregnancy	Cerebral venous sinus thrombosis, preeclampsia, RCVS, pituitary lesion, stroke
P4	Precipitated by Valsalva	Cough, sneeze, bending, straining	Intracranial/posterior fossa mass, Chiari malformation

CSF = cerebrospinal fluid.
[a] Data from Dodick DW, Semin Neurol.[3]

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CASE 1-1

A 38-year-old man presented to the emergency department for evaluation of headache. The headache began suddenly during intercourse and was throbbing in quality. It began in the occipital region, but then quickly generalized to envelop his entire head. He vomited twice and reported continued nausea and sensitivity to light, and the headache was made worse with movement.

His examination was notable for elevated blood pressure (160/98 mm Hg), but all other vital signs and neurologic examination were normal. Unenhanced head CT was normal, and a lumbar puncture was acellular with normal protein and glucose. The patient was diagnosed with migraine by the emergency department physician, reassured, and discharged with a prescription for 10 tablets of oxycodone.

The patient returned to the emergency department 2 days later with a recurrent headache that occurred while straining on the toilet. It was explosive and generalized, and again he vomited several times. Examination again revealed elevated blood pressure (170/100 mm Hg), and repeat head CT was again negative. MRI brain with gadolinium was ordered and revealed increased signal intensity in the posterior white matter of the occipital lobes on fluid-attenuated inversion recovery (FLAIR) sequences and gadolinium leakage through a breeched blood-brain barrier on contrast-enhanced FLAIR sequences. Magnetic resonance angiography (MRA) was ordered and showed multiple segmental areas of vasoconstriction in the basilar and middle cerebral arteries.

COMMENT

This patient has reversible cerebral vasoconstriction syndrome (RCVS). He was misdiagnosed with migraine because the headache and associated symptoms met *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for migraine.[4] However, he presented with a thunderclap headache and had no prior history of migraine or recurrent headache, and at least five attacks are required for the diagnosis of migraine. In addition, he had a negative CT and lumbar puncture, effectively ruling out subarachnoid hemorrhage. However, the most common cause of thunderclap headache is RCVS, which requires parenchymal brain imaging and noninvasive vascular imaging to make the diagnosis. Recurrent thunderclap headache is the hallmark of RCVS. The most common triggers are activities that induce a Valsalva maneuver, such as sexual intercourse and straining during defecation. Hypertension is present in 50% of patients with RCVS. The gadolinium-enhanced MRI revealed changes consistent with posterior reversible encephalopathy syndrome (PRES), which is present in at least 15% of patients, and gadolinium extravasation indicating endothelial dysfunction, which is present in about 70% of patients with definite RCVS. MRA demonstrated multifocal vasoconstriction. RCVS can present with intracerebral hemorrhage and ischemic stroke, the latter usually occurring in the second or third week after onset when vasoconstriction becomes most severe. This case illustrates the importance of imaging the brain and the cerebral vasculature with MRI in patients with thunderclap headache, especially after ruling out subarachnoid hemorrhage with a negative head CT and lumbar puncture.

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In addition to the red flag features within the $SNOOP_4$ acronym, a patient presenting for a single episode of headache as opposed to recurrent or persistent headache should always raise suspicion of a secondary cause. A particular headache that raised the patient's or a family member's concern may alert the clinician to a thunderclap headache or headache that was substantially different from previous headaches. Asking about whether a headache was sudden in onset is often not sufficient to determine whether a headache was thunderclap in onset. Being more specific by asking whether the headache went from zero to 10 in intensity within seconds or 1 minute or using a hand gesture, such as a clap, is prudent to make it clear that sudden means absent to severe within 1 minute and not over the course of many minutes to hours. It is also helpful to ask what the patient was doing when the headache began. Sometimes patients will then respond with information that they otherwise might not volunteer spontaneously and that may signify a truly thunderclap onset (eg, during sexual intercourse, during defecation) (**CASE 1-1**).

One pitfall that may be encountered in practice is to overlook a secondary cause for headache because the headache phenotype is consistent with migraine, tension-type headache, or a trigeminal autonomic cephalalgia, such as cluster headache. Although the number of primary headache disorders is substantial, the clinical features are usually restricted to one of these three phenotypes. In other words, the clinical features that are often associated with migraine (eg, unilateral headache, throbbing headache, photophobia, nausea), cluster headache (eg, unilateral lacrimation, nasal congestion, rhinorrhea), or tension-type headache (featureless dull pressure without accompanying symptoms) may be seen in a wide variety of neurologic and systemic diseases. The clinician should therefore be alert to the overlapping features of primary and secondary headaches and be vigilant about investigating for red flag features and assessing the temporal profile (sudden onset of a single headache or loss of pain-free periods between recurrent headaches) regardless of the clinical "phenotype" of the headache. This principle is the reason the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) diagnostic criteria for each headache disorder include an absolute criterion that must be met: "Not better accounted for by another *ICHD-3* diagnosis."[4]

NEUROIMAGING FOR HEADACHE

CT of the head has a very limited role in the evaluation of secondary headache disorders. Head CT without contrast is useful to exclude intracranial blood in patients suspected of having a subarachnoid hemorrhage, epidural or subdural hematoma, or intraparenchymal hemorrhage. It is also useful in identifying skull fractures in patients who have experienced trauma. An estimated 80 million CT scans are performed annually in the United States, and an estimated 50% of these imaging studies are believed to be medically unnecessary. Moreover, of particular concern is the overuse of CT in children, in whom the vulnerability to radiation exposure is higher and cumulative.[5] Indeed, epidemiologic studies have demonstrated an increased cancer risk associated with CT scans performed during childhood, and the National Cancer Institute has recently demonstrated that compared with the general population, the incidence of brain tumors was higher in a cohort of children who had undergone CT.

When evaluating a head CT for possible subarachnoid hemorrhage, it is important to identify the locations where subarachnoid blood may be less conspicuous and thus overlooked. The acronym PITS (**p**arenchymal, **i**ntraventricular,

KEY POINTS

- The $SNOOP_4$ acronym is a useful guide to assist clinicians in systematically evaluating for warning symptoms and signs of a secondary cause of headache.
- Since secondary causes of headache often have features that resemble migraine, tension-type headache, or a trigeminal autonomic cephalalgia, caution must be exercised and warning signs and symptoms of secondary headache must be evaluated.
- A headache history is the most important aspect of the evaluation of a patient presenting with headache, and eliciting worrisome features with directed questioning is necessary. The history must be taken without assuming that key features will be volunteered by the patient.
- Brain MRI is the imaging procedure of choice when evaluating for intracranial or neurovascular causes of headache. Other than the detection of skull fracture or acute intracranial blood, the use of CT in the evaluation of secondary headaches should be restricted, especially in children.

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truncal, sulci) may be useful in making certain these locations are systematically evaluated:

- **Parenchymal blood, especially when the sylvian fissure is compressed, may obscure the subarachnoid blood and a middle cerebral artery aneurysm that ruptured**
- **Intraventricular blood, especially a small amount of blood layering the dependent and posterior portion of the lateral ventricle, can also easily be overlooked when the focus is on the parenchyma**
- **Truncal (pons, sometimes referred to as the trunk) subarachnoid hemorrhage may be present in the prepontine, perimesencephalic, or interpeduncular cisterns**
- **Subarachnoid blood may be limited to the sulci in some patients, particularly after trauma or in those with reversible cerebral vasoconstriction syndrome (RCVS)**

For the majority of secondary intracranial causes of headache, MRI is the imaging study of choice if not contraindicated. For parenchymal, dural, leptomeningeal, posterior fossa, and intraventricular pathology, brain MRI increases the yield and resolution for identifying secondary causes. The acronym PIN ("pin" the diagnosis) can be helpful when considering the diagnoses that are best visualized by brain MRI:

- **Pressure abnormalities: intracranial hypertension (idiopathic intracranial hypertension and secondary), intracranial hypotension (CSF leaks)**
- **Infection: meningitis, encephalitis, cerebritis, sphenoid sinusitis**
- **Neoplastic disease: parenchymal and extraaxial neoplasms (especially posterior fossa), meningeal carcinomatosis, pituitary tumor, brain metastases**

When the index of suspicion for cerebrovascular pathology as a cause of headache is high, especially in context of a thunderclap headache, MRI or CT of the extracranial and intracranial arteries and the intracranial venous system is essential.[6] The vascular disorders that should be considered in the evaluation of thunderclap headache are outlined in TABLE 1-2.

MRI, when available, may be superior to CT imaging of the cerebrovasculature to avoid radiation and to enable comparison with follow-up scans, for which MRI

TABLE 1-2 Disorders Associated With Thunderclap Headache

Vascular (vascular imaging required)

- Subarachnoid hemorrhage
- Arterial (vertebral, carotid, intracranial artery) dissection
- Cerebral venous sinus/cortical vein thrombosis
- Reversible cerebral vasoconstriction syndrome

Nonvascular

- Spontaneous intracranial hypotension
- Pituitary apoplexy
- Colloid cyst of the third ventricle
- Acute hypertensive crisis

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may be more suitable. Imaging of the brain parenchyma with MRI is also necessary to rule out some early changes that may be consistent with certain secondary disorders, such as posterior reversible encephalopathy syndrome (PRES), or subclinical infarction in patients with arterial dissection. Even when appropriate diagnostic imaging has been obtained, distinguishing between certain secondary headaches can be challenging. For example, the diffuse multifocal vasoconstriction associated with RCVS may be difficult to distinguish from other arteriopathies, such as central nervous system vasculitis. Recently, a scoring algorithm was developed (the RCVS2 score), which demonstrated that a score or 5 or more had 99% specificity and 90% sensitivity for diagnosing RCVS, whereas a score of 2 or less had 100% specificity and 85% sensitivity for excluding RCVS.[7] Recurrent thunderclap headache over a period of days to weeks is the *sine que non* of RCVS, makes up half the total RCVS2 score, and will reliably distinguish RCVS from central nervous system vasculitis, especially when associated with a trigger (eg, sexual intercourse, straining, bathing) and normal parenchymal brain imaging on MRI.

When ordering an MRI for a presumed secondary cause for headache, it is important to know the correct sequences to request, when gadolinium is helpful, and the characteristic/diagnostic findings of the disease/disorder for which imaging is being done. Disorders of intracranial pressure are important causes of secondary headache that may be assessed with imaging. When examining a brain MRI for idiopathic intracranial hypertension and spontaneous intracranial hypotension secondary to a CSF leak, awareness of and a keen eye for the abnormalities that may be seen in both of these disorders is important (TABLE 1-3[8] and TABLE 1-4[9]).

Although several of the features of spontaneous intracranial hypotension listed in TABLE 1-4, including subdural fluid collections and pachymeningeal enhancement, are qualitatively distinctive and often easily recognizable on brain MRI, other features require a more objective and quantitative assessment. For example, with regard to venous sinus congestion, the venous distention sign is best seen on T1-weighted sagittal imaging of the transverse sinus.[10] Although not easily quantified, when the transverse sinus is visualized in its midportion on sagittal images of the brain, the contour of the dominant (larger) transverse sinus normally has a concave or straight inferior border, but in patients with intracranial hypotension, the inferior border takes on a distended appearance with a convex bulging of its inferior border. The sensitivity and specificity of the venous

Imaging Features of Idiopathic Intracranial Hypertension[a] TABLE 1-3

Imaging feature	Sensitivity/specificity
Reduced pituitary gland height (empty sella syndrome)	80%/64%
Increased optic nerve sheath diameter	51%/83%
Flattening of posterior globe	97%/53%
Transverse venous sinus stenosis	78%/unknown
Any three out of four features	64%/100%

[a] Data from Mallery RM, et al, J Neuroophthalmol.[8]

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distention sign for the diagnosis of intracranial hypotension is approximately 94%. Brain sagging occurs in 18% to 61% of individuals with intracranial hypotension, and both qualitative signs and quantitative measures can be helpful and important in radiologically confirming its presence. Ventricular effacement, narrowing of the chiasmatic cistern and the prepontine cistern, and cerebellar tonsillar descent are qualitative MRI features of a sagging brain.[11] Recently, a nine-point predictive scoring system based on the six most discriminating imaging features of spontaneous intracranial hypotension was developed and validated (TABLE 1-5).[12] The score is based on three qualitative and three quantitative signs and identifies a patient with a high (score ≥5), intermediate (score 3 to 4), or low (score ≤2) probability of having a CSF leak. This may guide the clinician's diagnostic and treatment decision making regarding myelographic procedures and targeted percutaneous or surgical dural sealing treatments.

Gadolinium may be helpful in characterizing parenchymal brain lesions and for diseases that are associated with pachymeningeal pathology (eg, CSF leak/intracranial hypotension, granulomatous pathology such as sarcoidosis and granulomatosis with polyangiitis) or leptomeningeal pathology (eg, leptomeningeal carcinomatosis). Gadolinium is also useful for characterizing intracranial tumors, infections, or other mass lesions and when evaluating for breakdown of the blood-brain barrier that may be seen in posttraumatic headache (postconcussion)[13] or in patients with RCVS.[14] The recommended MRI sequences when evaluating for thunderclap headache are outlined in TABLE 1-6.[15]

PRIMARY HEADACHE DISORDERS

Like secondary headache disorders, primary headache disorders are defined by a set of operational diagnostic criteria. The *ICHD-3* criteria define three major categories of disorders: primary headaches, secondary headaches, and cranial neuralgias and facial pain.[4] The three major and most common primary headache disorders are migraine, tension-type headache, and trigeminal autonomic cephalalgias. Although tension-type headache is the most common primary headache disorder in the general population, migraine is overwhelmingly the most common primary headache disorder presenting to clinicians, especially neurologists. In the Landmark Study involving 1203 male and female patients

TABLE 1-4 **Imaging Features of Intracranial Hypotension Using the Mnemonic SEEPS[a,b]**

Imaging feature	Prevalence range
Subdural fluid collection	36-50%
Enhancement of pachymeninges	56-83%
Engorgement of venous sinuses	48-93%
Pituitary enlargement/hyperemia	5-63%
Sagging of brain	18-61%

[a] Data from Schievink WI, JAMA.[9]
[b] Invariably secondary to spinal CSF leak.

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Scoring System Using Six Imaging Signs Most Discriminative for Spontaneous Intracranial Hypotension[a]

TABLE 1-5

Imaging characteristic	Point score
Engorgement of venous sinus	2
Pachymeningeal enhancement	2
Subdural fluid collection	1
Suprasellar cistern (≤4 mm)	2
Prepontine cistern (≤5 mm)	1
Mamillopontine distance (≤6.5 mm)	1

[a] Data from Dobrocky T, et al, JAMA Neurol.[12]

Recommended MRI Sequences When Evaluating for Thunderclap Headache[a]

TABLE 1-6

MRI sequences	Imaging features
T1, T2	Exclude structural lesions or blood products (eg, pituitary apoplexy)
Fluid-attenuated inversion recovery (FLAIR)/ contrast-enhanced FLAIR/dynamic contrast-enhanced MRI	White matter lesions and distal hyperintense vessels (RCVS), subtle (sulcal) subarachnoid hemorrhage (SAH), posterior reversible encephalopathy syndrome (PRES) (with/without RCVS)
Gradient recalled echo (GRE) (T2*) or susceptibility-weighted imaging (SWI)	Hemosiderin deposition from subtle SAH or parenchymal microbleeds
Diffusion-weighted imaging/apparent diffusion coefficient	Vasogenic and cytotoxic edema (eg, PRES versus ischemic stroke)
Magnetic resonance angiography (MRA)	Exclude vasoconstriction, aneurysm, dissection
Magnetic resonance venography (MRV)	Exclude cerebral venous sinus/cortical vein thrombosis
T1 with contrast (axial, sagittal, coronal)	CSF leak/spontaneous intracranial hypotension
Cervical T1 fat saturation with contrast	Exclude cervical carotid artery dissection

CSF = cerebrospinal fluid; MRI = magnetic resonance imaging.
[a] Data from Chen SP et. al, J Headache Pain.[15]

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between 18 and 65 years of age who consulted their primary care physician with headache as a primary or secondary concern, 94% of patients with either a physician diagnosis of migraine or nonmigraine primary headache actually had either migraine (76%) or probable migraine (18%).[16] Only 3% had episodic tension-type headache. The study concluded that the vast majority of patients consulting their physicians with episodic headache as a primary or secondary concern have migraine, regardless of whether or not the patients consider their headaches to be migraine.

Therefore, it is important for the clinician to have a working knowledge of the *ICHD-3* classification criteria for migraine (TABLE 1-7). A few caveats should be considered when applying the criteria that can help avoid pitfalls. First, at least five attacks meeting the criteria are required for the diagnosis. This avoids misdiagnosing a sinister secondary headache (eg, subarachnoid hemorrhage) that could otherwise meet the headache and associated symptom criteria for migraine. Second, no single feature is either necessary or sufficient to make the diagnosis; the diagnosis requires only two of the pain criteria and one associated symptom criterion. Third, in patients who meet either the pain criteria or the associated symptom criteria, the diagnosis is probable migraine. In other words, a bilateral and generalized squeezing headache of moderate intensity that causes avoidance of routine physical activity and is not associated with photophobia or nausea meets criteria for probable migraine. This type

TABLE 1-7 ***ICHD-3* Diagnostic Criteria for Migraine Without Aura[a]**

Migraine without aura

A At least five attacks[b] fulfilling criteria B-D

B Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[c,d]

C Headache has at least two of the following four characteristics:

- **1** Unilateral location
- **2** Pulsating quality
- **3** Moderate or severe pain intensity
- **4** Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D During headache at least one of the following:

- **1** Nausea and/or vomiting
- **2** Photophobia and phonophobia

E Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] One or a few migraine attacks may be difficult to distinguish from symptomatic migrainelike attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for migraine without aura but have had fewer than five attacks should be coded probable migraine without aura.

[c] When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.

[d] In children and adolescents (aged under 18 years), attacks may last 2-72 hours (the evidence for untreated durations of less than two hours in children has not been substantiated).

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of presentation, especially in patients with a history of anxiety or depression (a common comorbidity in patients with migraine) and especially if neck pain accompanies the headache (present in at least 70% of patients with migraine) often receives a misdiagnosis of tension-type headache.

Migraine is also associated with a variety of symptoms that occur commonly but are not part of the diagnostic criteria. Premonitory symptoms such as fatigue, impaired concentration, neck stiffness, yawning, photophobia, nausea, increased urination, irritability, and changes in mood occur hours or days before the onset of pain and are seen in about 70% of patients.[17] The presence of neck pain (75%), sinus pain/pressure (40%), and cranial parasympathetic

TABLE 1-8 ***ICHD-3* Diagnostic Criteria for Migraine With Aura and Migraine With Typical Aura[a]**

Migraine with aura

A At least two attacks fulfilling criteria B and C

B One or more of the following fully reversible aura symptoms:

- **1** Visual
- **2** Sensory
- **3** Speech and/or language
- **4** Motor
- **5** Brainstem
- **6** Retinal

C At least three of the following six characteristics:

- **1** At least one aura symptom spreads gradually over ≥5 minutes
- **2** Two or more aura symptoms occur in succession
- **3** Each individual aura symptom lasts 5-60 minutes[b]
- **4** At least one aura symptom is unilateral[c]
- **5** At least one aura symptom is positive[d]
- **6** The aura is accompanied, or followed within 60 minutes, by headache

D Not better accounted for by another *ICHD-3* diagnosis

Migraine with typical aura

A Attacks fulfilling criteria for migraine with aura and criterion B below

B Aura with both of the following:

- **1** Fully reversible visual, sensory, and/or speech/language symptoms
- **2** No motor, brainstem, or retinal symptoms

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 minutes. Motor symptoms may last up to 72 hours.

[c] Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

[d] Scintillations and pins and needles are positive symptoms of aura.

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symptoms such as lacrimation and nasal congestion (50%) is, in part, responsible for the frequent misdiagnosis of migraine as tension-type headache or sinus headache.

The most frequent subtypes of migraine seen in clinical practice are migraine without and with aura (TABLE 1-8) and chronic migraine (TABLE 1-9). Chronic migraine is often associated with the overuse of acute medications (TABLE 1-10). Both chronic migraine and medication-overuse headache may be overlooked in practice because patients with migraine may disregard and underreport days with headaches that are not severe, do not cause functional impairment, or that they do not believe to be consistent with migraine. Once a diagnosis of migraine is made, the following questions will ensure that the actual number of days with headache each month is accurately captured and that the diagnosis of chronic migraine or

TABLE 1-9 ***ICHD-3* Diagnostic Criteria for Chronic Migraine**[a]

Chronic migraine

A Headache (migrainelike or tension-type–like[b]) on ≥15 days/month for >3 months, and fulfilling criteria B and C

B Occurring in a patient who has had at least five attacks fulfilling criteria B-D for migraine without aura and/or criteria B and C for migraine with aura

C On ≥8 days/month for >3 months, fulfilling any of the following[c]:

- **1** Criteria C and D for migraine without aura
- **2** Criteria B and C for migraine with aura
- **3** Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D Not better accounted for by another *ICHD-3* diagnosis[d,e,f]

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] The reason for singling out chronic migraine from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migrainelike and tension-type–like headaches (but not secondary headaches).

[c] Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least 1 month.

[d] Because tension-type–like headache is within the diagnostic criteria for chronic migraine, this diagnosis excludes the diagnosis of tension-type headache or its types.

[e] New daily persistent headache may have features suggestive of chronic migraine. The latter disorder evolves over time from migraine without aura and/or migraine with aura; therefore, when these criteria A-C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as new daily persistent headache. When the manner of onset is not remembered or is otherwise uncertain, code as chronic migraine.

[f] The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under medication-overuse headache. Around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as chronic migraine. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of medication-overuse headache may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for chronic migraine and for medication-overuse headache should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic, and should be rediagnosed accordingly; in the latter case, the diagnosis of medication-overuse headache may be rescinded.

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medication-overuse headache (also known as rebound headache) is not overlooked (CASE 1-2):

- **How many days per month do you have a headache of any type or how many days per month are you completely free of headache (crystal clear) from morning until night?**
- **How many days per month do you take something, including prescription and over-the-counter medications, to alleviate a headache?**

CONCLUSION

Although headache is a ubiquitous symptom and a feature of many diseases and primary headache disorders, an accurate diagnosis of the underlying cause of headache can be accomplished by clinicians using a simplified and standardized approach. First, a history of features that raise the suspicion for a secondary cause must be actively elicited by the clinician when taking a history. Using the $SNOOP_4$ mnemonic can assist in identifying these worrisome features and guiding appropriate diagnostic investigations. Imaging is invariably an essential investigation in excluding most secondary causes, but it is important to select the most appropriate imaging study and be aware of the pitfalls and pearls in the interpretation of these imaging studies, especially for the most common secondary causes of headache. MRI of the brain parenchyma, dura, and cerebral blood vessels is the most appropriate imaging modality in the majority of cases. Special attention must be paid to patients with thunderclap headache as the cause is often vascular, treatment varies according to the cause, and the morbidity can be serious if these disorders are missed. Cardinal imaging features and novel scoring systems have

ICHD-3 Diagnostic Criteria for Medication-Overuse Headache[a,b]

TABLE 1-10

Medication-overuse headache

A Headache occurring on ≥15 days/month in a patient with a preexisting headache disorder

B Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[c,d,e]

C Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] Overuse is defined by the use of all acute medication on >10 days per month except for simple analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs), for which overuse is defined as use on >15 days per month.

[c] Patients should be coded for one or more subtypes of medication-overuse headache according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for triptan-overuse headache and the criteria for one of the subforms of nonopioid analgesic–overuse headache should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded combination-analgesic-overuse headache and not according to each constituent of the combination-analgesic medication.

[d] Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded medication-overuse headache attributed to multiple drug classes not individually overused.

[e] Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes until better information is available. In almost all cases, this necessitates diary follow-up.

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recently emerged for some of the most common, serious, and disabling secondary headache disorders. Awareness of these features is important as they can guide clinical decision making regarding treatment or subsequent investigations. If a secondary headache disorder is excluded, a primary headache disorder diagnosis should be made. "Headache not otherwise specified" is not an acceptable diagnosis. Since the vast majority of patients presenting to clinical attention with a primary headache disorder will have a subtype of migraine, a working familiarity with the diagnostic criteria for migraine is essential. However, it must always be kept in mind that if worrisome features are present, regardless of the phenotype of the headache or prior history of a primary headache disorder, further diagnostic investigations are inevitably appropriate and essential.

CASE 1-2

A 32-year-old woman presented for evaluation of headaches. The headaches had begun after the birth of her first child 2 years ago. They were preceded by yawning, fatigue, and irritability about 2 hours before the onset of headache. The headaches occurred about twice per week and reached a peak intensity of at least moderate pain within 30 minutes, typically beginning in the frontal and temporal head regions but spreading to involve the occiput and cervical and trapezius muscles. The headaches were throbbing in quality and were associated with tearing of both eyes, nausea, and a sensation of dizziness (disequilibrium). She had difficulty concentrating and processing information during the headaches. The headaches lasted about 12 hours, but the patient felt lethargic, nauseated, and in a "cognitive fog" for about 24 hours. When questioned further, she said she also had milder headaches that were throbbing and limited her activity to some extent, but they lasted only about 4 hours and were relieved with simple analgesics. These occurred about twice per week. The patient was taking an over-the-counter combination analgesic to treat or preempt the headaches at least 5 days per week. This pattern had been present for the past 18 months. The patient's general physical and neurologic examination was normal.

COMMENT

This patient has migraine without aura, chronic migraine, and medication-overuse headache. The occurrence in the postpartum period is not uncommon. Her headaches meet *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for chronic migraine and medication-overuse headache as migraine headaches occur at least 8 days per month, and she has at least 15 days of headache each month and uses an analgesic about 20 days per month. She has a premonitory phase and a postdromal phase that impair her ability to function for longer than the duration of the headache itself. Only when questioned about days of the month without any headache and days of the month when she took something to relieve the pain did it become evident that she has chronic migraine and medication-overuse headache.

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KEY POINTS

- **PITS (parenchymal, intraventricular, truncal, sulci) is a useful acronym that highlights the anatomic areas where subarachnoid blood can be overlooked.**
- **In the setting of a thunderclap headache, MRI of the brain and intracranial and extracranial vasculature should always be obtained after subarachnoid hemorrhage is excluded.**
- **Knowledge of the qualitative and quantitative findings on MRI in patients suspected of having intracranial hypertension or hypotension is important and can help support a diagnosis.**
- **The overwhelming majority (94%) of patients presenting with recurrent nonsecondary headaches as a chief complaint in clinical practice have migraine.**
- **If clinicians remember any part of the *International Classification of Headache Disorders, Third Edition*, it should be the diagnostic criteria for migraine, chronic migraine, and medication-overuse headache as these are the most common primary headaches seen in clinical practice.**

DISCLOSURE

Continued from page 572

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Pathophysiology of Migraine

By Ana Recober, MD

ABSTRACT

PURPOSE OF REVIEW: This article summarizes the current understanding of the pathophysiology of migraine, including some controversial aspects of the underlying mechanisms of the disorder.

RECENT FINDINGS: Recent functional neuroimaging studies focusing on the nonpainful symptoms of migraine have identified key areas of the central nervous system implicated in the early phases of a migraine attack. Clinical studies of spontaneous and provoked migraine attacks, together with preclinical studies using translational animal models, have led to a better understanding of the disease and the development of disease-specific and targeted therapies.

SUMMARY: Our knowledge of the pathophysiology of migraine has advanced significantly in the past decades. Current evidence supports our understanding of migraine as a complex cyclical brain disorder that likely results from dysfunctional sensory processing and dysregulation of homeostatic mechanisms. This article reviews the underlying mechanisms of the clinical manifestations of each phase of the migraine cycle.

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INTRODUCTION

Migraine is a highly prevalent, complex neurologic disorder characterized by recurrent episodes of headache with other associated symptoms. Neurologic dysfunction is also present in the period between attacks of migraine headache, known as the interictal phase. It is now widely accepted that migraine is an inherited disorder of sensory processing.[1,2] The early vascular theory proposed vasoconstriction as the mechanism of the migraine aura and vasodilation as the mechanism of migraine pain, which is not supported by available evidence. Over the past decades, significant progress has been made in our understanding of the pathophysiology of migraine. However, many aspects of the underlying genetic, anatomic, physiologic, molecular, and pharmacologic basis of this disorder still remain unknown.

A practical way to frame the discussion of the pathophysiology of migraine is by describing the neurobiological basis of the cyclical clinical manifestations of the disorder (FIGURE 2-1[3]). In general, five phases are recognized: prodromal or premonitory, aura, headache, postdrome, and interictal. These phases may overlap or may not occur consistently from attack to attack within an individual or from person to person.[4,5] Despite this variability, some have proposed, based

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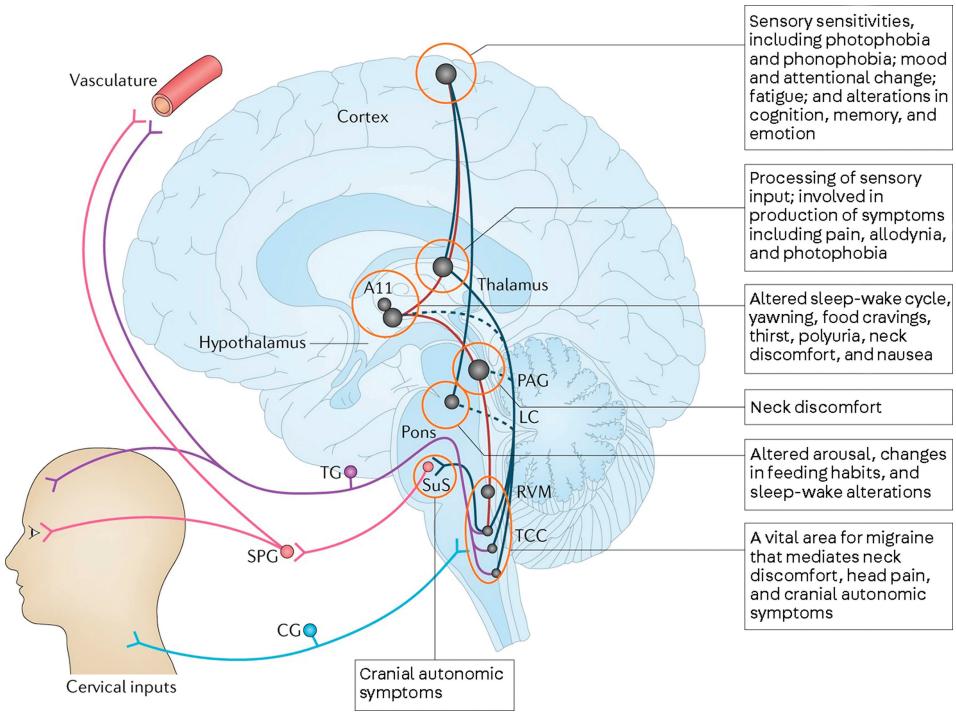

FIGURE 2-1

Pathophysiology of migraine in relation to its clinical manifestations. Trigeminal afferents arise from the trigeminal ganglion (TG) and innervate cranial structures, vasculature, and the dura. These sensory afferents converge with cervical afferents from the upper cervical dorsal root ganglion (CG) in the trigeminocervical complex (TCC) in the brainstem and upper cervical spine. Second-order neurons from the TCC project to the thalamus, from which thalamocortical neurons relay sensory information to multiple cortical areas. Several structures, such as the rostroventral medulla (RVM), locus coeruleus (LC), periaqueductal gray (PAG), and hypothalamic nuclei, have been implicated in trigeminovascular sensory modulation. The parasympathetic pathway mediates cranial autonomic symptoms through the superior salivatory nucleus (SuS) and the sphenopalatine ganglion (SPG). The boxes summarize the clinical manifestations of migraine attributed to each relevant anatomic area.

A11 = diencephalic A11 area.

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KEY POINTS

- **It is widely accepted that migraine is an inherited disorder of sensory processing, but many aspects of the underlying basis of this disorder still remain unknown.**
- **Migraine attacks are often preceded by alterations in homeostasis, supporting the role of the hypothalamus in the prodromal phase.**
- **Neuroimaging studies have found hypothalamic activation and altered connectivity with other brain and brainstem regions that could explain the polyuria, yawning, food cravings, and changes in appetite reported in the prodromal phase.**

on clinical, electrophysiologic, and neuroimaging data, that the preictal or prodromal phase should be defined as the 48 hours preceding the headache and the postictal or postdromal phase should be defined as the 24 hours following resolution of the headache.[6] The preferred term for the preictal phase (previously known as the premonitory phase) is the *prodromal phase*.[7]

PRODROMAL (PREMONITORY) PHASE

Around 80% of people with migraine report premonitory symptoms hours to days before the onset of headache or aura.[8] Symptoms often reported in this phase include yawning, polyuria, food cravings, mood changes, irritability, light sensitivity, neck pain, and cognitive dysfunction.[9-16]

Migraine attacks are often preceded by alterations in homeostasis, supporting the role of the hypothalamus in this phase.[2,10] Neuroimaging studies using positron emission tomography (PET) scans and functional MRI (fMRI) have found hypothalamic activation and altered connectivity with other brain and brainstem regions that could explain the polyuria, yawning, food cravings, and

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changes in appetite reported by people with migraine during this phase.[17,18] In an fMRI study of spontaneous migraine attacks, the authors found that the hypothalamus is significantly more active and shows the greatest functional coupling with the spinal trigeminal nucleus during the 24 hours before the onset of headache.[18] In addition to activation of the posterolateral hypothalamus, a PET study showed activation of the midbrain tegmental area, substantia nigra, periaqueductal gray, dorsal pons, and several cortical areas, including the occipital, temporal, and prefrontal cortex, during the early prodromal phase of nitroglycerin-induced migraine attacks.[17]

The locus coeruleus has also been implicated in the prodromal phase of migraine, in particular because of the link between sleep disturbances and migraine.[19] The locus coeruleus receives projections from the hypothalamus[20] and plays a role in pain modulation[21] and specifically in trigeminal nociceptive processing.[22]

Additional evidence of altered sensory processing during the prodromal phase from psychophysical studies measuring pain perception in the days and hours preceding a migraine attack suggests reduced habituation (ie, repeated stimulation does not result in expected decrement in response; the phenomenon underlying hypersensitivity to light, sounds, smells, and somatic stimuli) in patients with migraine.[23-25]

Nausea and photophobia, other symptoms typically associated with migraine headache, are present in a significant proportion of patients during the prodromal phase. These symptoms have been studied using PET imaging before the onset of headache in nitroglycerin-induced migraine attacks.[26,27] These studies found photic hypersensitivity associated with activation of the visual cortex[26] and activation in the rostral dorsal medulla and periaqueductal gray associated with nausea[27] during the prodromal phase.

Neck stiffness or discomfort is often present during the prodromal phase. This symptom is attributed to early activation of the trigeminocervical complex, the region of the brainstem and upper cervical spinal cord where pain signals from the trigeminal and cervical nerves converge.[2,28,29]

Taken together, the nature of the symptoms present during this phase and the results of the research discussed support the current understanding of migraine as a disorder of the central nervous system and not as a vascular disorder. Although the exact initiating event of a migraine attack remains unknown, the overwhelming evidence points toward a central origin.

AURA PHASE

About one-third of individuals with migraine experience an aura associated with at least some of their attacks.[30] Aura may consist of visual, sensory, motor, language, or brainstem disturbances.[7] Traditionally, aura has been described as preceding the headache phase; however, this phase can overlap with headache, and it is not rare for the aura to occur in the absence of headache. In a prospective study using electronic diaries in real time at the onset of the aura, almost 75% of individuals had headache, almost 90% had photophobia, and 50% had nausea concurrently with their aura.[4] More than half of the patients in this study had headache fulfilling the criteria for migraine within the first 15 minutes of the beginning of their aura phase.[4]

The role of aura and its underlying mechanism in the rest of the migraine attack remains controversial. Indirect evidence supports the widely accepted hypothesis that the pathophysiologic mechanism of the aura is cortical spreading depolarization, initially described by Leao[31] in the 1940s as cortical spreading

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depression. Cortical spreading depolarization is a bioelectrical phenomenon consisting of a wave of intense cortical neuronal activity associated with hyperemia followed by a more prolonged period of neuronal activity suppression associated with cortical oligemia. Cortical spreading depolarization has been demonstrated to occur in the human brain as a result of acute injury in the setting of stroke or traumatic brain injury[32,33]; however, no direct evidence of the simultaneous occurrence of cortical spreading depolarization and aura has been seen in humans.[34] Furthermore, significant controversy surrounds the concept of cortical spreading depolarization triggering the rest of the attack or directly causing headache.[2,34-37]

Several novel concepts of interest have emerged in the past decade regarding the underlying mechanisms of migraine aura based on a unique clinical study.[38] The authors analyzed the drawings of an individual who methodically recorded his visual percept in real time over 18 years, providing information from more than 1000 visual auras documented with great temporal and spatial resolution. The findings of this original study suggest that the aura can start in multiple sites of the visual cortex in the same individual, although certain areas show higher propensity to be the initiating focus. This study suggests that the mechanisms underlying visual aura appear to propagate in a linear fashion along gyri or sulci, rather than spreading as a concentric wave as usually depicted based on studies of cortical spreading depolarization in animal models. This study also supports the concept that the aura may propagate silently in the cortex, without clinical manifestations.[38] This conclusion can be drawn by the methodical records of the visual percept.

Several epidemiologic studies have found an association between migraine with aura and an increased risk of several comorbidities, including ischemic stroke, patent foramen ovale, Parkinson disease, bipolar disease, and panic disorder.[39] Several potential hypotheses have been proposed, such as shared genetic factors, neurochemical function, and cortical excitability. Paradoxical emboli or deoxygenated blood via right-to-left shunt associated with patent foramen ovale has been speculated to trigger migraine aura. Additional research is needed to determine the exact mechanisms underlying these associations.

HEADACHE PHASE

The clinical hallmark of a migraine attack is head pain, typically described as moderate or severe, unilateral, and throbbing or pulsatile, that is aggravated by regular physical activity and associated with other symptoms, such as nausea and sensitivity to light and sound, among other symptoms.[7]

Migraine pain is mediated by the trigeminovascular pathway.[40,41] Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain and implicate cortical spreading depolarization and peripheral sensitization of perivascular sensory nerve terminals.[42] Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.[2] Although the exact events that lead to activation of this pathway remain unclear, many aspects of the trigeminovascular pain processing pathway are well established. Trigeminal afferents consist of thinly myelinated and unmyelinated Aδ and C fibers that arise from the trigeminal ganglion and innervate most cranial structures. These trigeminal afferents, together with cervical afferents from the upper cervical dorsal root ganglion,

KEY POINTS

- During the prodromal phase, photophobia is associated with activation of the visual cortex, and nausea is associated with activation of the rostral dorsal medulla and periaqueductal gray. Neck stiffness or discomfort is attributed to early activation of the trigeminocervical complex, the region of the brainstem and upper cervical spinal cord where pain signals from the trigeminal and cervical nerves converge.
- Taken together, the nature of the symptoms and neuroimaging findings support the current understanding of migraine as a disorder of the central nervous system and not as a vascular disorder.
- Traditionally, aura has been described as preceding the headache phase; however, the aura can overlap with headache, and it is not rare for the aura to occur in the absence of headache.
- Cortical spreading depolarization is widely accepted to be the pathophysiologic mechanism of aura.
- Cortical spreading depolarization is a bioelectrical phenomenon consisting of a wave of intense cortical neuronal activity associated with hyperemia, followed by a more prolonged period of neuronal activity suppression associated with cortical oligemia.

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synapse on second-order neurons in the dorsal horn of the trigeminal nucleus caudalis and its cervical extension (trigeminocervical complex).[2] From the trigeminocervical complex, second-order neurons project to the thalamus and other key regions of the central nervous system that modulate sensory processing before thalamocortical neurons relay sensory information to multiple cortical areas. Several medullary, brainstem, and hypothalamic nuclei have been implicated in trigeminovascular sensory modulation. Recently discovered direct projections from the trigeminal ganglia to the parabrachial nucleus in mice have been proposed as the underlying mechanism to explain heightened craniofacial affective pain in comparison to extracephalic pain.[43]

Whereas the anatomic pathway is relatively well known, the actual event that leads to activation of this pathway and generation of migraine headache remains unknown and a point of controversy.[44,45] Some experts believe that cortical spreading depolarization is the direct cause of head pain. This is based on animal research showing that cortical spreading depolarization results in activation of meningeal nociceptors via local release of adenosine triphosphate, glutamate, potassium, calcitonin gene-related peptide (CGRP), and nitric oxide.[45] Others, based on neuroimaging studies and the evidence presented in prior sections of this article (ie, premonitory symptoms precede the aura or headache phases by hours or days and headache may occur in the absence of a clinical aura or may start with the onset of the aura), propose that dysfunction of the hypothalamus-brainstem connectivity is responsible for the initiation of a migraine attack.[18,46] These two hypotheses are not mutually exclusive, but they both await confirmation.

The throbbing character of migraine headache has been attributed to peripheral sensitization of trigeminovascular nociceptors innervating extracranial, dural, and pial arteries.[35,40,42] However, human studies have challenged the presumption that the pulsating quality of pain in migraine is determined by arterial pulsations.[47-50] Using psychophysical and electrophysiologic recording methods, investigators found no temporal relationship between heart rate or arterial pulsation and throbbing pain of different etiologies. Furthermore, they also reported that the magnitude of alpha oscillations fluctuated over time in a rhythmic fashion in synchrony with the subjective report of throbbing pulsations, and the degree of synchrony correlated with throbbing intensity. Taken together, these findings suggest a neuronal instead of vascular "pacemaker" of the throbbing pain in migraine.[47-50]

Nausea is one of the cardinal symptoms included in the diagnostic criteria of migraine.[7] About 50% of people with migraine experience significant nausea in half or more of their attacks.[51] Interestingly, nausea can occur also during the aura and prodromal phases, before the onset of headache. Nausea was recently demonstrated to occur in the prodromal phase of nitroglycerin-induced migraine before the development of pain and independent of trigeminal activation. Using PET, the authors of the study found activation of the rostral dorsal medulla and periaqueductal gray in the group of patients that developed nausea and not in the group without nausea.[27] This offers additional evidence supporting the role of the brainstem in the initiation of a migraine attack.

POSTDROMAL PHASE

This phase, although well recognized clinically and often debilitating for people with migraine, is perhaps one of the least-studied aspects of migraine and

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remains poorly understood. Additional research focusing on the postdrome may help identify possible therapeutic interventions to terminate a migraine attack and accelerate the return to normal function.

More than 80% of patients report nonheadache symptoms during the 24 to 48 hours following resolution of their migraine headaches.[52,53] In a prospective study, patients with migraine were asked to keep an electronic diary on a daily basis for 3 months. The most common postdromal symptom was being tired or weary, reported in 88% of postdromes. Difficulty concentrating occurred in more than half and stiff neck in 42% of the attacks with postdrome. Other migraine-associated symptoms, such as nausea, photophobia, and phonophobia, were also reported but were less frequent than tiredness, difficulty concentrating, and neck stiffness. In this study, about half of the attacks resolved completely within 6 hours of the resolution of the headache, and only 7% lasted more than 24 hours.[53] Interestingly, acute treatment and comorbidities do not appear to have any effect on the occurrence of the postdrome.[52]

It has been proposed that the brain regions and mechanisms responsible for the prodromal phase could also play a role in the postdromal phase. Based on the limited available evidence, some experts have suggested that global reductions in cerebral blood flow could occur in this phase and could be mediated by activation of brainstem nuclei, resulting in widespread vasoconstriction. An alternative explanation for this reduction in regional cerebral blood flow could be the persistent hypoperfusion that follows the bioelectric phenomenon of cortical spreading depolarization.[52]

Neurophysiologic studies that have investigated the postdrome in migraine include EEG and visual processing studies that suggest changes in the excitatory/inhibitory equilibrium within the visual cortex.[6] Alterations in EEG recordings lasted for up to 48 hours after headache resolution.[54] However, visual processing differences normalized after 24 hours.[55,56] This is consistent with data from a functional neuroimaging study showing activation of the visual cortex during the 24 hours following the resolution of headache.[18]

INTERICTAL PHASE

This phase of the migraine cycle is of utmost importance as it can help in understanding the pathophysiology of the disorder and improve therapeutic approaches.

Although patients are relatively symptom free during this phase, they often describe hypersensitivity to light, sounds, and odors even when they do not have any other migraine symptoms. Other common symptoms are cognitive dysfunction and dizziness or a sense of being off balance. In general, the different symptoms can be grouped into several categories, including sensory hypersensitivity, autonomic symptoms, and cognitive dysfunction. The underlying neural mechanisms of these symptoms remain poorly understood, and further research is needed to elucidate the relationship between the clinical manifestations and findings from neurophysiologic and neuroimaging studies.

Resting-state functional connectivity MRI has been used extensively in the past decade to investigate migraine; however, it is difficult to interpret the results and compare the findings because of high variability in methodology. This has led to a recent call for guidelines for resting-state functional connectivity studies in migraine.[57] Altered network connectivity has been demonstrated in multiple cortical and subcortical brain regions during the interictal phase when comparing

KEY POINTS

- Cortical spreading depolarization has been demonstrated to occur in the human brain as a result of acute injury in the setting of stroke or traumatic brain injury; however, no direct evidence of the simultaneous occurrence of cortical spreading depolarization and aura has been seen in humans.
- The aura can start in multiple sites of the visual cortex in the same individual, although certain areas show higher propensity to be the initiating focus.
- The mechanisms underlying visual aura appear to propagate in a linear fashion along gyri or sulci, rather than spreading as a concentric wave as usually depicted based on studies of cortical spreading depolarization in animal models.
- The aura may propagate silently in the cortex, without clinical manifestations.
- Migraine pain is mediated by the trigeminovascular pathway.
- Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain and implicate cortical spreading depolarization and peripheral sensitization of perivascular sensory nerve terminals. Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.

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people with migraine during the interictal phase with healthy nonheadache controls as well as comparing people with migraine during and outside their migraine attacks.[57] More than 20 networks have been identified as having altered resting-state functional connectivity, including several cortical regions[58-60] and the thalamus,[60,61] hypothalamus,[18,62] brainstem,[59,63] amygdala,[64-66] and cerebellum.[58,59] How specific to migraine these abnormalities are remains undetermined. Nevertheless, these studies suggest widespread altered brain function in people with migraine that could explain some of the interictal cognitive, autonomic, and sensory symptoms.

Psychophysical and electrophysiologic studies have also found cyclic changes in sensation.[18,23,24] Some of these findings point toward reduced habituation before the onset of headache independent of prodromal symptoms.[24] Similar to the caveats mentioned for functional imaging studies, these psychophysical and electrophysiologic studies vary in methodology; some of the findings are stimulus dependent and need to be reproduced.

Together, these data support the notion of generalized alterations in brain function, not only during the migraine attacks but also during the interictal period, resulting in hyperresponsivity and lack of habituation.

MOLECULAR MEDIATORS

At the molecular level, multiple neurotransmitters, neuropeptides, and neurochemical systems play a role in migraine.[3,39,67] CGRP has been the focus of research in the field for more than 2 decades.[68] This has resulted in the development of the first group of targeted and migraine-specific preventive treatments, the monoclonal antibodies against CGRP or its receptor erenumab, fremanezumab, galcanezumab, and eptinezumab, all currently US Food and Drug Administration (FDA) approved. At the time of this writing, two CGRP antagonists are also available, ubrogepant and rimegepant, which are FDA approved for the acute treatment of migraine, and several others are in development for preventive and acute treatment. CGRP is a ubiquitous neuropeptide with multiple physiologic functions in the nervous system, vasculature, and other organs and systems. In migraine, CGRP plays a key role in the pathophysiology of the disorder through arterial vasodilation, neurogenic inflammation, and activation of meningeal nociceptors. CGRP can enhance synaptic transmission through glutamatergic signaling and may contribute to peripheral and central sensitization.[68,69] Furthermore, a bidirectional model linking CGRP and cortical spreading depolarization has been proposed as part of the vascular and neuronal interactions during a migraine attack.[70] Whereas this would implicate CGRP in the aura phase and CGRP is known to play a role in head pain, it is also important to point out that CGRP-related mechanisms are involved in other migraine symptoms, such as photophobia[71,72] and diarrhea.[73]

Similar to CGRP, pituitary adenylate cyclase-activating polypeptide (PACAP) is elevated during spontaneous migraine attacks, and systemic administration of PACAP precipitates a migraine attack in people with migraine.[74] In the past decade, PACAP has emerged as a potential therapeutic target for migraine and a significant focus for research.

Serotonin has been established as an important mediator in the pathophysiology of migraine for decades.[75] The triptans, 5-hydroxytryptamine, serotonin $(5\text{-HT})_{1B/1D}$ receptor agonists, remain the cornerstone of acute migraine treatment. However, their vasoconstrictive effect represents a hurdle

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and contraindication for a subset of patients. Recently, a new class of more selective serotonin receptor agonists targeting 5-HT_{1F} receptors, which are absent on blood vessels, has emerged as an alternative to triptans. Lasmiditan, the first drug in this new class named ditans, has recently been approved for acute migraine treatment.

Dopaminergic mechanisms are likely to mediate some of the symptoms of migraine in different phases, more notably yawning, nausea, and difficulty concentrating. The orexigenic system has been implicated in the alterations of sleep and fatigue in migraine. Furthermore, orexin A and B modulate dural nociceptive input.[76] In the locus coeruleus, noradrenergic activity plays a role in sleep-wake regulation and arousal as well as pain in migraine. Multiple neuroendocrine mediators, such as insulin, glucagon, leptin, and neuropeptide Y, have effects on the trigeminovascular system, linking changes in appetite, food cravings, and migraine.[3,77]

Other emergent neurochemical systems that may be implicated in migraine include somatostatin, cholecystokinin, antidiuretic hormone, and melatonin.[3] Additional research is needed to confirm their role in migraine pathophysiology.

CONCLUSION

Migraine is a complex brain disorder with cyclic manifestations that can be heterogeneous among different people and within the same individual. Functional neuroimaging, electrophysiologic and psychophysical studies, and clinical observations suggest that migraine is a disorder of dysfunctional network connectivity. Whereas the exact site and mechanism of initiation of a migraine attack remains unknown, a central origin is currently widely accepted.

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KEY POINTS

- **Some studies have challenged the presumption that the pulsating quality of pain in migraine is determined by arterial pulsations and suggest a neuronal rather than vascular "pacemaker" of the throbbing pain in migraine.**
- **The postdrome can last for 24 to 48 hours after resolution of the headache. Some experts have suggested that global reductions in cerebral blood flow could occur in this phase and could be mediated by activation of brainstem nuclei, resulting in widespread vasoconstriction. Alternatively, this reduction in regional cerebral blood flow has been attributed to the persistent hypoperfusion that follows cortical spreading depolarization.**
- **People with migraine report cognitive, autonomic, and sensory symptoms between their migraine attacks. Resting-state functional connectivity MRI studies have demonstrated altered network connectivity in multiple cortical and subcortical brain regions during the interictal phase.**
- **Multiple neurotransmitters, neuropeptides, and neurochemical systems play a role in migraine. The most studied include calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), serotonin, and noradrenergic and dopaminergic mechanisms.**

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Acute Migraine Treatment

By Jessica Ailani, MD, FAHS, FAAN

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **Migraine is a disabling disease of attacks of moderate to severe pain with associated symptoms. Every person with migraine requires treatment for acute attacks. Treatments can range from behavioral management and nonspecific medications to migraine-specific medications and neuromodulation. For many with migraine, having a combination of tools allows for effective treatment of all types of attacks.**

RECENT FINDINGS: **Over the past several years, four neuromodulation devices have been cleared by the US Food and Drug Administration (FDA) for treatment of acute migraine, and three medications with novel mechanisms of action have been FDA approved. They add to the arsenal available to people with migraine and focus on migraine-specific pathways to allow for precise care with fewer side effects.**

SUMMARY: **This article discusses acute migraine therapy, focusing on best-level evidence.**

INTRODUCTION

A migraine attack can become significantly disabling over a short period of time. Ninety-one percent of people with migraine report functional impairment with their headaches, and 53% report severe headache causing significant impairment in activities or requiring bedrest.[1] Thirty-one percent of people with migraine have missed at least 1 day of work or school within a 3-month period (CASE 3-1).[1] Having a strategy in place to treat attacks is essential for every person with migraine. Many people self-treat with over-the-counter medications and remedies, but for people with moderate to severe attacks, prescription medications may be needed to self-manage. Untreated attacks or attacks that do not respond well to therapy can lead to longer attacks with greater disability and, over time,[2] become a risk factor for patients to develop chronic migraine.[3] For some people, untreated attacks can lead to emergency department (ED) visits. In the CaMEO (Chronic Migraine Epidemiology and Outcomes) study, a large web-based survey evaluating migraine treatment and impact, 4.8% of responders had used the ED or urgent care for headache treatment in the prior 6 months.[4] Burch and colleagues[5] evaluated migraine treatment using US civilian and active-duty military databases and found that from 2009 to 2010, migraine was the fourth leading cause of ED visits.

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Numerous types of therapies are available to treat attacks of migraine, ranging from nonspecific pain medications that are available both over the counter and by prescription to migraine-specific acute medications and neuromodulation devices that are available by prescription only; behavioral techniques such as biofeedback, deep breathing, and meditation; a multitude of topical agents; ice caps and bands; essential oils; specialty glasses; therapeutic lights; acupuncture; and massage (TABLE 3-1). Most people with migraine seek an evaluation for their symptoms with their primary care provider, and the number of available options can be overwhelming for both the provider and patient.[6] Although triptans are still the most frequently prescribed acute migraine treatment with studies showing that they are prescribed for approximately 33% of people seen for migraine, many patients are still being prescribed opioids and barbiturates to manage their migraine attacks, which can lead to dependence and an increase in migraine frequency.[6] In the past several years, numerous advances have been made in the science of migraine that have made available more specific migraine treatment options. Ditans and gepants are two new categories of medications that provide acute migraine relief. Numerous neuromodulation devices for migraine attacks have also become available. These treatments represent a new era in migraine care, allowing for more precise attack treatment with fewer side effects.

This article lays the foundation for acute migraine treatment, first by reviewing guidelines and consensus for acute treatment, then discussing nonspecific, migraine-specific, and neuromodulation therapies.

GUIDELINES AND CONSENSUS FOR ACUTE MIGRAINE TREATMENT

In 2013, the Canadian Headache Society published acute migraine treatment guidelines,[7] and in 2015, the American Headache Society (AHS) published its

CASE 3-1

A 25-year-old woman presented to clinic to discuss symptoms of headache. Her headaches were gradual in onset, building to moderate left temple pounding pain. The pain could become severe over several hours. With severe pain, she had associated nausea and light sensitivity. She had tried over-the-counter medications, including acetaminophen, ibuprofen, and naproxen, for treatment in the past. She tended to wait until the headache was more moderate and pounding before treatment. These treatments had become less effective, and she had recently missed 2 days of work because of an unmanageable attack.

COMMENT

This case is an example of a typical patient with migraine without aura who has tried to treat attacks on her own before presenting to clinic. Patients should be asked about prior treatments tried, disability related to headache, when they treat during the course of the attack, and the inciting incident that may have pushed them to seek care. Having this kind of information can help clinicians when discussing treatment options with the patient. For example, this patient should be offered prescription migraine acute treatment to reduce disability and education should be provided about treating her attacks early to avoid reduced efficacy of treatment.

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acute treatment guidelines.[8] The guidelines agree that triptans, acetaminophen, aspirin, diclofenac sodium, naproxen, and ibuprofen all have strong evidence for the acute treatment of migraine.[7,8] The Canadian guidelines rated evidence for dihydroergotamine (DHE), ergotamine, codeine-containing compounds, and tramadol-containing compounds as weak and did not recommend them for routine use.[7] The Canadian guidelines also outlined which options should be used depending on the severity of migraine attacks: mild to moderate, moderate to severe, refractory, or unresponsive to first-line or contraindication to first-line treatments.[7] The AHS guidelines included DHE nasal spray, butorphanol nasal spray, and acetaminophen/aspirin/caffeine combination tablets as having Level A evidence for acute migraine attack treatment (TABLE 3-2).[8] Differences exist between the two guidelines and relate to recommendations on first-line use of butorphanol. Although the guidelines rate evidence on DHE differently, the Canadian guidelines do recommend DHE for first-line use in certain scenarios.[7]

With several new treatments becoming available since the publication of the guidelines, the AHS published a position paper in 2019 with considerations for new treatments for patients with migraine.[9] This statement was published before the US Food and Drug Administration (FDA) approval of lasmiditan, ubrogepant, and rimegepant but is still relevant when considering use of a nongeneric or nonoral option for patients.[9] The consensus statement made clear that evidence-based treatments should be used when possible, migraine attacks should be treated early, and medication should be able to be self-administered.[9] A nonoral route is preferred in patients with nausea or vomiting or rapid-onset attacks. When selecting medications, safety and tolerability concerns should be considered. Neuromodulation and behavioral therapies are appropriate depending on the patient and may be useful for patients who prefer nondrug therapy or cannot tolerate, do not respond well to, or have contraindications to medications.[9]

How can the guidelines and consensus statement be considered when helping patients choose the right acute treatment for their migraine attacks? No one single treatment is correct for every patient. This is an exciting time in headache medicine as clinicians are able to provide more precise care for patients and for the various types of attacks they may have. Patients with migraine may need more than one available option to treat their attacks, which is termed *stratified care*.[10] Making stratified care effective requires educating the patient about using the correct choice for their migraine attack. For example, for a sudden-onset attack with associated nausea, a nonoral triptan may be best. For the

Nonpharmacologic Treatments for Acute Attacks TABLE 3-1

- Rest in a dark, quiet space
- Hydration
- Ice pack/ice hat/ice helmet/ice cap
- Creams containing menthol, camphor, lidocaine, or essential oils
- Deep breathing
- Guided meditation
- Biofeedback; need to be trained before the attack

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gradual-onset migraine that occurs in the middle of the day, patients may choose to treat with a gepant.

The remainder of this article outlines the various treatment options with strong evidence for acute migraine attacks, including the two new acute treatment categories (ditans and gepants) and neuromodulation.

NONSPECIFIC TREATMENT

For people with mild to moderate migraine attacks, treatments that are not specifically designed for migraine can be used effectively for acute attacks.

Acetaminophen

For nonincapacitating migraine attacks, 1000 mg oral acetaminophen has proven efficacy over placebo, with 2-hour pain freedom in 22.4% of treated patients compared to 11.3% of patients treated with placebo (P=.01).[11] Side effects include nausea, vomiting, headache, and insomnia. At higher frequent dosing, acetaminophen is associated with hepatotoxicity.[12] Most people with migraine have tried acetaminophen before being seen by a health care provider, but information on dosing should be obtained.

Nonsteroidal Anti-inflammatory Drugs

Aspirin (900 mg), diclofenac (50 mg, 100 mg, and oral dissolvable powder), ibuprofen (200 mg, 400 mg), and naproxen (500 mg, 550 mg) all have Level A evidence for the acute treatment of migraine.[8,12] Nonsteroidal anti-inflammatory

TABLE 3-2 **Select Summary of American and Canadian Headache Societies Guidelines for Acute Migraine Treatment**

Medication	American Headache Society[8]	Canadian Headache Society[7]
Acetaminophen 1000 mg for nonincapacitating attacks	Strong evidence (Level A)	Strong evidence
Aspirin 500 mg, diclofenac 50 mg or 100 mg, ibuprofen 200 mg or 400 mg, naproxen 500 mg or 550 mg	Strong evidence (Level A)	Strong evidence
Triptans	Strong evidence (Level A)	Strong evidence
Dihydroergotamine nasal spray	Strong evidence (Level A)	Weak evidence but may be first line in some cases
Dihydroergotamine IV/IM/subcutaneous	Medium evidence (Level B)	Weak evidence but may be first line in some cases
Acetaminophen/aspirin/caffeine	Strong evidence (Level A)	Not addressed
Butorphanol nasal spray	Strong evidence (Level A)	Weak evidence, should not use
Codeine	Medium to weak evidence (Level B/C)	Weak evidence, should not use
Tramadol	Medium evidence (Level B)	Weak evidence, should not use

IM = intramuscular; IV = intravenous.

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drugs (NSAIDs) are often used as a first-line treatment for mild to moderate migraine attacks. NSAIDs carry gastrointestinal risk, which includes ulcers and bleeding. They are also associated with an increased risk of cardiovascular events and carry a boxed warning to indicate this hazard.[13] When used more than 15 days per month, they have the potential to be associated with medication-overuse headache.[14]

Opioids and Butalbital-containing Products

Opioids and butalbital-containing products have limited use in migraine, and evidence suggests that use of these products is likely to cause more harm than benefit in people with migraine.[15] Opioids and butalbital-containing products should not be prescribed for long periods of time or as a first-line treatment for people with migraine.[16]

MIGRAINE-SPECIFIC TREATMENT

For people with moderate to severe migraine attacks, treatment designed specifically for migraine should be offered to treat attacks.

Triptans

Triptans are selective 5-hydroxytryptamine, serotonin $(5\text{-HT})_{1B/D}$ agonists (some also have an affinity for the 5-HT_{1F} receptor) designed specifically for acute migraine treatment. They were developed to cause vasoconstriction when migraine was believed to primarily be a vascular event.[12] It is now understood that in addition to vasoconstriction, triptans work on other migraine-specific pathways, such as serotonin agonism and reduction of trigeminal nerve activation. Triptans are considered first-line treatment for moderate to severe migraine attacks.[8] Most triptans are now available as generic options and have a long history of safety and efficacy; they are available in oral, nasal, and subcutaneous formulations. Even with their ease of availability and specificity to migraine, they are widely underprescribed, as only one in five people with migraine uses a triptan for acute attacks.[17]

Seven different available triptans are FDA approved for the acute treatment of migraine in adults. Sumatriptan is available as an oral tablet, nasal spray, and subcutaneous injection as well as in a combination tablet with naproxen. Rizatriptan is available as an oral tablet and an orally disintegrating tablet. Zolmitriptan is available as an oral tablet, an orally disintegrating tablet, and a nasal spray. The rest are available as oral tablets. Frovatriptan and naratriptan have longer half-lives, ranging from 6 to 26 hours, whereas the rest have half-lives that range from 2 to 4 hours. Two new formulations of sumatriptan have been FDA approved in the past few years, sumatriptan 3 mg subcutaneous injection and DFN-02 (sumatriptan 10 mg with a permeation enhancer) nasal spray.[18,19] Both have shown efficacy compared to placebo in clinical trials, with sumatriptan 3 mg subcutaneous injection having fewer side effects than the 6 mg injection.[18,19] Pain-free rates at 2 hours were 51.0% compared to 30.8% for placebo (P=.0023) for the 3 mg injection and 43.8% compared to 22.5% for placebo (P=.44) for the nasal spray.[18,19]

When making choices about which triptan to prescribe, consider the length of the attack (longer attacks may benefit from a medication with a longer half-life), the speed of onset of attack (rapid-onset attacks benefit from a nonoral route of medication), formulary preference, and data from meta-analyses. If a patient

KEY POINTS

- Migraine attacks are disabling and require treatment. Ineffective treatment can increase emergency department visits and place the patient at increased risk for chronic migraine.
- Acute treatment can be nonspecific or migraine specific. Opioids and barbiturates should be limited in their use for migraine.
- Triptans, acetaminophen, aspirin, ibuprofen, naproxen, and diclofenac sodium have Level A evidence for the acute treatment of migraine.
- A nonoral route for migraine medication is preferred in patients with nausea or vomiting or rapid-onset attacks.
- Stratified care is best for patients with multiple types of migraine attacks.
- Triptans are considered first-line treatment for moderate to severe migraine attacks.

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needs both an oral tablet and a nonoral formulation, choosing a triptan that has both formulations allows for better layering of treatment.

A 2015 meta-analysis of triptans for the acute treatment of migraine concluded that standard-dose triptans provide 2-hour pain relief for 42% to 76% of patients, which are better outcomes than ergots (38%), equal to or better than NSAIDs (46% to 52%), and equal to or worse than combination medications (62% to 80%).[20] When comparing the triptans, subcutaneous sumatriptan, rizatriptan orally disintegrating tablet, zolmitriptan orally disintegrating tablet, and eletriptan tablets had the most favorable outcomes.[20] Combining a triptan with aspirin or acetaminophen or using a nonoral formulation may produce better outcomes.[20]

TABLE 3-3 **Side Effects of Acute Migraine Medications**[a]

Medication	Most common adverse events and warnings
Acetaminophen	Nausea, vomiting, headache, and insomnia
Nonsteroidal anti-inflammatory drugs (NSAIDs)	NSAIDs have a US Food and Drug Administration (FDA) boxed warning regarding cardiovascular and gastrointestinal risk; discuss medication-overuse headache with patients
	Common side effects of NSAIDs include nausea, vomiting, constipation, diarrhea, reduced appetite, headache, dizziness, rash, and drowsiness
	Other possible adverse events include edema, renal failure, liver failure, allergic reaction causing anaphylaxis, and bleeding
	NSAIDs (except aspirin) may increase the risk of myocardial infarction or stroke with increased duration of use and when used in those with underlying risk factors for cardiovascular disease
Triptans	Triptans have an FDA boxed warning regarding cerebrovascular or cardiovascular disease and risk of serotonin syndrome when used with other serotonin drugs; discuss medication-overuse headache with patients
	Triptans are contraindicated in patients with a history of cardiovascular or cerebrovascular disease, including those with uncontrolled hypertension, peripheral vascular disease, or cardiac arrhythmias; patients with ischemic bowel disease; and those with hemiplegic migraine.
	Common side effects can include nausea, dizziness, somnolence, paresthesia, dry mouth, dyspepsia, feeling hot or cold, chest pain/tightness, flushing, throat/neck symptoms, heaviness sensation
Ergotamines	FDA boxed warnings for ergotamines include risk of life-threatening peripheral ischemia with coadministration with potent cytochrome P450 3A4 isozyme (CYP3A4) inhibitors
	Common side effects of dihydroergotamine include rhinitis, nausea, altered sense of taste, dizziness, vomiting, flushing
Ditans	Warning for medication-overuse headache and driving restriction for 8 hours after use; Schedule V controlled substance
	Common side effects include dizziness, fatigue, paresthesia, and sedation
Gepants	Use with caution in medications that use the CYP3A4 system and breast cancer resistance protein or P-glycoprotein–only inhibitors
	Common side effects include nausea and somnolence

[a] Data from Cooper W, et al, Postgrad Med.[12]

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Side effects of triptans include fatigue, dizziness, chest discomfort, somnolence, and nausea (TABLE 3-3).[12] A 2016 meta-analysis of tolerability of treatments for acute migraine revealed that triptans had a higher risk of adverse events compared to placebo or nontriptans.[21] Almotriptan, naratriptan, and frovatriptan have been shown to have fewer side effects and better tolerability than other triptans.[8,21]

Limitations of triptans include the need to use them early during a migraine attack, inadequate response (30% to 40% of people with migraine do not respond to triptans),[22] headache recurrence (in about one-third of patients), and side effects.[23-25] If used more than 10 days per month, they have the potential to be associated with medication-overuse headache.[14] Triptans are safe when used appropriately; however, although considered to have a low incidence of serious cardiovascular events, they are nevertheless contraindicated in those with vascular disease because of their vasoconstrictive properties.[26] In the United States, migraine epidemiology studies indicate that 900,000 people with episodic migraine have contraindications to triptans.[27] Contraindications include a history of myocardial infarction or other ischemic heart disease, cerebrovascular event including transient ischemic attack, cardiac accessory conduction pathway arrhythmias, coronary artery vasospasm, uncontrolled hypertension, severe hepatic impairment, or ischemic bowel disease. Although triptans carry a warning regarding potential for serotonin syndrome, the risk in coprescription with other serotonergic medications is exceedingly low and in clinical practice such events are extraordinarily rare.[28]

KEY POINTS

- Triptans are contraindicated in people with vascular disease.
- Dihydroergotamine has shown to be effective early or late in a migraine attack. Consider dihydroergotamine in a patient who has found triptans to be ineffective.

Ergots

Ergots have been used to treat migraine since the Middle Ages but have poor tolerability because of nausea, vomiting, and cardiovascular effects.[12] DHE is a synthetic ergotamine that has been used to treat migraine since 1945 and has fewer side effects than previously used ergotamines.[29] DHE has poor oral bioavailability and is dosed intravenously, intramuscularly, subcutaneously, or nasally.[29] DHE is an agonist at 5-$HT_{1B/1D/1F}$ receptors and binds to 5-HT_{1A} and 5-HT_{2A} receptors and to adrenergic, cholinergic, and dopaminergic receptors.[30] Its wide effects may result in better efficacy for migraine, especially in patients who do not respond to triptans. Its slow dissociation from 5-$HT_{1B/1D}$ receptors may explain why it can have a longer efficacy during migraine attacks and may be useful when administered parenterally over consecutive days.[30] DHE has been shown to be effective early or late in a migraine attack and in attacks with allodynia.[31,32]

As it is a nonoral agent and can be expensive or difficult to obtain, DHE is often given to patients for whom a triptan is ineffective. It can be useful in patients with moderate to severe migraine attacks who need a nonoral administration (such as in waking with migraine in which the attack has already been ongoing for some time and fast-onset medication is desired) or in patients who have longer attacks or attacks with allodynia. The nasal route of administration carries Level A evidence from the AHS, with pain relief in 30% to 61% of treated participants compared to 20% to 33% for placebo.[8,33] Injectable DHE has Level B evidence, with the best-known study published by Neil Raskin,[34] with his use of IV DHE every 8 hours over 3 days showing that 89% of patients treated with repetitive IV DHE achieved headache freedom in 48 hours.[8] Later studies have mimicked these results at inpatient units.[35,36]

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The side effects of DHE depend on the route of administration. Intranasal DHE can cause rhinitis, altered sense of taste, application site reactions, nausea, vomiting, and dizziness.[29] IV DHE can cause dizziness, drowsiness, headache, nausea, vomiting, diarrhea, flushing, increased sweating, anxiety, or skin rash.[29] DHE should be avoided in patients with peripheral vascular disease, cardiovascular disease, and uncontrolled hypertension.[8]

Ditans

Ditans are a novel category of acute migraine treatments that are selective 5-HT_{1F} receptor agonists. They act on the trigeminal system but do not cause vasoconstriction because of their low affinity for 5-HT_{1B} receptors.[37] Lasmiditan 2-hour pain freedom rates were between 28% and 39% at doses of 50 mg, 100 mg, and 200 mg versus 15% for placebo (P<.001).[37,38] Two-hour resolution of most bothersome symptom was 41% for lasmiditan (50 mg, 100 mg, 200 mg) versus 30% for placebo (P<.001).[37,38] A second dose of lasmiditan does not offer clear benefit, so it should be dosed only once in 24 hours for an attack.[39] A 52-week long-term safety study evaluated up to four doses of lasmiditan per month for acute attacks and showed no new safety signals or adverse events.[40]

As lasmiditan does not cause vasoconstriction, it is likely safe to use in patients who have vascular risk factors. This property can be particularly helpful for a patient who may have responded well to a triptan but has developed vascular contraindications. A post hoc analysis of pooled results from two phase 3 single-attack studies evaluated treatment with lasmiditan in patients who had cardiovascular risk factors.[41] Of patients in the trials, 78.8% had more than one cardiovascular risk factor and 41.3% had more than two cardiovascular risk factors at baseline, and these patients did not experience a greater frequency of cardiovascular treatment emergent adverse events compared to those without cardiovascular risk.[41]

Side effects of lasmiditan include dizziness, fatigue, paresthesia, and sedation.[37,38] Side effects are greater on the higher doses of lasmiditan but were rated in the clinical trials as mild to moderate.[37] As lasmiditan works on the serotonin system, it carries a boxed warning, similar to triptans, about serotonin syndrome when used with other serotonin-activating medications. Lasmiditan may also cause medication-overuse headache based on its mechanism of action. Patients should be cautioned to avoid overuse of lasmiditan; the long-term safety study did not evaluate more than four doses of lasmiditan per month.[40] As lasmiditan has central activity, the FDA mandated driving studies and a study evaluating its abuse potential. Driving studies revealed healthy participants had driving impairments after one dose of lasmiditan from 90 minutes up until 8 hours after the dose.[42] A phase 1 abuse potential study revealed that recreational polydrug users preferred lasmiditan to placebo but not to alprazolam, suggesting that lasmiditan has a low potential for abuse.[43] As a result of these studies, lasmiditan is a Schedule V controlled substance. Patients should be advised to avoid driving for 8 hours after the use of lasmiditan.

Lasmiditan may be considered for a patient who has inadequate response to or contraindication to a triptan. It may also be beneficial for people who have migraine onset later in the day or may choose to use lasmiditan before sleep as it may carry a sedating effect for a small portion of patients.

Gepants

Calcitonin gene-related peptide (CGRP) was discovered to play an important role in migraine pathophysiology in the mid-1980s.[44] By blocking its activity,

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migraine attacks may be aborted and reduced in frequency.[45] CGRP receptor antagonists (called gepants) have been studied over the past 2 decades, and between 2019 and 2020, two gepants were FDA approved for the acute treatment of migraine in adults: ubrogepant and rimegepant. Both of these small molecule receptor antagonists have shown efficacy in resolving migraine attacks with a reduced number of side effects when compared to traditional acute migraine-specific therapies.[46-49]

In phase 3 single-attack treatment trials, doses of ubrogepant (50 mg, 100 mg) were found to have 2-hour pain freedom rates at 19% for 50 mg ubrogepant compared to 12% for placebo (P=.002) and 22% for 100 mg ubrogepant compared to 14% for placebo (P<.001) and 2-hour freedom from most bothersome symptom at 38% for 50 mg and 39% for 100 mg compared to 28% for placebo (P<.05).[46,47] Subjects were allowed to rescue with their own acute treatment, including NSAIDs and triptans, or, if they chose a second dose of ubrogepant, were randomly assigned again to placebo or ubrogepant.[46,47] The second dose of ubrogepant showed efficacy after use, with up to 55% of subjects who experienced pain relief after the first dose achieving pain freedom in 2 hours.[50] Side effects are nausea, somnolence, and dry mouth (for 100 mg).[46,47] A 52-week long-term safety study evaluating ubrogepant for the treatment of migraine attacks found no new safety signals or side effects when used for up to eight doses per month.[51] Ubrogepant is dosed as needed for migraine, with an additional dose as needed in 2 to 24 hours.

Rimegepant has shown significant benefit in two phase 3 single-attack treatment trials, with 2-hour pain freedom rates between 20% and 21% for rimegepant compared to 11% to 12% for placebo (P<.001) and 2-hour freedom from most bothersome symptom at 35% for rimegepant compared to 25% for placebo (P<.001) and 38% for rimegepant compared to 27% for placebo (P=.0009).[48,49] Subjects were able to rescue with their own acute treatment, but triptan use was not allowed in the study. Side effects of rimegepant are nausea and hypersensitivity reactions.[48,49] A 52-week long-term safety study had a unique design in that some subjects were enrolled in an alternate-day dosing arm with additional as-needed dosing.[52] Results showed no new safety signals or side effects when used for up to 15 doses per month.[52] Rimegepant is dosed once a day as needed for migraine and is available as an orally disintegrating tablet.

CGRP receptor antagonism does not cause vasoconstriction, theoretically making it safe to use in people with stable cardiovascular disease.[53-55] Gepants, however, have not been studied in people who had a recent (within 6 months) vascular event, such as a stroke or myocardial infarction. A 2020 study evaluating olcegepant and rimegepant administration in mice after middle cerebral artery occlusion revealed increased infarct risk in these mice between 12 and 20 minutes after occlusion, increased infarct volumes, and worsening neurologic deficits.[56] Therefore, consider using gepants with caution in individuals at high risk of cerebrovascular events, such as those with recent stroke. As blocking CGRP can reduce migraine frequency, gepants may not cause medication-overuse headache, and neither ubrogepant nor rimegepant have a medication-overuse headache warning on their label. It is important, however, to realize that in long-term safety studies, ubrogepant has been studied at eight doses per month and rimegepant has been studied at 15 doses per month.

The use of gepants should be considered in people with migraine for whom triptans have been ineffective or who have contraindications to or have experienced side effects from triptans (CASE 3-2).[9] When making a decision

KEY POINTS

- Lasmiditan 50 mg, 100 mg, or 200 mg can be considered in patients with cardiovascular contraindications to triptans.
- Patients who are prescribed lasmiditan must be instructed not to drive for 8 hours after taking medication.
- Ubrogepant is dosed as needed for migraine, with an additional second dose as needed in 2 to 24 hours.
- Rimegepant is dosed once a day as needed for migraine.

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between gepants, discussing with the patient if they want the ability to repeat dosing versus taking a single dose of an orally disintegrating tablet for a migraine attack may help differentiate between the two available medications.

Neuromodulation

Four noninvasive neuromodulation devices have been studied and cleared by the FDA for treatment of acute migraine attacks: external trigeminal nerve stimulation, single-pulse transcranial magnetic stimulation, noninvasive vagus nerve stimulation, and remote electrical neuromodulation (TABLE 3-4).[57-60] These devices are placed against the skin and are thought to modulate pain by electrical or magnetic impulses that translate to reduced activation of peripheral or central pain pathways.[61] It is important to have nonpharmacologic options for the treatment of migraine to help mitigate potential side effects and interactions patients may experience with medications, but it is also imperative to understand the difference between trial designs for neuromodulation compared to pharmacologic studies. By the nature of device studies, sham stimulation is used as a comparator to device stimulation. This is not the same as a placebo, as sham can deliver some amount of stimulation. It is an estimate that the stimulation delivered is under the amount needed to treat the disease process; nonetheless, some subjects may have benefited from sham stimulation. Device studies historically have also used different end points, often evaluating pain relief

CASE 3-2

A 32-year-old woman with migraine without aura returned to clinic for follow-up. She was having six migraine attacks per month lasting 6 hours untreated. Her attacks were moderate to severe right-sided back of the head pounding pain that was worse with movement. She had associated light sensitivity and nausea if not treated. She had tried ibuprofen, naproxen, and acetaminophen/aspirin/caffeine. Acetaminophen/aspirin/caffeine improved her attacks 75% of the time but never resolved the attack; although she felt better, she noted she performed at about 50% because of lingering pain and photophobia. She had been prescribed an oral triptan but delayed treatment because of side effects of sedation. When she used her triptan, she had pain freedom and freedom from photophobia within 1 hour. She said she was not satisfied with her acute treatment as she felt she could not plan to be fully functional after taking the medication because of side effects and the need to supplement with over-the-counter medications.

COMMENT

The patient in this case had a great response to a prescription triptan but delayed using it because of side effects, which then caused her to use over-the-counter treatment that was not as effective. She had continued disability from her migraine because of ineffective treatment and was at risk of developing medication-overuse headache and chronic migraine. This case represents an appropriate situation for a discussion about newer acute treatment options, such as a gepant, which may have a more favorable adverse effect profile.

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instead of pain freedom, which is the recommended end point for migraine acute treatment trials.[62]

External trigeminal nerve stimulation was evaluated in a double-blind randomized sham-controlled study in 99 adults with migraine with or without aura.[57] Subjects treated a migraine for 1 hour. The primary outcome was mean change in pain intensity at 1 hour. The treatment group had a reduction of 3.46 ± 2.32 points in pain compared to 1.78 ± 1.89 (P<.0001) for sham. Pain freedom at 2 hours, a standard recommended end point for acute treatment of migraine, was an exploratory end point and not statistically significant. Adverse events reported in trials included paresthesia in the distribution of the stimulated nerve and a single case of nausea.

Single-pulse transcranial magnetic stimulation was studied in 164 adults with migraine with aura.[58] This double-blind randomized parallel-group sham-controlled study evaluated for pain freedom at 2 hours after treatment for a migraine attack. Of those treated with single-pulse transcranial magnetic stimulation, 39% achieved 2-hour pain freedom compared to 22% treated with sham (P=.0179). Adverse events in the trial were headache, migraine, and sinusitis in 2% or less of subjects.

Noninvasive vagus nerve stimulation has been evaluated in the treatment of migraine attacks.[59] A double-blind randomized sham-controlled trial of 219 adult subjects with migraine with or without aura were evaluated for 2-hour pain freedom after treatment of the first migraine attack. Secondary end points included pain freedom rates at 30 minutes and 60 minutes. This study did not meet the primary end point; 12.7% of subjects were pain free at 30 minutes (P=.012). Although not meeting the primary end point, this study did evaluate treatment of multiple attacks and followed with an open-label period. What was seen was that those who responded to treatment with the first attack had consistent pain-free response with future attacks (30.4% of subjects). This indicates that for a portion of patients with migraine, noninvasive vagus nerve stimulation, if effective, may continue to remain an effective treatment option. Common adverse events were application site discomfort and nasopharyngitis.

Remote electrical neuromodulation (a device that stimulates the upper arm peripheral nerves to induce conditioned pain modulation) has been studied for the treatment of migraine attacks.[60] A randomized double-blind sham-controlled study evaluated 202 subjects with migraine with or without aura. The primary end point was pain relief 2 hours posttreatment; pain freedom

Neuromodulation Dosing and Side Effects TABLE 3-4

Device	Dosing	Side effects
External trigeminal stimulation	1 hour during migraine attack	Paresthesia
Single-pulse transcranial magnetic stimulation	Three pulses up to 3 times per attack as needed	Lightheaded, tingling, tinnitus
Noninvasive vagus nerve stimulation	Bilateral 120 seconds to right and left of neck within 20 minutes of onset of attack; repeat once after 15 minutes	Application site discomfort, nasopharyngitis
Remote electrical neuromodulation	To upper arm for 45 minutes within 1 hour of onset; increase stimulation until perceptible but nonpainful	Transient warmth, redness, or tingling sensation into the arm

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CASE 3-3

A 41-year-old man presented for evaluation and treatment of his migraine attacks. He started having migraine attacks at age 30 and treated them with ibuprofen. The attacks started in his right temple, spread across his forehead, and had associated light sensitivity. They were moderate at onset and built gradually, often starting in the afternoon while he was at work. He preferred to rest for 30 minutes in a dark cool space to treat his attack. In the previous 5 years, he had noted some changes with his migraine that were making ibuprofen ineffective.

COMMENT

The following comments apply the treatment approaches discussed in this article to the case above, using five different potential clinical scenarios.

Scenario 1: The patient had occasional attacks upon awakening, and ibuprofen was not effective.

Migraine attacks can occur upon awakening for a proportion of patients, and others may be gradual in onset and occur during the day. For the attacks this patient awakens with, he would do well with a nonoral treatment option. As he is naïve to prescription medications, a trial of a nonoral triptan, such as sumatriptan subcutaneous, sumatriptan nasal, or zolmitriptan nasal, would be a good starting option for his morning attacks.

Scenario 2: The patient had been diagnosed with hypertension and hyperlipidemia and was struggling to keep his blood pressure in normal range.

With uncontrolled hypertension, triptans and ergots should be avoided. In this patient, a prescription of a ditan should be considered if he has a plan in place to get home without driving. Another option would be a gepant, which, so far, carries no clear cardiovascular contraindications and may be well tolerated.

Scenario 3: The patient had been prescribed a triptan and had not found it effective.

If he has tried a triptan and found it ineffective and has no vascular contraindications, his options would be nasal dihydroergotamine, an oral ditan, an oral gepant, or a neuromodulation device. Decision factors between these options include patient preference on route and speed of administration/action, insurance coverage and cost, ability to get a ride after use of medication, and his feelings about the side effect profile of each medication. This conversation can be covered quickly by asking the patient if he prefers rapid onset, if he has limits with side effects, and if he has a preference with insurance coverage.

Scenario 4: The patient was having 16 attacks per month and successfully using triptans for all attacks.

In this patient, options that will help reduce triptan use and not cause medication-overuse headache are needed. His options are a gepant for some attacks or use of a neuromodulation device, or both, and the elevated attack frequency also warrants the use of a preventive therapy.

Scenario 5: The patient wanted to try nonpharmacologic options.

A discussion about neuromodulation and some behavioral techniques to help with his attacks would be beneficial (TABLE 3-1).

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at 2 hours was a secondary end point. Two-hour pain relief was experienced by a greater proportion of subjects treated with remote electrical neuromodulation (66.7%) compared to sham (38.8%) in 2 hours (P=.0008). Pain freedom at 2 hours was 37.4% for subjects treated with remote electrical neuromodulation compared to 18.4% for sham-treated subjects (P=.003). Adverse events reported in the trial were primarily device-related events (sensation of warmth, numbness in the arm/hand, redness, itching, muscle spasm).

Neuromodulation is an accessible option for patients, although cost can be a limiting factor as most insurers do not cover devices. Side effects are usually mild, with few patients choosing to discontinue because of intolerance.[61]

Neuromodulation should be considered in patients who have poor tolerance of their current therapy, have found triptans to be ineffective, have contraindications to standard therapy, are overusing standard treatment, or prefer nondrug therapy.[9]

UNMET ACUTE TREATMENT NEEDS

Even with the variety of acute treatment options available, many patients continue to have unmet treatment needs. To address these needs, patients should be asked about how they treat their migraine attacks and how consistently their medications are effective. The goals of acute treatment are to treat attacks quickly and consistently, prevent recurrence, and restore the patient to functionality.[2] To achieve this goal, patients should not need rescue medications and treatments should have minimal to no adverse events.[2]

Studies indicate that 35% of people with migraine do not have optimized acute treatment.[4] Sixty-two percent of patients with episodic migraine and 95% of patients with chronic migraine have more than one unmet acute treatment need.[4] Of responders to the CaMEO survey, 36.3% use or keep opioids on hand for acute treatment of migraine.[63] Compared to patients with migraine who did not use opioids, those who used opioids had poorer quality of life and a higher headache-related burden.[63]

A variety of screening instruments are available to address the efficacy of acute treatment in clinical practice. An example is the Migraine-ACT questionnaire, which asks four questions to identify patients who need to change their acute migraine treatment:

- **Does your migraine medication work consistently in the majority of your attacks?**
- **Does the headache pain disappear within 2 hours?**
- **Are you able to function normally within 2 hours?**
- **Are you comfortable enough with your medication to be able to plan your daily activities?[64]**

By asking questions about the consistency of effect of medication and functionality, clinicians can quickly identify who may need a change in their acute treatment, which can lead to reduced disability from migraine attacks and improved patient satisfaction.

MAKING DECISIONS ABOUT TREATMENT OPTIONS

With numerous acute migraine treatments available, how does one make a choice? CASE 3-3 applies the treatments discussed in this article to approach a patient with migraine, looking at various scenarios.

KEY POINTS

- **Consider adding neuromodulation in patients who have side effects to current therapy, prefer nondrug therapy, or are overusing acute medications.**
- **The goals of acute migraine treatment are to treat attacks quickly and consistently, prevent recurrence, and restore the patient to functionality.**

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CONCLUSION

Acute treatment is important for all patients with migraine, with migraine-specific medications preferred in those with moderate to severe attacks with associated disability. If acute attacks are not properly treated, the risk of increased frequency of migraine and migraine-related disability rises. Novel treatment options may come with reduced cardiovascular risk to patients, and some have a lower side effect profile. Neuromodulation is an option for patients who would like a nonmedication acute treatment or who are having side effects or efficacy issues with their current acute treatment option. Nonoral options should be considered for all acute attacks with associated nausea or attacks that have rapid or early onset. Attack-specific treatments should be prescribed when possible, with patients having a clear understanding of how to stratify their care for optimized acute management.

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Preventive Migraine Treatment

By Rebecca Burch, MD, FAHS

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article provides an overview of preventive interventions for migraine, including when to start and how to choose a treatment, pharmacologic options (both older oral treatments and new monoclonal antibodies to calcitonin gene-related peptide [CGRP] or its receptor), nonpharmacologic treatment such as neuromodulation, and preventive treatment of refractory migraine.**

RECENT FINDINGS: **The migraine preventive treatment landscape has been transformed by the development of monoclonal antibodies targeting CGRP or its receptor. These treatments, which are given subcutaneously or intravenously monthly or quarterly, have high efficacy and were well tolerated in clinical trials. Emerging real-world studies have found higher rates of adverse events than were seen in clinical trials. They are currently recommended for use if two traditional preventive therapies have proven inadequate. Since the commonly cited 2012 American Headache Society/American Academy of Neurology migraine prevention guidelines were released, clinical trials supporting the preventive use of lisinopril, candesartan, and memantine have been published. Neuromodulation devices, including external trigeminal nerve stimulation and single-pulse transcranial magnetic stimulation devices, have modest evidence to support preventive use. The American Headache Society/American Academy of Neurology guidelines for the preventive treatment of migraine are currently being updated. A new class of oral CGRP receptor antagonists (gepants) is being tested for migraine prevention.**

SUMMARY: **Successful preventive treatment of migraine reduces disease burden and improves quality of life. Many pharmacologic and nonpharmacologic treatment options are available for the prevention of migraine, including newer therapies aimed at the CGRP pathway as well as older treatments with good evidence for efficacy. Multiple treatment trials may be required to find the best preventive for an individual patient.**

INTRODUCTION

Preventive therapies are among the most powerful tools available to improve the well-being of people with migraine. Studies consistently show that effective preventive treatment of migraine is associated with reduced disability and improved quality of life over and above the reduction in attack frequency. Recent analyses from trials of

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RELATIONSHIP DISCLOSURE:
Dr Burch serves on the board of directors of the American Headache Society and the Headache Cooperative of New England, and as an associate editor for *Neurology*.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Burch discusses the unlabeled/investigational use of amitriptyline and other tricyclic antidepressants, candesartan, cyproheptadine, gabapentin, lisinopril, memantine, metoprolol, venlafaxine and other serotonin norepinephrine reuptake inhibitors, and herbs and nutritional supplements for the preventive treatment of migraine.

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monoclonal antibodies to calcitonin gene-related peptide (CGRP) or its receptor show that these treatments reduce disability even on nonheadache days.[1] Headache frequency is one of the strongest predictors for transformation from episodic migraine to chronic migraine.[2] Effective prevention may help prevent this transition.

Despite these many benefits, successful preventive treatment can sometimes be challenging. According to analyses of insurance claims data, adherence to preventive migraine medications may be as low as 25% at 1 year after prescription.[3] Patients may discontinue migraine preventives for many reasons. Many medications have potentially bothersome side effects, and people with migraine may be more sensitive to such adverse effects than people without migraine.[4] Even the most effective preventive medications reduce headache frequency by half in only 50% to 60% of patients who try them. Response to preventive medication can be idiosyncratic, an expression of the pathophysiologic heterogeneity that likely underlies the phenotypic expression of migraine. The resulting trial and error process may be frustrating to patients looking for relief. Some patients may have difficulty with daily medication use. For some patients, starting a preventive treatment for migraine may be the first time they have had to acknowledge having a serious illness. For others, cost, access, or insurance status may be limiting factors.

The chances for success of prevention can be increased by giving the patient a sense of ownership of the treatment plan. Actively soliciting a patient's treatment-related goals, concerns, and priorities sets a collaborative tone and is the basis for shared decision making. It may be helpful to present preventive medication use as a time-limited trial rather than as a permanent requirement. Patients can be reassured that many options are available and that lack of response to initial treatment should be taken as information rather than defeat. Because significant variability is seen in response to different doses of

TABLE 4-1 **Classes of Treatments Used for Preventive Treatment of Migraine**

Class	Drugs
Antiepileptic drugs	Divalproex sodium,[a] topiramate,[a] gabapentin
Antidepressant drugs	Amitriptyline and other tricyclic antidepressants, venlafaxine and other serotonin norepinephrine reuptake inhibitors (SNRIs)
Beta-blockers	Propranolol,[a] metoprolol, timolol[a]
Other antihypertensive drugs	Verapamil, lisinopril, candesartan
Neurotoxins	OnabotulinumtoxinA[a]
Calcitonin gene-related peptide monoclonal antibodies	Erenumab,[a] fremanezumab,[a] galcanezumab,[a] eptinezumab[a]
Other	Memantine, cyproheptadine
Herbal and nutritional supplements	Magnesium, vitamin B_2 (riboflavin), feverfew, coenzyme Q10, melatonin

[a] US Food and Drug Administration (FDA)–approved for prevention of either episodic or chronic migraine.

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preventive medications and because of concerns about side effects, it can be helpful to start medications at a low dose and increase slowly, such as weekly.

It is also useful to discuss goals of preventive treatment with patients at the time of prescription. A reduction in headache frequency of 50% or more is considered a good response to treatment. An effective preventive medication may also reduce the severity or duration of headache attacks, reduce the need for acute treatment, and improve efficacy of acute treatments. Taken together, the overall goal of preventive medication is to reduce the overall burden and disability of migraine. Use of a headache diary provides a more reliable measure of headache frequency and severity than recall. This documentation can be helpful because a reduction in headache severity without reduction in frequency can have a meaningful effect on quality of life. Other objective measures include quantification of headache disability, such as the Migraine Disability Assessment (MIDAS) (headaches.org/wp-content/uploads/2018/02/MIDAS.pdf)[5,6] or the six-item Headache Impact Test (HIT-6) (headaches.org/wp-content/uploads/2018/02/HIT-6.pdf),[5,7] days of missed work or decreased work productivity, or visits to urgent care or the emergency department. That said, the most important metric of all is the patient's global impression: Is the patient better on the preventive medication?

Few studies have rigorously examined parameters for initiation of migraine preventive therapy. Commonly used criteria for considering preventive therapy, largely derived from expert opinion, include the following:

- Two severe or disabling or four less disabling migraine attacks per month
- Acute migraine treatment is ineffective or contraindicated
- Medication-overuse headache is present
- Highly disabling migraine attacks (eg, hemiplegic migraine or migraine with brainstem aura)
- Patient preference[8,9]

Another common clinical question is when to consider withdrawing a patient from preventive treatment. Few studies are available to guide decision making in this area. One study that compared the duration of propranolol treatment before withdrawal found that a longer duration of treatment before attempting to withdraw the medication was associated with a lower risk of recurrence. This suggests that it is probably better to continue prevention if any concerns exist about withdrawing. One approach is to wait for 3 to 6 months of headache freedom before attempting a slow taper of prevention, although tapering by dose is not generally feasible with many treatments, such as CGRP monoclonal antibodies and onabotulinumtoxinA.

ORAL PHARMACOLOGIC PREVENTION

Many different classes of medications are used for preventive treatment of migraine (TABLE 4-1). Before the development of CGRP monoclonal antibodies, only one medication (methysergide, no longer in use) had been developed specifically for migraine prevention. Migraine prevention is therefore a secondary indication for most drugs currently in use as oral preventive agents. Despite this path for their use, many such medications are efficacious as migraine preventives. The most commonly cited systematic assessment of efficacy is a

KEY POINTS

- Preventive treatment reduces migraine-related disability over and above the associated reduction in attack frequency.
- A collaborative approach to choosing preventive treatment may improve adherence and patient satisfaction with treatment options.
- The goal of preventive treatment is reduction of disability and improvement in quality of life rather than complete relief from migraine attacks.
- Objective measures are helpful for tracking response to preventive treatment and may be more reliable than patient recall.
- Prevention is started when migraine attacks are frequent, disabling, or hard to treat, or if acute medications have been overused.

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2012 guideline codeveloped by the American Headache Society (AHS) and American Academy of Neurology (AAN).[10] TABLE 4-2 lists currently available migraine preventives, the level of evidence for efficacy, and notes to guide treatment.[11] In the 2012 AAN/AHS guidelines, treatments are rated as follows: Level A (established as effective) if two high-quality studies support efficacy, Level B (probably effective) if one good-quality or two lower-quality studies support efficacy, Level C (possibly effective) if one lower-quality or two lowest-quality studies support efficacy, and Level U (data inadequate or conflicting) if studies are conflicting or available studies are of insufficient quality to contribute to knowledge.

Preventive medication guidelines have also been published by European and Canadian neurologic societies, both of which account for side effect profiles as well as efficacy.[12] Preventive medications that received high ratings

TABLE 4-2 **Medications Used for Prevention of Migraine**

Medication	Target dosing[a]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Divalproex sodium	250-500 mg 2 times a day or 500-1000 mg delayed release once daily	A	May cause thrombocytopenia or hepatotoxicity; monitoring is required; contraindicated during pregnancy; use limited by side effect burden despite efficacy
Topiramate	100 mg once daily or 50 mg 2 times a day	A	May cause weight loss, which some patients find beneficial; contraindicated in patients with nephrolithiasis
Metoprolol	50 mg 2 times a day	A	Unlikely to worsen asthma (highly cardioselective)
Propranolol	60 mg once daily or 2 times a day	A	Contraindicated in people with asthma; evidence that beta-blockers worsen depression has been challenged in recent years
Eptinezumab	100-300 mg IV every 3 months	N/A	Faster onset because of IV administration
Erenumab	70 mg or 140 mg subcutaneous monthly	N/A	Constipation, hypertension, hypersensitivity reaction
Fremanezumab	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	N/A	
Galcanezumab	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly	N/A	
OnabotulinumtoxinA	155 units subcutaneous monthly	A	Lack of systemic side effects and drug interactions makes this a high-priority option for patients with chronic migraine
Amitriptyline	50 mg nightly	B	Generally better tolerated when started at lower doses and increased slowly

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in all three guidelines include sodium valproate, topiramate, propranolol, and metoprolol. Amitriptyline was also rated highly by the European and Canadian guidelines. It received a Level B rating from the AAN/AHS because of insufficient completion rates in the included trials but would otherwise have been a Level A drug and could therefore also be considered as a recommended treatment.

Antidepressant Medications

The tricyclic antidepressant amitriptyline is one of the oldest medications used for migraine prevention.[13] Amitriptyline was rated as having Level B evidence for efficacy in the 2012 guidelines. The rating was downgraded from Level A because of a significant proportion of patients dropping out of the treatment arm of the relevant clinical trials. These trials typically started amitriptyline at 25 mg to 50 mg.

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Medication	Target dosing[a]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Venlafaxine	75-225 mg extended release once daily	B	May worsen headaches in some patients; withdrawal syndrome can be prolonged and bothersome
Candesartan	8-16 mg once daily	C	Generally well tolerated
Lisinopril	10-40 mg once daily	C	Generally well tolerated
Cyproheptadine	4-8 mg once daily or divided 2 times a day	C	Use limited by sedation and weight gain
Gabapentin	900-3600 mg total daily dose, divided 3 times a day	U	Frequently used despite lack of clinical trial data; dose amounts and frequency have high variability
Verapamil	120-240 mg once daily	U	Frequently used despite lack of clinical trial data, likely because of the benign side effect profile
Memantine	10 mg 2 times a day	None	Generally well tolerated
Duloxetine	60 mg once daily	None	Used in place of venlafaxine because of decreased risk of withdrawal syndrome; better evidence for use in pain conditions globally
Levetiracetam	500-1000 mg 2 times a day	None	Recent evidence suggests possible benefit[11]
Nortriptyline	50 mg once daily	None	Used in place of amitriptyline because of decreased anticholinergic effects
Pregabalin	25-75 mg 3 times a day	None	Used if gabapentin is effective but not tolerated or loses efficacy

AAN = American Academy of Neurology; AHS = American Headache Society; IV = intravenous; N/A = not available.
[a] Many patients with migraine respond to lower doses of preventive medication, whereas others may need higher doses.

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When started at lower doses and increased slowly, amitriptyline is typically well tolerated.[14] Nortriptyline is less well studied but often used because of its lower anticholinergic profile. The serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine has Level B evidence for prevention of migraine. Venlafaxine can have a significant withdrawal syndrome. Duloxetine, although not studied in randomized controlled trials for migraine, is sometimes used instead of venlafaxine because of patient reports of less severe withdrawal symptoms.[15,16]

Antihypertensive Medications

The most commonly prescribed antihypertensive agent for migraine prevention is the nonselective beta-blocker propranolol. Metoprolol is cardioselective and also has good evidence for efficacy. Timolol is US Food and Drug Administration

TABLE 4-3 **Preventive Medication Choices Based on Side Effects, Contraindications, and Comorbidities**

Area of concern	Consider	Avoid
Side effects[a]		
General	Verapamil and memantine well tolerated; lisinopril and candesartan if normal blood pressure	Valproate, topiramate, amitriptyline
Weight gain	Topiramate, venlafaxine	Valproate, amitriptyline, cyproheptadine
Fatigue/exercise intolerance	Topiramate, venlafaxine	Beta-blockers, amitriptyline, verapamil
Cognitive symptoms	Verapamil, lisinopril, candesartan, venlafaxine, memantine	Antiepileptic drugs
Contraindications		
Hypotension		Antihypertensive drugs
Nephrolithiasis		Topiramate, zonisamide
Possibility of pregnancy	Propranolol first line; amitriptyline, verapamil, coenzyme Q10 second line	Valproate, topiramate, lisinopril, candesartan, feverfew
Glaucoma		Topiramate (narrow-angle glaucoma), amitriptyline
Comorbidities		
Insomnia	Amitriptyline, melatonin	Memantine
Anxiety	Beta-blockers	Topiramate
Depression	Venlafaxine	Beta-blockers
Hypertension	Antihypertensive drugs	Erenumab, venlafaxine, duloxetine
Obesity	Topiramate	Valproate, amitriptyline
Frequent migraine aura	Verapamil, valproate, magnesium, topiramate	None identified

[a] Herbal and nutritional supplements and behavioral treatments are good choices for patients with side effect concerns.

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(FDA) approved for migraine prevention but used infrequently in clinical practice. The calcium channel blocker verapamil was rated as Level U in the 2012 guidelines, but a widespread clinical impression of benefit exists despite this rating. Verapamil has a relatively benign side effect profile, with constipation being the most commonly reported adverse effect. Verapamil may also be helpful in patients with migraine aura, particularly prolonged, bothersome, or brainstem aura, and hemiplegic migraine. Studies supporting the efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, specifically lisinopril and candesartan, for migraine prevention have been published since the 2012 guidelines.[17] The evidence levels for these medications will be reassessed in the next guideline update and are likely to change. Like verapamil, these antihypertensive agents also have a benign side effect profile. These agents should be avoided in people with hypotension or who could become pregnant but are otherwise a good choice for patients who are concerned about side effects.

Antiepileptic Medications

Compared to other classes of preventive medications, antiepileptic drugs tend to have a higher side effect profile but may also have greater efficacy. Topiramate has Level A evidence and is widely used as a first-line preventive. The most bothersome side effect reported by patients is cognitive slowing, including perceived memory deficits and word-finding difficulties. Sodium valproate is also highly effective but is limited by a high side effect burden, including somnolence, weight gain, hair loss, and possible hepatotoxicity and thrombocytopenia. Sodium valproate is also highly teratogenic and must always be avoided in people who could become pregnant. The evidence for efficacy of gabapentin was rated as uncertain in the 2012 guidelines, but it is still used in clinical practice. Its frequent use may be partly because of the significant flexibility in dosing and a lower side effect profile than other antiepileptic drugs. Gabapentin may also be particularly helpful for patients with medication-overuse headache because it may have both acute and preventive effects. Pregabalin, although not specifically studied for prevention of migraine in randomized trials, is sometimes used. Zonisamide use has been supported by small studies, and zonisamide may be useful in patients who improve on but are unable to tolerate the related drug topiramate.[18] Results for the effectiveness of levetiracetam for migraine prevention have been conflicting.[11]

Other Medications

Memantine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of Alzheimer disease, has also shown efficacy for migraine prevention in two small clinical trials and one prospective observational study.[19] The evidence levels for memantine will be reassessed in the next guideline update. Cyproheptadine has Level C evidence but is rarely used outside of pediatric settings because of high rates of sedation and weight gain.

Choosing Oral Preventive Treatments

A combination of level of evidence, side effect profile, contraindications, and patient preference typically affects the choice of preventive medication. A common treatment paradigm is to choose from the Level A medications based on patient comorbidities and contraindications, then move on to Level B and lower levels. Medication choices based on contraindications and comorbidities are listed in TABLE 4-3. Migraine is most highly prevalent in female individuals of

KEY POINTS

- Oral preventive treatments with good evidence include sodium valproate, topiramate, propranolol, metoprolol, and amitriptyline.
- Amitriptyline and venlafaxine are the antidepressant drugs with the best evidence for prevention of migraine.
- Propranolol and verapamil are the antihypertensive drugs most commonly used for migraine prevention and are generally well tolerated.
- Recent evidence suggests that lisinopril and candesartan are effective migraine preventives with a good side effect profile.
- Topiramate and sodium valproate are potent migraine preventives but have a higher side effect burden than other preventives.
- Antiepileptic drugs sometimes used for prevention include gabapentin, pregabalin, and zonisamide.
- Oral medication choice depends on effectiveness, side effect profile, contraindications, and patient preference.

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reproductive age, and pregnancy safety is another important consideration. Particular attention should be paid to contraceptive status when prescribing medications contraindicated in pregnancy. For more information on medication safety during pregnancy, refer to the article "Headache in Women" by Jelena M. Pavlović, MD, PhD,[20] in this issue of *Continuum*. **CASE 4-1** illustrates taking patient concerns about side effects into account when deciding to start prevention.

CASE 4-1

A 27-year-old woman presented for the treatment of migraine. She reported having had headaches meeting the criteria for migraine with and without aura since her teens. The headaches had been increasing in frequency for the past 2 years and were now occurring about 10 days per month. Acute treatment with eletriptan 40 mg had become less effective as time went on. She had to leave work early with about half of her headaches and missed 1 or 2 days of work completely each month. Her past medical history was notable only for a history of gastroesophageal reflux disease.

Her blood pressure was 128/81 mm Hg, and her pulse was 74 beats/min. Her neurologic examination was normal.

She was concerned about the risk of side effects of preventive medication, particularly weight gain because of a family history of diabetes. She also reported that a friend had tried topiramate and "felt like a zombie." She had heard that new treatments for migraine were available and wondered if she might be eligible.

COMMENT

This case presents a common clinical scenario in an outpatient neurology setting. This patient meets multiple criteria for considering prevention: she has high-frequency episodic migraine and is at risk for migraine chronification, her acute treatment is not reliably effective, and she has significant migraine-related disability. When a patient expresses concern about starting a preventive, it can be helpful to revisit the patient's goals for treatment, solicit any concerns about treatment, and present preventive treatment as a time-limited trial.

Options in this case are not limited by comorbidities or contraindications. Considering preventive treatments with Level A evidence, propranolol is least likely to cause weight gain or cognitive side effects. Other options to consider might include low-dose amitriptyline or nortriptyline (Level B), verapamil (particularly because the patient has migraine with aura), and venlafaxine (Level B) or duloxetine. Topiramate and sodium valproate, although Level A, should be avoided because of her side effect concerns. Both of these drugs should also be avoided because she is a woman of childbearing age, and sodium valproate is absolutely contraindicated if any risk of pregnancy exists. If two or three of the oral preventives are not effective, she would be a candidate for a calcitonin gene-related peptide monoclonal antibody, which carries a low risk for weight gain and has not been associated with cognitive side effects.

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CALCITONIN GENE-RELATED PEPTIDE MONOCLONAL ANTIBODIES

CGRP is a neuropeptide found throughout the central and peripheral nervous systems that is intrinsically involved in migraine pathogenesis. Drugs directly antagonizing the CGRP receptor were initially evaluated as preventive treatments in the 2000s but were associated with an increased risk of liver toxicity. This ultimately led to the development of monoclonal antibodies to CGRP or its receptor. The first of these, erenumab, became available in May 2018, and three other CGRP monoclonal antibodies have followed. TABLE 4-4 lists key information about the four currently available CGRP monoclonal antibodies.[21] The first three CGRP monoclonal antibodies that were approved are self-administered monthly or quarterly subcutaneous injections. The last drug to be approved, eptinezumab, is administered quarterly by IV infusion.

Efficacy

Placebo-controlled randomized clinical trials showed that CGRP monoclonal antibodies are effective treatments for both episodic and chronic migraine. Trials of the subcutaneous CGRP monoclonal antibodies found an additional reduction of approximately 1 to 2 headache days per month compared to placebo.[22] A network meta-analysis performed by the Institute for Clinical and Economic Review (ICER) found that this improvement was similar to other treatments commonly used for treatment of episodic or chronic migraine, including topiramate, propranolol, and onabotulinumtoxinA.[23] On average, 50% responder rates (the number of participants who have at least a 50% reduction in headache frequency) for CGRP monoclonal antibodies were around 50% to 60% in the

Antibodies to Calcitonin Gene-Related Peptide or Its Receptor[a] TABLE 4-4

	Eptinezumab	Erenumab	Fremanezumab	Galcanezumab
Target	Ligand	Receptor	Ligand	Ligand
Subclass	Humanized	Human	Humanized	Humanized
Production	Yeast	Chinese hamster ovary	Chinese hamster ovary	Chinese hamster ovary
Dose	100-300 mg IV every 3 months	70 or 140 mg subcutaneous monthly	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly
Time to maximum (T_{max})	2-5 hours	5.5 days	5-7 days	7-13 days
Half-life	27 days	21-23 days	31 days	28 days
Notes	IV administration leads to fastest onset of efficacy	Clinical experience suggests higher risk of constipation than with other monoclonal antibodies	Higher risk of injection site reactions than for erenumab; quarterly dosing may be convenient for some patients	Higher risk of injection site reactions than for erenumab

IV = intravenous.
[a] Data from Do TP, et al, J Headache Pain.[21]

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treatment groups.[24] Early evidence from real-world studies is also now available, showing that efficacy in clinical practice may be even greater. For example, one retrospective study performed in a tertiary headache center found that 74% of patients who used erenumab felt that it had helped their headaches.[25] Some patients achieve complete cessation of headache.[26] Further studies have extended the evidence for efficacy of CGRP monoclonal antibodies to those with lack of response to at least two to four prior preventive medication trials.[27] Long-term response has also been evaluated, and sustained response over a period of 1 to 3 years has been reported for various CGRP monoclonal antibodies.[28,29]

Side Effects

CGRP monoclonal antibodies were initially believed to have a lower side effect profile than previously available oral medications. Discontinuation rates because of adverse events were less than 5% in CGRP monoclonal antibody clinical trials. Side effects identified in clinical trials included constipation, injection site reactions, and, less commonly, upper respiratory symptoms such as nasopharyngitis.[30] However, the product insert for erenumab has been updated for safety concerns 3 times since approval in May 2018. These updates describe the risk of severe constipation with obstipation, hypersensitivity reactions, and development of hypertension or worsening of preexisting hypertension. The multiple updates to the safety label raise the possibility that the full side effect profile of erenumab (and possibly other CGRP monoclonal antibodies) was not captured in the clinical trials. In clinical practice, patients have also reported side effects that have yet to be well captured systematically, such as worsened headache and hair loss. The real-world side effect profile of CGRP monoclonal antibodies is likely to be an evolving area of research.

CGRP has wide-reaching effects throughout the body. CGRP is involved in physiologic activities as diverse as wound and bone healing; regulation of gastrointestinal motility and healing of gastric mucosal damage; maintenance of homeostasis, including temperature, heart rate, and appetite; and regulation of blood pressure and maintenance of vasodilation during cardiac and other ischemic events.[31] Clinical trials have not shown an increased risk in cardiovascular events with CGRP monoclonal antibody use. Retrospective population level studies are needed to determine whether CGRP monoclonal antibody use increases the risk of rare but serious events. At the time a CGRP monoclonal antibody is prescribed, patients should be counseled about the risk of hypertension (with erenumab specifically), hypersensitivity reactions, and constipation and the possibility of very rare but serious risks that have not yet been identified.

Use in Clinical Practice

The advantages of CGRP monoclonal antibodies include robust efficacy, a potentially lower side effect burden, and convenient monthly or quarterly dosing. Monoclonal antibodies do not interact with other medications and are excellent for patients with polypharmacy. Compared to older oral preventive medications, CGRP monoclonal antibodies likely have a faster onset of action.[32,33] Most monoclonal antibody clinical trials showed improvement in the treatment group compared to placebo starting in the first week after treatment that was sustained throughout the duration of the trial.[24] Eptinezumab, which is administered as an IV infusion, may lead to benefit over placebo in the first day

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after administration.[33] The CGRP monoclonal antibodies also represent a new class of treatments that can be tried in patients who have not responded to previous preventive medication trials.

In addition to the safety concerns raised above, CGRP monoclonal antibodies have several other drawbacks. They are expensive, and insurance coverage may be a limiting factor. Manufacturer assistance programs may be offered but are not available to patients with government insurance, who are often the patients least able to afford expensive medications. The long half-life of the CGRP monoclonal antibodies means that any side effects can take several months to resolve even after treatment is stopped. CGRP monoclonal antibodies are also contraindicated in pregnancy and breastfeeding. The optimal interval to wait before attempting pregnancy after stopping CGRP monoclonal antibodies is not known.

For all of these reasons, CGRP monoclonal antibodies are not considered first-line treatments at this time. A position statement from the AHS published in 2019 gives guidance on how to integrate CGRP monoclonal antibodies into clinical practice.[34] The statement suggests that CGRP monoclonal antibodies should be considered in patients who have an inability to tolerate or inadequate response to a 6-week trial of two conventional preventive therapies. CGRP monoclonal antibodies are also used in patients for whom conventional preventives are contraindicated because of coexisting medical conditions. Other clinical considerations are that clinical trials of CGRP monoclonal antibodies excluded people older than 70 years of age, and they have also not been tested in the pediatric population.

No contraindication exists to the concurrent use of other migraine preventive treatments, thus other preventives do not need to be stopped before initiation of a CGRP monoclonal antibody. Another common clinical question is whether a patient who does not respond to one CGRP monoclonal antibody will respond to another. The author's current clinical practice is to try one monoclonal antibody targeted at the CGRP receptor and one at the ligand before moving on to a different treatment class.

PREVENTIVE TREATMENT OF CHRONIC MIGRAINE AND MEDICATION-OVERUSE HEADACHE

Although few preventive treatments are specifically FDA approved for chronic migraine, several oral treatments have been studied for prevention in this population.[35] Topiramate has a high level of evidence for efficacy, whereas amitriptyline, gabapentin, sodium valproate, and the muscle relaxant tizanidine each have one randomized controlled trial supporting use.[35] The CGRP monoclonal antibodies are all FDA approved for migraine regardless of frequency, and trials evaluating effectiveness in chronic migraine specifically were positive. They should therefore be considered good treatment options in this population.

OnabotulinumtoxinA is FDA approved for chronic migraine only and has Level A evidence for prevention of chronic migraine.[36] Head-to-head comparisons of onabotulinumtoxinA to CGRP monoclonal antibodies for chronic migraine prevention are lacking, although the ICER network meta-analysis suggested roughly equivalent efficacy. Treatment choice therefore depends on provider and patient preference and insurance coverage. Expert opinions vary about whether CGRP monoclonal antibodies should be layered with onabotulinumtoxinA, but most headache specialists feel comfortable using

KEY POINTS

- Four calcitonin gene-related peptide (CGRP) monoclonal antibodies are now US Food and Drug Administration approved for migraine prevention.
- CGRP monoclonal antibodies are given monthly or quarterly, either subcutaneously or intravenously.
- CGRP monoclonal antibodies are effective for migraine prevention, with up to 60% of patients seeing a 50% or greater reduction in headache days.
- Studies showed that CGRP monoclonal antibodies are effective for refractory migraine and sustain efficacy over several years.
- Discontinuation because of adverse events was less than 5% in clinical trials of CGRP monoclonal antibodies, but these trials may not have accurately captured the side effects seen in clinical practice.
- The long-term safety of CGRP blockade, particularly the risk of rare but serious cardiovascular events, is not completely known.
- CGRP monoclonal antibodies may have a faster onset of action than oral preventives.
- Limitations of CGRP monoclonal antibody use include cost and access issues, long duration of any side effects that may occur, and the need to avoid use during pregnancy.

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these treatments in combination. Evidence from rodent studies suggests that the effect of CGRP receptor antagonism and onabotulinumtoxinA may be synergistic.[37]

Many patients with chronic migraine have comorbid medication overuse or medication-overuse headache, or both.[2] Medication overuse is diagnosed when a patient uses a triptan, ergot, opioid, combination analgesic, or any combination of acute treatments more than 10 days a month, or acetaminophen or nonsteroidal anti-inflammatory drugs alone more than 15 days a month. Medication overuse can complicate preventive treatment, and clinical experience

CASE 4-2

A 54-year-old man presented for a second opinion about his daily headaches. He had a history of migrainous headaches starting in his early twenties, which had increased in frequency over time and were daily for the prior 9 years. He had tried several preventives, including amitriptyline, topiramate, propranolol, sodium valproate, and gabapentin, without significant benefit. For the previous year, he had been using over-the-counter analgesics 2 to 3 times a day. The headaches resolved for several hours after acute treatment but always recurred. He reported significant job stress, poor sleep and snoring, and feeling irritable at times. He also reported that the pain was "starting to really get to me," making it hard for him to enjoy life even when the headache was less severe. The neurologic examination was normal. A normal MRI of his brain had been obtained a few years earlier.

COMMENT

This patient has refractory chronic migraine combined with medication overuse and likely medication-overuse headache. As is common for patients with chronic migraine, several comorbidities are likely contributing to the headache severity, including stress, likely obstructive sleep apnea, and mood symptoms. This patient will benefit from a multifocused approach that includes preventive medications, treatment of medication overuse, diagnosis and treatment of medical comorbidities (such as sleep disorders), addressing mood symptoms, and making lifestyle changes (such as increasing physical activity). It can be helpful to pick a few of these areas to address at each visit to prevent the patient from feeling overwhelmed. Gains in each of these areas may be incremental initially, but over time they can add up to significant improvement in the patient's overall quality of life.

This patient had not had a trial of onabotulinumtoxinA and opted to try this next, although venlafaxine or duloxetine would also have been good choices given his mood symptoms, and he would also be eligible for a calcitonin gene-related peptide monoclonal antibody. He was referred for a sleep study and for mindfulness-based stress reduction. He responded well to onabotulinumtoxinA treatments and, over time, was able to reduce acute medication use without an explicit plan. Over time, treatment of his obstructive sleep apnea, stress reduction techniques, and counseling additionally improved his overall quality of life.

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suggests that medication overuse may decrease response to preventive treatment. Medication-overuse headache is typically addressed by discontinuation of the overused medication, and preventive medication is often started at that time. A 2016 systematic review surveying approaches to the treatment of medication-overuse headache found that commonly used preventive medications included amitriptyline, onabotulinumtoxinA, pregabalin, propranolol, topiramate, sodium valproate, and selective serotonin reuptake inhibitors (SSRIs).[38] This review found the best evidence for use of onabotulinumtoxinA and topiramate in patients with chronic migraine and medication overuse, although a 2019 randomized controlled trial did not show efficacy for onabotulinumtoxinA after 12 weeks of treatment.[39]

Patients with chronic migraine have a higher burden of medical and psychiatric comorbidities than those with episodic migraine.[40] In addition to preventive treatment and addressing medication overuse, optimal treatment of chronic migraine typically includes identifying and addressing comorbidities, including insomnia and sleep apnea, depression, anxiety, and lack of physical activity. Studies examining the effect of cognitive-behavioral therapy for insomnia on migraine days have been very positive.[41] Layering pharmacologic and nonpharmacologic treatment approaches can be particularly helpful in treatment of chronic migraine. Many patients also find benefit from combinations of preventive treatment. Although the only clinical trial evaluating this approach was negative, extensive clinical experience supports using combinations of preventive medications.[42] CASE 4-2 illustrates a typical approach to treatment of refractory migraine.

NONPHARMACOLOGIC AND INTEGRATIVE INTERVENTIONS

Nonpharmacologic treatments, including lifestyle modifications, behavioral and mind-body treatments, herbal and nutritional supplements, and physical treatments, are a core component of the migraine treatment plan. The evidence base for the value of nonpharmacologic and integrative (also called complementary or alternative) interventions for migraine continues to grow. Advantages of nonpharmacologic treatments include synergistic effects with medication therapy, a lower risk of systemic side effects, and the fostering of a sense of patient self-efficacy and agency.

Lifestyle Modifications

Lifestyle factors are an essential component of migraine management and can be thought of as one element of prevention. Important lifestyle factors to consider include getting adequate and good-quality sleep, maintaining good hydration, eating well-balanced frequent meals, avoiding alcohol, keeping caffeine to a modest level and at a regular time each morning, and participating in regular physical activity. Intentional stress management is also a necessity for most people with migraine. Dietary interventions have poor evidence for efficacy, but individual patients may find a specific diet helpful. Dietary changes should be considered a form of intervention and assessed with the same rigor as any other preventive treatment.

Herbal and Nutritional Supplements

Several herbal and nutritional supplements have been studied for the preventive treatment of migraine (TABLE 4-5[43-46]), although none are approved by the FDA

KEY POINTS

- American Headache Society guidelines suggest that CGRP monoclonal antibodies may be considered if two traditional (oral or neurotoxin) preventives are not effective or not tolerated.
- OnabotulinumtoxinA, topiramate, and the CGRP monoclonal antibodies have good evidence for prevention of chronic migraine.
- Medication-overuse headache is often treated with a combination of discontinuation of the overused medication and starting preventive medication. OnabotulinumtoxinA and topiramate have the best evidence for prevention in patients with medication overuse.
- Patients with chronic migraine have a higher burden of medical and psychiatric comorbidity and benefit significantly from a multidisciplinary approach.
- Important lifestyle factors to consider in people with migraine include getting adequate and good-quality sleep, maintaining good hydration, eating well-balanced frequent meals, avoiding alcohol, keeping caffeine to a modest level and at a regular time each morning, managing stress, and participating in regular physical activity.

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for treatment of migraine. According to the 2012 AAN/AHS guidelines, the supplements magnesium and vitamin B_2 (riboflavin) and the herb feverfew have Level B evidence for efficacy in prevention of migraine.[47] More recent systematic reviews also supported the efficacy of magnesium and riboflavin, whereas evidence for feverfew was mixed and inconclusive.[43,46,48] Coenzyme Q10 was rated as having Level C evidence. Over-the-counter preparations of various combinations of these supplements are also available.[49] Both magnesium and feverfew have been specifically studied for the acute treatment of migraine aura.[50,51] It may be that these compounds are also helpful for prevention in patients with migraine with aura. Since the 2012 guidelines were published, several studies of other herbal and nutritional supplements have been published. These include melatonin and vitamin D. A clinical trial found that the combination of vitamin D and simvastatin reduced headache days compared to placebo.[52] A small study of the synthetic cannabinoid nabilone demonstrated efficacy in patients with chronic migraine and medication-overuse headache.[53]

Petasites (butterbur) was rated as having Level A evidence for efficacy in the 2012 guidelines. Subsequent evidence found that *Petasites* extracts may contain a hepatotoxic pyrrolizidine alkaloid; although one preparation has not demonstrated causality with liver injury, most headache specialists avoid recommending *Petasites* at this time.[54] If *Petasites* is used, liver function should be checked periodically.

TABLE 4-5 **Herbal and Nutritional Supplements for Prevention of Migraine**

Name	Common dosing	Common side effects	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Magnesium	400-600 mg once daily or 200-300 mg 2 times a day	Diarrhea, nausea	B	Best studied/bioavailable formulations are magnesium oxide, magnesium gluconate/glycinate/aspartate (sometimes sold as chelated magnesium)
Riboflavin (vitamin B_2)	400 mg once daily	Diarrhea, frequent urination, yellow urine discoloration	B	Recent systematic review showed benefit in adults but not children[43]
Coenzyme Q10	300 mg once daily	None reported	C	Level C evidence in 2012 guidelines
Melatonin	3 mg nightly	Sedation, fatigue	None	Recent pediatric trial was positive; randomized controlled trial results in adults have been conflicting[44,45]
Feverfew	50-300 mg once daily	Nausea, bloating; avoid in people with allergies to ragweed or chamomile	B	Recent systematic review found conflicting evidence[46]
***Petasites* (butterbur)**	Use not recommended		A	Not recommended because of risk of hepatotoxicity

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Mind/Body and Behavioral Interventions

Behavioral therapies with good-quality evidence to support efficacy in migraine prevention include cognitive-behavioral therapy, relaxation training, and thermal or electromyographic biofeedback.[55] Several small studies evaluating yoga for migraine prevention were positive.[56] A 2020 clinical trial in India evaluating yoga as an add-on to pharmacologic prevention was also positive.[57] Recent studies have also shown benefit from meditation, particularly mindfulness-based meditation such as mindfulness-based stress reduction.[58] Evidence also supports the combination of pharmacologic and nonpharmacologic treatments. A clinical trial examining cognitive-behavioral therapy or propranolol alone compared to in combination found the greatest reduction in headache days in the combination treatment group.[59] A secondary analysis of this trial suggested that patients with comorbid mood disorders may particularly benefit from the combination of pharmacologic and behavioral or mind/body treatments.[60]

Physical Treatments

Acupuncture is one of the most frequently studied nonpharmacologic interventions for migraine prevention. A 2016 Cochrane Review found that 41% of participants who received acupuncture had at least a 50% reduction in headache frequency compared to 17% in the sham arms.[61] Acupuncture is generally well tolerated and may be of particular interest to patients who prefer to avoid medications. Acupuncture is a heterogeneous modality, with different treatment paradigms and point selection, and studies are often unable to take these differences into account. Studies have also examined and support massage and osteopathic manipulation. Integration of nonpharmacologic treatment into practice is illustrated in CASE 4-3.

NEUROMODULATION

Neuromodulation devices have increasingly been studied for the acute and preventive treatment of migraine, particularly over the past decade.[62,63] Devices are of particular interest because they are noninvasive and do not cause systemic side effects. Use of devices in clinical practice seems largely driven by insurance coverage, as they can be costly and are generally not covered by insurance. The exception is the external trigeminal nerve stimulation device, which is covered by the US Department of Veterans Affairs system and used widely in this setting. In addition to the external trigeminal nerve stimulation device, two other noninvasive neuromodulation devices have been evaluated for the preventive treatment of migraine: a single-pulse transcranial magnetic stimulation device and a noninvasive vagus nerve stimulator.

Preventive use of the external trigeminal nerve stimulation device involves a 20-minute daily session. In a small trial, the active group saw a reduction of 2 headache days monthly, whereas the sham group saw no difference.[64] Subsequent open-label studies have evaluated the external trigeminal nerve stimulation device in patients with chronic and refractory migraine and found modest benefit without serious or limiting side effects.[65,66] The single-pulse transcranial magnetic stimulation device, originally developed for acute treatment of migraine, was evaluated for migraine prevention in an open-label observational study. Participants in the active group delivered four single-pulse transcranial magnetic stimulation pulses twice a day and saw an average of 2.75 fewer migraine days per month than statistically estimated response to placebo.[67]

KEY POINTS

- The herbal and nutritional supplements with the best evidence for migraine prevention are magnesium and riboflavin. Evidence for feverfew has been conflicting.
- *Petasites* (butterbur) is no longer recommended as a preventive because of possible contamination with hepatotoxic alkaloids.
- Behavioral therapies with good evidence for migraine prevention include cognitive-behavioral therapy, relaxation training, thermal or electromyographic biofeedback, and mindfulness meditation.
- Layering behavioral and pharmacologic treatment is more effective than either approach alone, particularly for people with both migraine and mood disorders.
- Acupuncture is a popular nonpharmacologic treatment that has good evidence for use in migraine prevention and is generally well tolerated.
- The decision on whether to use devices for migraine prevention in clinical practice is often driven by cost and access concerns.
- The external trigeminal nerve stimulation device and the single-pulse transcranial magnetic stimulation device have evidence for migraine prevention.

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Other smaller observational studies have also been supportive. Studies of the noninvasive vagus nerve stimulator device for migraine prevention have been negative to date.[63]

Evidence regarding the effectiveness of occipital nerve stimulation for migraine prevention is conflicting, and implanted stimulators also demonstrated a high rate of serious adverse events, including lead migration and infection. It is therefore not favored for migraine prevention at this time.

FUTURE DIRECTIONS FOR PREVENTION

The AAN and AHS are in the process of updating the guidelines for preventive treatment of migraine. This update in the levels of evidence will further inform practice and may alter the order of preference of preventive treatments. As further safety data emerge for the CGRP monoclonal antibodies, these may become more or less preferable to other treatments. Research into the efficacy of

CASE 4-3

A 33-year-old man with an 11-year history of migraine presented to an outpatient neurology clinic to discuss treatment options. He was having about 18 headache days per month, although most of these were mild to moderate. His past medical history included anxiety, multiple environmental and medication allergies, and colitis, and he did not want to try a preventive medication because of concerns about side effects and allergic reactions. In reviewing factors that might be contributing to his headaches, he reported significant work-related stress, poor sleep, and little physical activity. He had never tried a relaxation or mindfulness practice and was interested in learning more about integrative therapies for migraine management. The neurologic examination was normal.

COMMENT

Many patients with migraine are interested in nonpharmacologic treatment, either as the primary migraine treatment modality or in combination with pharmacologic treatments. This patient would benefit from lifestyle management, particularly improving the quality of his sleep. He would be an excellent candidate for cognitive-behavioral therapy for insomnia, which has been shown to reduce headache days in people with migraine and insomnia. A mechanism for managing stress would also be beneficial, which could include biofeedback if locally available, a relaxation or mindfulness practice, or gradually increasing physical activity. Lifestyle changes such as these are often gradual and may require setting modest goals, creatively solving barriers to change, and celebrating incremental gains.

Among integrative interventions for migraine, acupuncture has the best evidence for efficacy. Some patients find craniosacral therapy, massage therapy, or physical therapy helpful, particularly if there is a musculoskeletal contribution to the headache burden. If cost is not a barrier to access, he may find external trigeminal nerve stimulation helpful. This device, which can be used when needed as well as preventively and is completely controlled by the patient, can be particularly helpful for patients with concerns about side effects of preventive treatment.

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devices for preventive treatment of migraine continues and will likely provide more information about who is most likely to benefit. Additionally, an oral daily CGRP receptor small molecule antagonist medication (atogepant) has shown efficacy in phase 3 trials. A preventive trial of another CGRP receptor antagonist, rimegepant, found that dosing every other day modestly reduced monthly headache days.[68] These medications may provide the benefits of CGRP antagonism without the concerns associated with the long half-life of CGRP monoclonal antibodies.

CONCLUSION

Preventive interventions, whether pharmacologic, nonpharmacologic, or a combination of the two, have great capacity to improve the quality of life of people with migraine. Evidence of efficacy of an intervention must be balanced against potential side effects. Patient comorbidities and preferences regarding side effects, mode of administration, efficacy, and other factors should be considered when choosing a preventive medication. The advent of CGRP monoclonal antibodies has broadened the range of options available, and future introductions should continue to fill gaps in treatment. Patient response to preventive treatment can be variable, and patients may need several trials of prevention before finding the most effective one for them.

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Cluster Headache and Other Trigeminal Autonomic Cephalalgias

By Stephanie J. Nahas, MD, MSEd, FAHS, FAAN

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: **The trigeminal autonomic cephalalgias (TACs) are relatively rare, but they represent a distinct set of syndromes that are important to recognize. Despite their unique features, TACs often go undiagnosed or misdiagnosed for several years, leading to unnecessary pain and suffering. A significant proportion of TAC presentations may have secondary causes.**

RECENT FINDINGS: **The underlying pathophysiology of TACs is likely rooted in hypothalamic dysfunction and derangements in the interplay of circuitry involving trigeminovascular, trigeminocervical, trigeminoautonomic, circadian, and nociceptive systems. Recent therapeutic advancements include a better understanding of how to use older therapies more effectively and the identification of new approaches.**

SUMMARY: **TAC syndromes are rare but important to recognize because of their debilitating nature and greater likelihood for having potentially serious underlying causes. Although treatment options have remained somewhat limited, scientific inquiry is continually advancing our understanding of these syndromes and how best to manage them.**

INTRODUCTION

The trigeminal autonomic cephalalgias (TACs) comprise a distinct set of headache diseases typified by shorter-lasting attacks of unilateral intense pain in the trigeminal distribution with ipsilateral cranial autonomic symptoms.[1] Although considered rare by many, their prevalence is almost as high as other diseases that are more readily recognized, such as multiple sclerosis. In fact, these syndromes should be appreciated instantly because of the dramatic nature of recurrent attacks of very severe pain and autonomic features. Despite their distinctive phenotype, diagnostic delays of up to several years, even decades, continue.[2,3] Diagnosis is just the first step, after which an informed and appropriate management plan must be set into motion. In addition, a surprising number of TAC cases have potentially ominous secondary causes, underscoring the need for early identification and proper diagnosis to steer therapy.[4,5]

The classic TAC is cluster headache, also known as suicide headache because of the unfortunate number of people with the disease who ultimately take this

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Dr Nahas serves on advisory boards for Allergan/AbbVie Inc and Zosano Pharma Corporation and as a consultant for Alder BioPharmaceuticals, Inc/Lundbeck; Allergan/AbbVie Inc; Amgen Inc/Novartis AG; Biohaven Pharmaceuticals; Impel NeuroPharma, Inc; Lilly; Nesos Corp (formerly Vorso Corporation); Supernus Pharmaceuticals, Inc; Teva Pharmaceutical Industries Ltd; Theranica Bio-Electronics Ltd; and Zosano Pharma Corporation. Dr Nahas serves on the editorial board of *Current Pain and Headache Reports* and UpToDate, Inc and as a contributing author for the

Continued on page 651

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Nahas discusses the unlabeled/investigational use of medications for the treatment of cluster headache and other trigeminal autonomic cephalalgias, of which only galcanezumab, sumatriptan, and the noninvasive vagus nerve stimulator are approved or cleared by the US Food and Drug Administration for this indication.

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drastic step after concluding that a life of continued pain is not worth living.[6] Other TACs include paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attack (SUNHA) syndromes, and hemicrania continua. All TACs can present in episodic or chronic forms or, in the case of hemicrania continua, remitting or unremitting forms.

The available evidence suggests that the underlying pathophysiology of TAC syndromes is most likely rooted in hypothalamic dysfunction and related effects through hypothalamic connections.[7-9] The interplay of trigeminovascular, trigeminocervical, and trigeminoautonomic reflex alterations with hypothalamic, pituitary, and nociceptive system malfunction could explain much of TAC phenomenology. Secondary causes of TACs often involve pathology affecting the trigeminal root, hypothalamus, pituitary gland, or cavernous sinus, supporting clinicoanatomic theories.

Management of these syndromes is different from that of migraine, despite some overlap in pathophysiology, clinical features, and therapies.[8,10] A few

TABLE 5-1 **Clinical Characteristics That Help to Distinguish Trigeminal Autonomic Cephalalgias and Other Primary Headache Syndromes**

Syndrome	Pain location	Attack duration	Autonomic features	Migrainous features	Exacerbants
Trigeminal autonomic cephalalgias					
Cluster	Unilateral frontal/temporal/periorbital	Minutes to hours	Always	Sometimes	Alcohol, sleep
Paroxysmal hemicrania	Unilateral frontal/temporal/periorbital	Minutes	Always	Sometimes	Neck turning
Short-lasting unilateral neuralgiform headache attack syndromes (SUNHA)	Unilateral V1	Seconds to minutes	Always	Rarely	Cutaneous, thermal, mechanical
Hemicrania continua	Unilateral	Minutes or hours superimposed on baseline pain	Always	Often	Variable
Other primary headache syndromes					
Migraine	Variable, unilateral in 60%	Hours to days	Sometimes	Always	Menses, pregnancy, perimenopause/menopause, stressful life events, strenuous activity, bright/flickering lights
Trigeminal neuralgia	Unilateral (V2-V3 distribution much more often than V1)	Seconds	Rarely	Rarely	Cutaneous, thermal, mechanical
Primary stabbing headache	Variable, but often unilateral frontal/temporal/periorbital	Seconds	Rarely	Rarely	Variable

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important distinctions in the approach to TAC syndromes include greater focus on the possibility of a secondary cause, differing doses or routes of administration of certain therapies, distinct options for first-line therapies, and, in some cases, medication or other approaches that are unique to this spectrum of disease.

WHAT ARE THE TRIGEMINAL AUTONOMIC CEPHALALGIAS?

As the name would imply, TACs are syndromes involving intense pain and autonomic symptoms in a trigeminal distribution, typically in the first division. The TACs are believed to result from dysfunction in the trigeminal and cranial autonomic systems and their connections, modulated by the hypothalamus. These syndromes are distinguished based on clinical features, typical triggers, responsiveness to therapy, and the exclusion of an underlying secondary cause. There are four main categories of TACs: cluster headache, paroxysmal hemicrania, SUNHA, and hemicrania continua. In contrast to migraine, the pain of these syndromes is, by definition, almost universally unilateral, prominently located in the V1 distribution, shorter-lasting (with the exception of hemicrania continua), and more intense. Overshadowing nausea, photophobia, or phonophobia, the predominant associated features are autonomic in nature, such as ptosis, miosis, lacrimation, periorbital edema, rhinorrhea, forehead/facial sweating/flushing, and aural fullness. Other features, including migrainous symptoms and neck pain, can be present but are not listed within diagnostic criteria. Generally speaking, the shorter the name of the syndrome, the longer and less frequent are the attacks of pain throughout the day. Agitation is more specific to cluster headache, the hemicranias respond to indomethacin, and, as the name implies, neuralgiform pain typifies SUNHA. Each TAC may be subcategorized further based on the nature of certain symptoms and their persistence over time. The differential diagnosis of TACs includes not only secondary causes but also other shorter-lasting syndromes, such as trigeminal neuralgia and primary stabbing headache. TABLE 5-1 lists the distinguishing and overlapping features that aid in ascribing the correct diagnosis.

CLUSTER HEADACHE

The exact prevalence of cluster headache is unknown, owing to so many yet-to-be-diagnosed cases, but a meta-analysis from 2008 indicated a 1-year prevalence ranging from 3 per 100,000 to 150 per 100,000 and an estimated lifetime prevalence of 0.12%.[11] Cluster headache accounts for the vast majority of cases in the TAC spectrum (>90%). Historically, cluster headache was considered a disease seen predominantly in men, much in the same way that migraine is considered a disease seen predominantly in women, although, over time, it has become more apparent that the sex difference is not as great as once thought. The estimated male to female ratio has changed from as high as 7:1 to as low as 2:1 to 3:1.[8] In part, this is because of diagnostic error in the past from bias and lack of knowledge. Cluster headache affects people of all ages from childhood through senescence, but peak prevalence is from 20 to 50 years of age. Smoking, passive smoke exposure, head trauma, and genetics are all implicated as risk factors for developing the disease.[8] Cluster headache is increasingly recognized as a source of socioeconomic burden.[12,13]

The pathophysiology of TACs is complex and incompletely understood, which is also true of cluster headache. Theories regarding pathogenesis have

KEY POINTS

- The trigeminal autonomic cephalalgias share some similarity with migraine phenotype, pathophysiology, and therapy but represent a distinct set of syndromes requiring different management.
- The pain of trigeminal autonomic cephalalgias tends to be relatively short and intense, and, by definition, it is accompanied by symptoms reflective of autonomic dysfunction.
- The pathophysiology of trigeminal autonomic cephalalgias is likely linked to dysfunction of the hypothalamus, trigeminally mediated reflexes, and nociception.
- Trigeminal autonomic cephalalgias are distinguished clinically by temporal patterns and combinations of symptoms.

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originated from the clinical features, known secondary causes, functional imaging studies in humans, and animal experiments. For primary cluster headache, the important clinical elements to consider are the trigeminal location of pain, the prominence of autonomic features, and the seasonal/circadian periodicity commonly seen in persons with the disease.[14] This symptomatology invokes a theory that the pain of cluster headache is caused by activation of trigeminal nociception, particularly the first division, along with a logical supposition that cranial autonomic dysregulation also occurs as a result of trigeminal autonomic reflex activation. The periodicity suggests that the process is driven by the hypothalamus.[15] The trigeminal autonomic reflex can be activated peripherally as illustrated by painful stimuli to trigeminal afferents resulting in tearing or lacrimation, an experience most people have at some point in their lives and has been shown in animal models and human experiments. Central activation can occur in the brainstem through the superior salivatory nucleus, which is the origin of cranial parasympathetic autonomic vasodilator fibers. The sphenopalatine ganglion and trigeminal ganglion can influence the activity in this reflex. These effects are mediated by substances such as calcitonin gene-related peptide, pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal peptide, and nitric oxide.[16] It is believed that central activation is what is important to drive cluster headache, particularly via activation of the posterior hypothalamus, which has direct connections to the trigeminal system. Lending credence to this theory is evidence from functional neuroimaging studies demonstrating ipsilateral posterior hypothalamic activation during attacks in humans[17] as well as observations that individuals with cluster headache may have lower levels of testosterone, reduced responses to thyrotropin-releasing hormone, and blunted nocturnal melatonin peaks when in cycle.[18] An abundance of animal modeling data also support such a concept. Given that many secondary cases of cluster headache syndromes are because of pathology involving the hypothalamus, pituitary gland, cavernous sinus, or other structures within these pathways, it seems reasonable to conclude that these are the important anatomic correlates. This principle is in keeping with some of the shared clinical expressions and therapeutic responses between cluster headache and migraine and has spurred the development of unique treatment approaches, such as testosterone[19] and melatonin[20] supplementation, sphenopalatine ganglion or vagus nerve stimulation intended to normalize physiology,[21] and even desensitization strategies with capsaicin.[22] **FIGURE 5-1** depicts our understanding of TAC pathophysiology and its response to therapeutic options.[23]

The clinical manifestations of cluster headache lend themselves to the mnemonic SEAR for recognizing it in contrast to the much more common entity of migraine. The word *sear* itself hearkens to the intense pain that is often described as searing in quality. *S* stands for side-locked, which is the rule rather than the exception; this contrasts with migraine, which, despite the etymology of the term, is bilateral in about 40% of cases. *E* stands for excruciating, as this pain is referred to as the worst known to humankind (indeed, women with cluster headache who have given birth agree that the pain of labor pales in comparison to cluster headache). *A* stands for agitating, a feature almost never seen with migraine, and *R* refers to regularly recurring attacks with circadian and circannual periodicity and predictability, which is very rarely the case with migraine. Also, in contrast to migraine, the attacks

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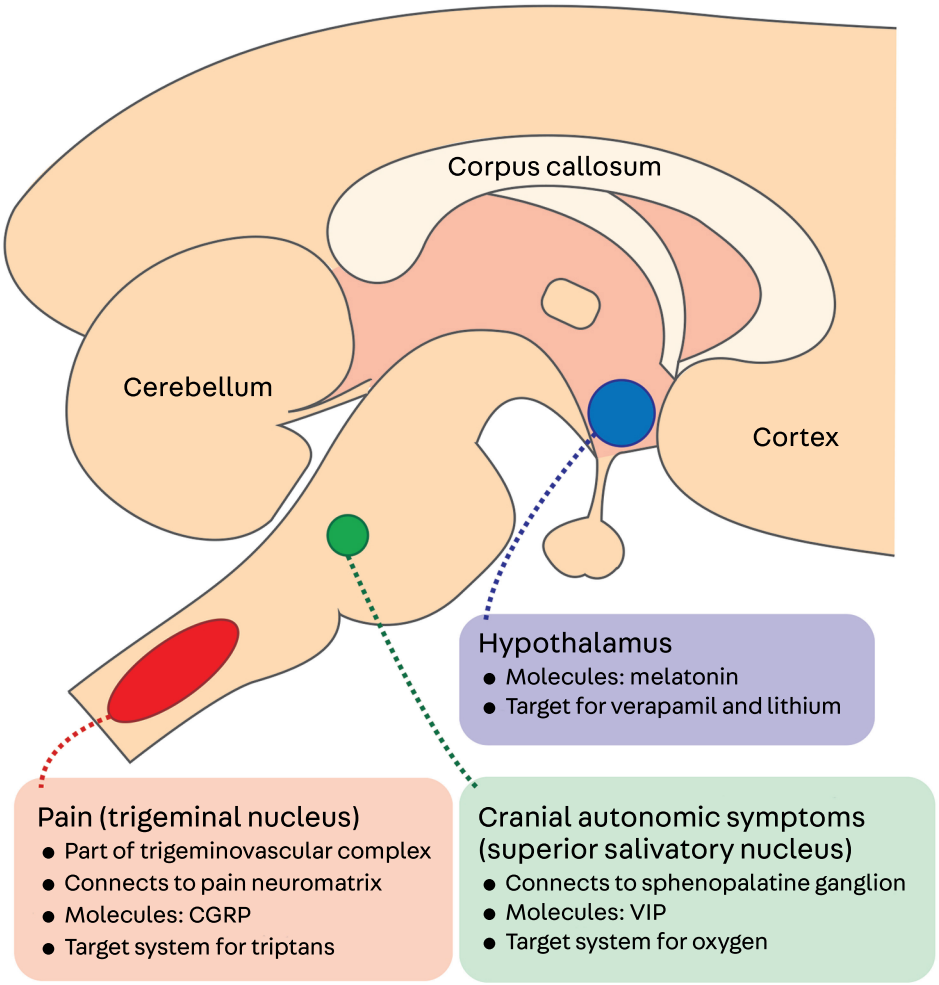

FIGURE 5-1

Pathogenesis of trigeminal autonomic cephalalgias. At least three systems are involved, including the pain system (the trigeminal nerve, trigeminovascular complex, and general pain system called the pain neuromatrix), the cranial autonomic system (the superior salivatory nucleus and sphenopalatine ganglion), and the hypothalamus. Human studies have shown alterations in several molecules, and animal research has suggested that cluster headache medications work on different systems as shown.

CGRP = calcitonin gene-related peptide; VIP = vasoactive intestinal peptide.

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are shorter and autonomic features are more prominent. The diagnostic criteria for cluster headache are shown in TABLE 5-2. Some people with cluster headache experience interictal pain, intermittently or continuously, at varying intensities. This is often referred to as *shadow headache*. The disease is also typified by temporal predictability and periodicity, which is one of the reasons for the name of the disease, with attacks clustering around typical times of day (almost universally soon after sleep onset as well as midmorning, midafternoon, and late evening) and times of year (often spring and fall).[14] Cluster headache can be divided into episodic and chronic forms based on the presence and duration of remission periods between bouts (also known as cycles). Most patients have the episodic form, in which remission periods last at least 3 months annually.

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In most cases, the attacks are always on the same side. For some individuals, the attacks may switch sides between bouts, from one day to the next within a bout, within the same day, or, very rarely, even within the same attack. Cluster headache may evolve over time (CASE 5-1).

Secondary causes of cluster headache are described with increasing frequency in the literature and are encountered with increasing regularity in clinical practice.[4,5] Therefore, it is recommended to obtain neuroimaging (preferably brain MRI with contrast and vessel imaging when clinically indicated) in all patients with TACs, especially when new onset, in the presence of atypical features or if the neurologic examination is abnormal.[24,25] Other studies (eg, laboratory investigation and lumbar puncture) are not usually helpful except in certain cases, such as when suspicion of a pituitary abnormality or disorder of CSF composition, volume, or pressure exists. TABLE 5-3 lists selected vascular and nonvascular secondary causes or mimics of cluster headache syndromes.

Cluster headache therapy involves acute, transitional, and maintenance approaches. For acute treatment of attacks to be effective, the onset of action must be rapid. This means inhaling or injecting medication or using neurostimulation. Transitional treatment is intended to hasten the resolution of the current cluster bout. Most commonly, this is achieved with corticosteroids. The goal of maintenance treatment is to reduce the frequency and intensity of cluster headache symptoms until the cycle ends. The American Headache Society has issued evidence-based guidelines with respect to such therapies (TABLE 5-4).[26]

TABLE 5-2 ***ICHD-3* Diagnostic Criteria for Cluster Headache[a]**

Cluster headache

- **A** At least five attacks fulfilling criteria B-D
- **B** Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15-180 minutes (when untreated)[b]
- **C** Either or both of the following:
  - **1** At least one of the following symptoms or signs, ipsilateral to the headache:
    - **a** Conjunctival injection and/or lacrimation
    - **b** Nasal congestion and/or rhinorrhea
    - **c** Eyelid edema
    - **d** Forehead and facial sweating
    - **e** Miosis and/or ptosis
  - **2** A sense of restlessness or agitation
- **D** Occurring with a frequency between one every other day and eight per day[c]
- **E** Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2018 International Headache Society.

[b] During part, but less than half, of the active time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

[c] During part, but less than half, of the active time-course of cluster headache, attacks may be less frequent.

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CASE 5-1

A 29-year-old man presented with a past history of nondescript headaches that had started around puberty, which were responsive to ibuprofen. At around age 15, he saw a neurologist, who ordered an MRI of the brain and told him it was normal. Age 18, he saw another neurologist because of increasing intensity and frequency of headache attacks with new symptoms. He described localized pain on either side of the head accompanied by anxiety, restlessness, and ipsilateral rhinorrhea and lacrimation. Attacks lasted about 2 hours regardless of whether or not he took ibuprofen. The timing of the attacks had no specific pattern. A brain MRI was repeated and again yielded normal results. Oral sumatriptan was helpful to manage his pain.

Over time, he noted that in spring and fall, he would have several weeks of daily attacks occurring up to 3 times a day, and he would be mostly pain free between these periods of time. By age 27, oral sumatriptan was no longer fully effective, and he was experiencing three to four cycles of these attacks per year.

He was diagnosed with cluster headache, sumatriptan was changed from oral to injectable, and he was instructed to take a tapering course of oral prednisone at the start of bouts, which was most effective when started early. At age 29, he reported that his cycles would build up slowly over a few weeks and peak with three to four attacks per day for a few more weeks, then gradually the symptoms would fade over the course of a few more weeks. He reported the pain of his right-sided attacks to be most intense in the eye and the pain of his left-sided attacks most intense in his jaw. On any given day during any given bout, he could have attacks on either side, but he never experienced side-switching during an attack. He acknowledged concomitant anxiety; restlessness; and ipsilateral congestion, tearing, and ptosis. Attacks would resolve completely within 10 minutes of sumatriptan injection. Some attacks were mild and required no medication, resolving spontaneously within 2 hours. Oral prednisone usually stopped a bout within 10 days.

COMMENT

This presentation is consistent with a diagnosis of cluster headache. Some individuals with cluster headache have an antecedent history of headache not clearly of cluster phenotype, sometimes for many years before the diagnosis becomes clear. This patient also represents a small subset of individuals with side-switching cluster headache. Enhancements to the plan of care for this patient could include the addition of high-flow oxygen to manage acute attacks and additional treatment with verapamil, lithium, or galcanezumab at the start of bouts to reduce the intensity and frequency of attacks and hasten the cessation of the cycle.

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TABLE 5-3 Some Secondary Causes or Mimics of Trigeminal Autonomic Cephalalgias

Vascular

- Cervical arterial dissection
- Intracavernous carotid artery thrombosis
- Carotid-cavernous sinus fistula
- Cerebral venous or cavernous sinus thrombosis
- Subclavian steal
- Lateral medullary infarction

Nonvascular

- Glaucoma
- Sinusitis (especially sphenoid)
- Trigeminal nerve root compression
- Cavernous sinus metastasis
- Giant meningioma
- Pituitary tumor
- Clival epidermoid
- Idiopathic intracranial hypertension

TABLE 5-4 Evidence-based Guidelines for the Treatment of Cluster Headache From the American Headache Society[a]

	Acute	Preventive
Level A use	Subcutaneous sumatriptan, zolmitriptan nasal spray, 100% oxygen	Suboccipital steroid injection
Level B use	Sumatriptan nasal spray, oral zolmitriptan	Zucapsaicin nasal spray (not currently available in the United States)
Level C use	Lidocaine nasal spray, subcutaneous octreotide	Lithium, verapamil, warfarin, melatonin
Level A do not use	None	None
Level B do not use	None	Sodium valproate, sumatriptan, deep brain stimulation
Level C do not use	None	Cimetidine/chlorpheniramine, misoprostol, hyperbaric oxygen, candesartan
Level U	Dihydroergotamine nasal spray, somatostatin, prednisone	Frovatriptan, intranasal capsaicin, nitrate tolerance, prednisone

[a] Data from Robbins MS, et al, Headache.[26]

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The only US Food and Drug Administration (FDA)–approved medication for the acute management of cluster headache attacks is subcutaneous sumatriptan. Commercially available doses are 3 mg, 4 mg, and 6 mg, and the maximum recommended daily dose is 12 mg. The only FDA-cleared device for the acute management of attacks is noninvasive vagus nerve stimulation, which is cleared to treat pain associated with episodic cluster headache in adults. Evidence-based acute therapies include oxygen, intranasal medications (sumatriptan, zolmitriptan, dihydroergotamine, lidocaine, capsaicin), and IV/IM dihydroergotamine. A microneedle patch zolmitriptan delivery system is in development. A few principles should be kept in mind when using oxygen therapy: (1) it must be delivered as 100% oxygen via nonrebreather mask at a rate of 10 to 15 liters per minute, (2) the patient should be sitting down and bent forward at the waist for better results, (3) oxygen should not be inhaled for more than 15 minutes without interruption, and (4) all incendiary sources must be kept distant from oxygen both while in use and while in storage.[27]

Common transitional strategies include a tapering course of oral corticosteroids, single or repeated boluses of IV corticosteroids, or suboccipital corticosteroid injection (usually with an anesthetic such as lidocaine).[28-31] The most recent evidence for oral corticosteroids supports the use of oral prednisone at a starting dose of 100 mg for 5 days followed by 3 days each of doses at 20-mg decrements.[32] Some clinicians may opt for differing dosing/duration or an alternative corticosteroid at a comparable dose, but the evidence for such practices is weaker. Less evidence exists for IV corticosteroids, although they are sometimes used in refractory cases. Randomized controlled trials support the use of ipsilateral suboccipital steroid injection combined with an anesthetic such as lidocaine. Methylprednisolone, triamcinolone, and dexamethasone are the most commonly used corticosteroids for this purpose. It should be noted that injection of corticosteroids into tissues carries a risk of tissue necrosis.[33] This risk might be lower when using a transparent corticosteroid solution lacking particulate material (eg, dexamethasone).

No medications have been approved by the FDA specifically for the preventive treatment of cluster headache. Galcanezumab, a monoclonal antibody targeting calcitonin gene-related peptide, is FDA approved for the treatment of episodic cluster headache in adults, although no clear specification has been made for preventive treatment. Galcanezumab 300 mg subcutaneously administered to patients with episodic cluster headache soon after the start of a bout demonstrated statistically significant and clinically meaningful reduction in the number of attacks over 3 weeks compared to placebo in a randomized controlled double-blind study (8.7 compared to 5.2, P=.036).[34] The same noninvasive vagus nerve stimulation device the FDA cleared for acute use in adults with episodic cluster headache is also FDA cleared for adjunctive use in the preventive treatment of cluster headache in adults. These decisions were rendered between July 2017 and July 2019. The scientific literature supports the use of daily oral medication for cluster headache prevention, with the strongest evidence being for verapamil[35] and lithium.[36] Experienced providers report better results with immediate-release verapamil as opposed to controlled-release preparations. A typical starting dose is 40 mg or 80 mg 3 times a day, escalated rapidly as tolerated to effect, with average daily doses often approaching, and sometimes exceeding, 400 mg/d. Before initiation and periodically thereafter, monitoring for the presence or

KEY POINTS

- **Cluster headache attacks must be addressed with rapid-onset therapies (eg, inhaled or injected), and, since attacks can be frequent, toxicity from repeated treatments must be considered.**
- **Corticosteroids (administered orally, via suboccipital injection, or, less commonly, intravenously) are instrumental as transitional therapy in cluster headache.**
- **Episodic cluster headache should be managed with maintenance therapy only during bouts, not continuously without interruption.**

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development of first-degree atrioventricular block via ECG is recommended.[37] Lithium titration is best guided by serum levels and tolerability. Anecdotally, some clinicians also find the anticonvulsants topiramate and gabapentin to be useful, but evidence is lacking. It is not recommended to use sodium valproate based on negative evidence. Most specialists agree that preventive treatment for episodic cluster headache should be continued until 2 weeks after the complete cessation of cluster symptoms and then discontinued until needed again for the next bout to prevent tachyphylaxis, as no evidence exists that such therapies can prevent the onset of the subsequent attack period.

Cluster headache in children is rarely recognized but does occur, with cases reported in children as young as 2 years of age. A survey of adults with cluster headache revealed that 22% of them noted symptom onset before age 18. Nothing is approved or cleared by the FDA for the treatment of children with cluster headache. Children are treated similarly to adults, with weight-based dosing adjustments when necessary.[38]

Some approaches have shown promise but are not readily available or recommendable for various reasons. A small implantable sphenopalatine ganglion stimulator became cleared for use in Europe based on positive clinical trial data but has faltered in the United States because of regulatory and financial barriers.[39-41] Peripheral sphenopalatine ganglion blockade can be useful,

TABLE 5-5 ***ICHD-3* Diagnostic Criteria for Paroxysmal Hemicrania[a]**

Paroxysmal hemicrania

A At least 20 attacks fulfilling criteria B-E

B Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2-30 minutes

C Either or both of the following:

- **1** At least one of the following symptoms or signs, ipsilateral to the headache:
  - **a** Conjunctival injection and/or lacrimation
  - **b** Nasal congestion and/or rhinorrhea
  - **c** Eyelid edema
  - **d** Forehead and facial sweating
  - **e** Miosis and/or ptosis
- **2** A sense of restlessness or agitation

D Occurring with a frequency of >5 per day[b]

E Prevented absolutely by therapeutic doses of indomethacin[c]

F Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] During part, but less than half, of the active time-course of paroxysmal hemicrania, attacks may be less frequent.

[c] In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

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although evidence is lacking and methods for performing the procedure are not uniformly accepted.[42,43] Experimental treatment with deep brain stimulation has been effective for a small number of individuals but generally is considered too dangerous to make the risk worth the benefit.[44,45]

Physicians caring for patients with cluster headache should be aware that some of them may resort to using hallucinogens such as psylocibin and D-lysergic acid (chemically related to ergots) to treat their intractable attacks. Although the efficacy of such hallucinogens is challenging to study, trials are under way to properly assess the efficacy and safety of hallucinogens, including regimens with low or no psychoactivity, in such a population.[46] Owing to our incomplete understanding of cluster headache and a relative paucity of safe and effective therapeutic options, the cluster headache community has become more involved in scientific research and advocacy, particularly with respect to controversial therapies such as hallucinogens, as illustrated by a large survey regarding medication and substance use.[47] A recent analysis of free-text responses to this survey revealed mixed beliefs and attitudes toward hallucinogens, in particular among persons with cluster headache, ranging from serious concerns about psychoactive effects or lack of efficacy to extraordinary gratitude for access to such substances, which they feel have been life-changing for them.[48]

PAROXYSMAL HEMICRANIA

Paroxysmal hemicrania attacks may be conceptualized as shorter-lasting cluster headache attacks that affect women more often than men, are associated with circadian periodicity, and respond exquisitely to indomethacin. The diagnostic criteria for paroxysmal hemicrania are listed in TABLE 5-5. Unlike cluster headache, attacks of paroxysmal hemicrania tend not to be triggered by alcohol but rather can be triggered by neck movements. Paroxysmal hemicrania is believed to account for about 5% of all TACs.[49] As with cluster headache, paroxysmal hemicrania can be divided into episodic and chronic forms based on the duration of remission periods, if present. If such remissions last at least 3 months annually, the disorder is defined as episodic. In contrast to cluster headache, in which most people have the episodic form, about 80% of paroxysmal hemicrania is chronic. It was first described as a clinical entity in 1974, when only chronic cases were as yet identified. By 1987, episodic forms were also reported. The pathophysiology of paroxysmal hemicrania is believed to be similar to that of cluster headache with an important distinction: functional imaging studies indicate hypothalamic dysfunction contralateral, rather than ipsilateral, to the expression of pain and autonomic features.[50]

The criterion for indomethacin responsiveness is peculiar but important. It is also somewhat controversial, as many cases have been described that otherwise meet the definition of paroxysmal hemicrania on all other criteria. Furthermore, indomethacin is contraindicated in some patients, making the established diagnostic criteria potentially impossible to ascribe. Understanding how to use indomethacin safely and effectively is critical in managing this problem. Like all nonsteroidal anti-inflammatory drugs, indomethacin carries risks of bleeding, gastritis/ulcer, renal damage, vascular events, and drug interactions, all of which must be considered before initiating a trial and some of which may require additional baseline testing to assess for risks of adverse events (eg, renal function, coronary status) in appropriate patients before a trial is undertaken.[51]

KEY POINTS

- Paroxysmal hemicrania is clusterlike, with a female predominance, greater attack frequency, less periodicity, different triggers, and, above all else, exquisite response to indomethacin.
- Indomethacin is most useful for paroxysmal hemicrania and hemicrania continua, requires proper titration, and monitoring for prolonged use for its potential adverse effects.
- If indomethacin is contraindicated or intolerable for patients with paroxysmal hemicrania and hemicrania continua, alternative therapies are available.
- If a chronic primary headache diagnosis is unclear, consider an indomethacin trial, particularly if there are no contraindications, and if cranial autonomic symptoms are present.
- Short-lasting unilateral neuralgiform headache attacks are like V1 trigeminal neuralgia, with autonomic features and no refractory period to cutaneous triggering (when present); look for pituitary pathology and vascular loop compression in all cases, repeatedly in refractory cases.
- Hemicrania continua is increasingly recognized as a mimic of chronic migraine.
- In many cases, syndromic overlap exists in the presentation of trigeminal autonomic cephalalgias, and treatment should be tailored initially to the entity with the closest fit based on diagnostic criteria.

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Consensus opinion dictates a starting dose of 25 mg 3 times a day for at least 3 days before escalating to 50 mg 3 times a day for 3 to 10 days before considering any further escalation. Response is usually rapid and robust, but some patients will respond more slowly and require higher doses. The maximum recommended dose is 225 mg/d in divided doses, although some experts advocate doses as high as 300 mg/d and report that response may take up to 4 weeks to develop. If indomethacin is to be maintained long term, caution and monitoring for adverse events are advised and the lowest effective dose should be targeted. It may be judicious to coprescribe a proton pump inhibitor to prevent gastritis/ulcer, and the preferred medication is pantoprazole. Weak evidence also exists for combination or alternative therapy with melatonin[20] or *Boswellia serrata*,[52] both of which are associated with fewer potential adverse events and are rarely contraindicated. The mechanism by which these treatments work remains elusive. It is interesting to note that indomethacin, melatonin, and serotonin all share similarity in chemical structure, although this could be purely coincidental, and serotonergic agents are generally ineffective in indomethacin-responsive syndromes.

When indomethacin is ineffective, poorly tolerated, or contraindicated, celecoxib, verapamil, topiramate, gabapentin, onabotulinumtoxinA, acetazolamide, or subcutaneous or intranasal triptans/dihydroergotamine can be considered as alternatives, but the evidence for these therapies is very weak.[53]

TABLE 5-6 ***ICHD-3* Diagnostic Criteria for Short-Lasting Unilateral Neuralgiform Headache Attacks**[a]

Short-lasting unilateral neuralgiform headache attacks

A At least 20 attacks fulfilling criteria B-D

B Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, series of stabs, or in a sawtooth pattern

C At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:

- **1** Conjunctival injection and/or lacrimation
- **2** Nasal congestion and/or rhinorrhea
- **3** Eyelid edema
- **4** Forehead and facial sweating
- **5** Forehead and facial flushing
- **6** Sensation of fullness in the ear
- **7** Miosis and/or ptosis

D Occurring with a frequency of at least one a day[b]

E Not better accounted for by another *ICHD-3* diagnosis

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[b] During part, but less than half, of the active time-course of short-lasting unilateral neuralgiform headache attacks, attacks may be less frequent.

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Indomethacin may also have a nonspecific degree of efficacy in a variety of refractory headache syndromes, regardless of the true underlying diagnosis.

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHE ATTACKS

Consider SUNHA as being similar to V1 trigeminal neuralgia but with autonomic features. The diagnostic criteria for SUNHA are listed in TABLE 5-6. The prevalence remains unclear, as this entity was only first described in 1978 and not studied more fully until around the turn of the century. The disorder often remains unrecognized, and patients remain undiagnosed. As with cluster headache and paroxysmal hemicrania, SUNHA can be divided into episodic and chronic forms based on the duration of remission periods, if present. If such remissions last at least 3 months annually, the disorder is defined as episodic. The majority of SUNHA syndromes are chronic in nature. The pathophysiology of SUNHA is believed to stem from trigeminal nerve irritation combined with hypothalamic dysfunction. Functional imaging studies demonstrate variable hypothalamic activation.[54,55] In addition, and akin to trigeminal neuralgia,

CASE 5-2

A 42-year-old man reported waking one day 6 years prior with "mini-explosions" in his head. He described constant, dull, right-sided headache with superimposed mini-explosions of 9 out of 10 pain shooting to his right ear, eye, or forehead. The right eye would sometimes tear. He noted that brushing his hair could trigger attacks. These episodes lasted 1 to 3 minutes and occurred up to 50 times per day, with a steady worsening over the years. He was very sensitive to loud noise. He denied any precipitating event. Propranolol, gabapentin, amitriptyline, topiramate, indomethacin, verapamil, occipital nerve blocks, lamotrigine, carbamazepine, and onabotulinumtoxinA were not effective. IV lidocaine helped for weeks to months, but the symptoms would always return. MRI of the brain, magnetic resonance angiography (MRA) of the head, and MRI of the cervical spine completed in the first year after symptom onset were all unremarkable.

Imaging was repeated with special attention to the pituitary gland and brainstem. This disclosed a vascular loop compressing the ipsilateral trigeminal nerve root. He underwent vascular decompression surgery, came off all medications, and remained pain free.

COMMENT

This is an unusual case that most closely fits the definition of short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Migraine symptoms and continuous underlying pain are atypical but do not exclude the diagnosis. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and SUNA tend to be quite refractory. A number of cases are associated with pituitary abnormalities or trigeminal nerve or root entry zone compression. In some cases, especially progressive ones, these anomalies may not be visible initially or may be missed if not specifically sought.

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vascular loop compression of the ipsilateral trigeminal nerve is identified in some cases, and surgical decompression or ablation has been reported to be effective.[56] Neuroimaging is recommended to assess for vascular loop compression and for pituitary abnormalities, both of which (but especially the latter) are reported at surprisingly high rates in conjunction with SUNHA.[57] Also similar to trigeminal neuralgia, a number of cutaneous, mechanical, and thermal triggers are described, but in contrast to trigeminal neuralgia, usually no refractory period is seen. Alcohol typically has no effect on this entity. Of course, exceptions to these observations exist and make the spectrum all the more intriguing.

SUNHA is further divided into short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). These two entities were listed separately in prior iterations of the *ICHD* but now reside under SUNHA with additional detail added to the criteria. In SUNCT, both conjunctival injection and tearing are present, whereas in SUNA, one of the two or neither are. **CASE 5-2** illustrates a somewhat unusual presentation consistent with SUNA. Further study is needed to determine the importance and utility of making this distinction as it may be purely phenotypic.

Since attacks are so short, medical therapy is preventive in nature, similar to in trigeminal neuralgia. However, response to medication is variable and usually incomplete. The best available evidence is for lamotrigine, followed by an assortment of therapies used for trigeminal neuralgia and other syndromes (eg, oxcarbazepine, topiramate, duloxetine, carbamazepine, gabapentin, pregabalin,

TABLE 5-7 ***ICHD-3* Diagnostic Criteria for Hemicrania Continua[a]**

Hemicrania continua

A Unilateral headache fulfilling criteria B-D

B Present for >3 months, with exacerbations of moderate or greater intensity

C Either or both of the following:

- **1** At least one of the following symptoms or signs, ipsilateral to the headache:
  - **a** Conjunctival injection and/or lacrimation
  - **b** Nasal congestion and/or rhinorrhea
  - **c** Eyelid edema
  - **d** Forehead and facial sweating
  - **e** Miosis and/or ptosis
- **2** A sense of restlessness or agitation, or aggravation of the pain by movement

D Responds absolutely to therapeutic doses of indomethacin[b]

E Not better accounted for by another *ICHD-3* diagnosis

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[b] In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased if necessary up to 225 mg daily. The dose by injection is 100-200 mg. Smaller maintenance doses are often employed.

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mexiletine). Peripheral nerve blockade with local anesthetic is reported to be helpful to varying degrees. IV lidocaine can be useful in patients with refractory attacks; this is usually administered in the inpatient setting with continuous telemetry cardiac monitoring.[56]

HEMICRANIA CONTINUA

Hemicrania continua is typified by constant unilateral baseline pain with superimposed attacks of more intense pain accompanied by autonomic features. The diagnostic criteria for hemicrania continua are listed in TABLE 5-7. A foreign body sensation in the ipsilateral eye and stabbing pains are very common. Migraine features are not unusual, which can make it difficult to distinguish from chronic migraine. The true prevalence is unknown, as the entity can be particularly challenging to diagnose (CASE 5-3). Functional MRI (fMRI) studies demonstrate contralateral hypothalamic activation, as with paroxysmal hemicrania,[58] and ipsilateral dorsal rostral pons activation, as can be seen in migraine.[59] As with paroxysmal hemicrania, first-line treatment is indomethacin, and responsiveness to it is a criterion for diagnosis. When indomethacin is contraindicated or not tolerated, a similar approach to that used in paroxysmal

CASE 5-3

A 34-year-old woman presented with very severe headache attacks for about 6 months, occurring up to 7 times per day and around the same times each day. They usually lasted 5 to 10 minutes but could go on for 30 minutes. The pain was mostly in and around the right eye and forehead and felt as if someone were drilling into her head. Her right eye drooped, turned red, watered profusely, and had a small pupil with the attacks. Sometimes the right side of her face looked puffy during attacks. Most days, she had continuous dull pain between these discrete attacks. Some days, she also experienced light and sound sensitivity. She also reported some periods of complete symptom freedom at random for 3 to 5 days at a time. She tried acetaminophen and ibuprofen, but they did not help. She reported no other medical conditions and used no medications. Her general medical and neurologic examination was normal.

COMMENT

This woman's presentation has features of migraine, cluster headache, paroxysmal hemicrania, and hemicrania continua. Strictly on the basis of diagnostic criteria, the best fit is hemicrania continua, remitting subtype. All trigeminal autonomic cephalalgia presentations should be investigated with neuroimaging (MRI brain with contrast is preferred), especially in cases of recent onset or with unusual features. Particular attention should be directed to the pituitary gland, hypothalamus, cavernous sinuses, trigeminal roots, and surrounding structures, as secondary cases in this spectrum of disease are often due to pathology in these locations. In the meantime, the most reasonable therapeutic approach would be to initiate a trial of oral indomethacin first, followed by other strategies for cluster headache and migraine if this approach is unsuccessful.

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hemicrania may be employed, again with weak evidence. Hemicrania continua is subdivided not into episodic or chronic forms but rather into remitting or unremitting subtypes based on the duration of pain-free intervals, if present. The unremitting subtype is defined as daily/continuous pain for at least 1 year with any remissions lasting under 24 hours.

CONCLUSION

TAC syndromes are relatively rare in the spectrum of headache disease, but it is of great importance to recognize them because of their debilitating nature, socioeconomic burden, and greater likelihood for having potentially serious underlying causes. TABLE 5-8 summarizes the key clinical features of and first-line therapies for these syndromes. Although treatment options have remained somewhat limited, scientific inquiry is continually advancing our understanding of these syndromes and how best to approach and manage them with both old and new therapies. Strengthening alliances between the medical and patient communities will help lead to further successes in these most terrible of all headache diseases. For further insights into the struggle and desperation experienced by people living with cluster headache, see the eye-opening article whose title includes this candid quote from a patient: "You will eat shoe polish if you think it would help."[48]

TABLE 5-8 **Clinical Characteristics Distinguishing the Trigeminal Autonomic Cephalalgias and First-line Therapies Used for Them**

Disease	Attack duration	Attack frequency	Sex ratio (F:M)	Acute treatment	Preventive/bridge treatment
Cluster headache	15-180 min	Every other day to eight per day	1:2 to 1:7 (older studies show greater male predominance)	Oxygen, subcutaneous sumatriptan, nasal spray sumatriptan or zolmitriptan, noninvasive vagus nerve stimulation	Suboccipital steroid injection, oral prednisone taper, verapamil, lithium, galcanezumab, noninvasive vagus nerve stimulation
Paroxysmal hemicrania	2-30 min	1-40 per day	2:1 to 3:1	N/A (attacks too short)	Indomethacin
Short-lasting unilateral neuralgiform headache attack syndromes (SUNHA)	1-600 sec	Dozens to hundreds per day	1:1.5	N/A (attacks too short)	Lamotrigine, topiramate, gabapentin, indomethacin (in some patients)
Hemicrania continua	Continuous pain with superimposed attacks lasting minutes to days	Up to dozens per day	2:1	N/A (superimposed exacerbations too short)	Indomethacin

N/A = not applicable.

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DISCLOSURE

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Other Primary Headache Disorders

By Jonathan H. Smith, MD, FAHS

ABSTRACT

PURPOSE: This article provides an overview of a diverse group of primary headache disorders that are categorized in the *International Classification of Headache Disorders, 3rd Edition* (*ICHD-3*), as "other primary headache disorders." This article provides clinicians with a distilled understanding of the diagnoses and their epidemiology, pathophysiology, and management.

RECENT FINDINGS: Cough-induced headache requires neuroimaging to exclude posterior fossa pathology and recently has been reported as a common symptom in patients with CSF-venous fistula. Clinical overlap is observed between patients with primary exercise headache and primary headache associated with sexual activity. Patients with recurrent thunderclap headache associated with sexual activity should be presumed to have reversible cerebral vasoconstriction syndrome until proven otherwise. De novo external-pressure headache is a common sequela among health care workers using personal protective equipment during the COVID-19 pandemic. New daily persistent headache is an important mimicker of chronic migraine or chronic tension-type headache and is distinguished by a daily-from-onset progression of persistent headache; a treatment-refractory course is often observed, and early involvement of a multidisciplinary team, including a psychotherapist, is advised.

SUMMARY: Patients with primary headache disorders that are classified as "other primary headache disorders" have presentations with unique diagnostic and management considerations. The disorders are highly recognizable, and an appreciation of the diagnoses will aid clinicians in providing safe and effective care for patients presenting with headache.

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Dr Smith discusses the unlabeled/investigational use of medications for the treatment of primary headache disorders, none of which are approved by the US Food and Drug Administration.

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INTRODUCTION

The category of "other primary headache disorders" in the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) includes several unrelated diagnoses.[1] It is important for neurologists to be familiar with this group because the headache diagnoses in this category frequently prompt evaluation for secondary causes (eg, posterior fossa lesion in suspected primary cough headache), are often important mimickers of chronic migraine (eg, new daily persistent headache), and are often associated with particular treatment considerations. This article provides a framework for a clinical approach to and management of this diverse category of headache disorders, which are distinct and highly recognizable with an

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appropriate history (FIGURE 6-1). The specific diagnostic criteria for these disorders can be found on the website of the International Headache Society (ichd-3.org),[2] which can be easily referenced during a patient encounter.

HEADACHES TRIGGERED BY PHYSICAL ACTIVITIES

Primary headaches triggered by specific physical activities (eg, cough, exertion, and sexual activity) are recognized as idiopathic disorders that require a diagnostic evaluation. A history of an ongoing headache that is intensified by a Valsalva maneuver is not a red flag and is consistent with meningeal sensitization as part of the migraine biology. A headache initially triggered by a Valsalva maneuver, however, is a red flag that mandates at the minimum MRI of the brain. Therefore, clinical distinction must be made between headache that is triggered by a Valsalva maneuver (a red flag) and headache that is aggravated by a Valsalva maneuver (typical of migraine). Overall, this subset of provoked headaches is thought to be uncommon in the general population, with cough headache the most likely to be encountered.[3] Cough headache is a distinct pathophysiologic entity, whereas exercise and sexual headaches overlap.[3]

Primary Cough Headache

The diagnosis of primary cough headache, previously known as benign cough headache, requires at least two headache episodes brought on by and occurring only with coughing, straining, or another Valsalva maneuver (eg, laughing or weightlifting). The headache must be abrupt in onset and 1 second to 2 hours in

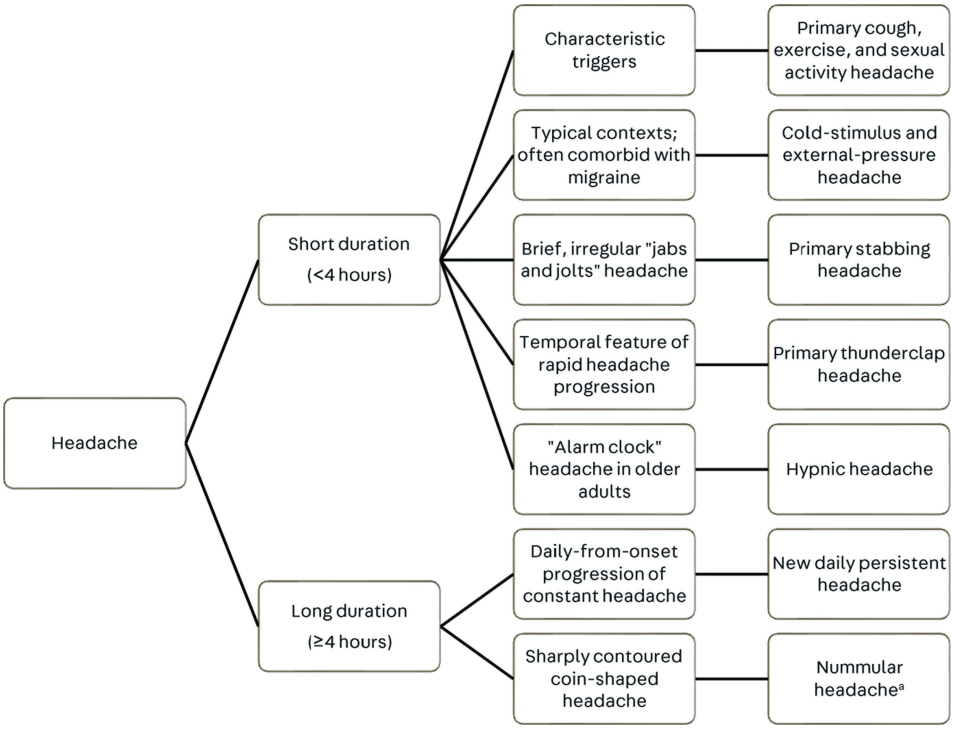

FIGURE 6-1
Overview of other primary headache disorders.
[a] The duration of nummular headache ranges from seconds to days.

KEY POINTS

- Clinical distinction must be made between headache that is triggered by a Valsalva maneuver (a red flag) and headache that is aggravated by a Valsalva maneuver (typical of migraine).
- In nearly two-thirds of patients, a history of cough-induced headache may indicate a posterior fossa lesion, most often a Chiari malformation type I.
- Although not part of the diagnostic criteria for primary cough headache, the disorder classically responds to treatment with indomethacin.
- Unlike migraine, primary exercise headache often has a short duration and generally does not have typical migraine features apart from a throbbing pain character.
- Among older adults at risk for coronary artery disease, cardiac angina may present with an exertional headache (termed *cardiac cephalalgia*).
- Primary exercise headache exists as a self-limited disorder in the majority of patients.
- Recurrent thunderclap headaches associated with sexual activity should be presumed to be reversible cerebral vasoconstriction syndrome until proven otherwise. A patient with an initial presentation of headache associated with sexual activity should be evaluated for the possibility of subarachnoid hemorrhage.

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duration (median duration is typically seconds). As with other primary headache disorders, the diagnosis mandates exclusion of other causes. In nearly two-thirds of patients, a history of cough-induced headache may indicate a posterior fossa lesion, most often a Chiari malformation type I.[3] Cough headache may be symptomatic of spontaneous intracranial hypotension, in which a radiographic Chiari-like lesion may be observed. Headache triggered by the Valsalva maneuver was commonly seen in a series of patients with intracranial hypotension secondary to CSF-venous fistula.[4] Whereas all patients with cough-induced headache require neuroimaging, those found to have a symptomatic etiology are, in general, more likely to have longer-duration headaches, occipital headaches, or posterior fossa symptoms or signs.

Primary cough headache is thought to be common (prevalence of about 1% in population-based studies and in specialty clinic populations).[3,5] The disorder occurs most often in older adults (average age at onset, 60 years), and one series reported a female predominance.[3]

The pathophysiology of primary cough headache is not well understood. A compensatory caudal flow of CSF that occurs after cough buffers the transient increase in intracranial pressure. A lesion at the foramen magnum, such as a Chiari malformation, may disrupt this mechanism and result in headache.[6] Patients with primary cough headache have a more crowded posterior fossa space.[7]

Various Valsalva maneuvers (eg, laughing) may precipitate the headache, so the disorder can be intrusive for patients. Because the headache is too brief to be treated acutely, prevention is fundamental to therapy. Treating the cough may be sufficient in some patients. Although not part of the diagnostic criteria for primary cough headache, the disorder classically responds to treatment with indomethacin (reported effective total daily dosing 50 mg to 200 mg). The dosage of indomethacin should be tapered periodically because spontaneous remission may occur. Other helpful but less consistent pharmacotherapies include topiramate, acetazolamide, and propranolol. High-volume lumbar puncture has been reported to result in sustained remission in a minority of patients, despite normal opening pressure measurement.[8] Noninvasive vagus nerve stimulation has been noted to be effective in a patient with indomethacin-responsive primary cough headache.[9]

Primary Exercise Headache

The diagnosis of primary exercise headache (previously termed *exertional headache*) requires at least two headache episodes brought on by and occurring only during or after strenuous physical exercise. The duration of the headache is less than 48 hours (sometimes <5 minutes). In about 50% of patients, primary exercise headache is comorbid with migraine, which may also be triggered by exercise. However, unlike migraine, primary exercise headache often has a short duration and generally does not have typical migraine features apart from a throbbing pain character.[10] Further, headache precipitated by sustained strenuous exertion (eg, weightlifting) would not be consistent with migraine. Primary exercise headache is most often bilateral and throbbing and is more likely to occur during hot weather and at higher altitudes.[1]

The diagnosis of primary exercise headache necessitates exclusion of many important secondary causes. Neurovascular imaging of the head and neck is important to rule out cervical artery dissection, intracranial vascular malformations (including aneurysmal rupture), and cerebral venous

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thrombosis.[11] Among older adults at risk for coronary artery disease, cardiac angina may present with an exertional headache (termed *cardiac cephalalgia*).[12] Similar to other headaches precipitated by a Valsalva maneuver, disorders of intracranial volume or pressure should be considered. Pheochromocytoma has been reported rarely with an exercise headache phenotype. Population-based estimates of prevalence of primary exercise headache have ranged from 1% to 12%.[5,13] Primary exercise headache is common in enriched cohorts of athletes.[11]

The mechanisms underlying primary exercise headache are not well understood. Hemodynamic measures (eg, heart rate and blood pressure) do not correspond with symptoms.[11] Because internal jugular vein valve incompetence is overrepresented among patients with primary exercise headache (70%) compared with controls (20%), contributing factors may include painful venous dilatation or transient intracranial hypertension (or both).[14] This finding, however, does not account for the spontaneous resolution that often occurs.

For unknown reasons, primary exercise headache exists as a self-limited disorder in the majority of patients.[15] Indomethacin is often effective, especially when dosed 30 to 60 minutes before exercise. Indomethacin can be given daily, if needed, depending on the nature of the triggering causes. Beta-blockers, such as propranolol and nadolol, have also been reported to be effective.[11]

Primary Headache Associated With Sexual Activity

Primary headache associated with sexual activity has been considered a subtype of primary exercise headache because the disorders may coexist and management of the two is similar. The diagnosis requires at least two episodes of headache or neck pain brought on by and occurring only during sexual activity. The onset may occur with "increasing sexual excitement" or just before or coincident with orgasm.[1] The headache should have severe intensity for 1 minute to 24 hours or a mild intensity for up to 72 hours. Prior classification schemes have distinguished preorgasmic and orgasmic subtypes, but this is no longer thought to have clinical significance.

If the headache is associated with a disturbance of consciousness, vomiting, or focal neurologic symptoms or signs, a secondary mechanism should be suspected. In a patient with a new presentation of headache associated with sexual activity, emergency evaluation should be considered to evaluate for subarachnoid hemorrhage with CT, followed by lumbar puncture if normal. Vascular imaging should be pursued to exclude arterial dissection, intracranial aneurysm, and reversible cerebral vasoconstriction syndrome (RCVS). Recurrent thunderclap headaches associated with sexual activity should be presumed to be RCVS until proved otherwise. In a prospective series of 30 patients reporting headache associated with sexual activity and no neurologic deficits, 18 (60%) had RCVS.[16]

EPIDEMIOLOGY. Primary sexual headache occurs in 1% of the general population.[5] Males appear to be at greater risk, and the typical age of patients is 20 to 45 years.[17] The pathophysiology is unknown, although hemodynamic factors have been speculated to be contributory. Patients with headache associated with sexual activity have more robust increases in systemic blood pressure with exercise than healthy controls and people with migraine.[18] Patients with headache associated with sexual activity also have greater increases in cerebral

KEY POINTS

- External-pressure headache should be considered in occupational groups in which helmets or personal protective equipment are commonly worn.
- Routine neuroimaging for suspected primary stabbing headache is not recommended in the absence of additional red flags.
- Patients with recurrent thunderclap headache should be initially presumed to have a clinical diagnosis of reversible cerebral vasoconstriction syndrome. Patients with a new presentation of thunderclap headache should first be evaluated for subarachnoid hemorrhage.
- To help distinguish hypnic headache from cluster headache, the diagnostic criteria specify that hypnic headache is not associated with cranial autonomic symptoms or restlessness.
- Hypnic headache appears to occur more often in adults older than 50 years.
- Polysomnography has not shown a consistent association with sleep stage and hypnic headache onset.
- Hypnic headache is unique relative to other headache disorders because frequent caffeine use is advocated as therapy.
- The scalp area affected by the nummular headache should be examined for alopecia or a visible skin lesion, which may indicate a dermatologic condition.

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blood flow velocity after administration of acetazolamide, which suggests aberrant neurovascular coupling.[18]

Similar to primary exercise headache, primary headache associated with sexual activity may have a self-limited course in most patients. Approximately 15% of patients may experience a relapsing-remitting course, in which they may be susceptible to headache with sexual activity only temporarily (typically for 2 months at a time). Patients who never experience periods of remission appear to have a higher risk of a chronic course.[19] Nonpharmacologic management by assuming a more passive position during sexual activity may also reduce the incidence or severity of attacks. The preferred preventive option is indomethacin or sumatriptan (as long as RCVS is not present) administered 30 to 60 minutes before sexual activity. For patients with frequent attacks, propranolol or indomethacin (or both) may be used daily for prevention.

COLD-STIMULUS HEADACHE

Two subtypes of cold-stimulus headache are recognized by the *ICHD-3*: headache attributed to external application of a cold stimulus (eg, diving in cold water) and headache attributed to ingestion ("brain freeze") or inhalation of a cold stimulus.[1] The diagnosis requires that the headache occurs exclusively with exposure to cold and that the headache resolves within 30 minutes after removal of the external application or within 10 minutes after the causative ingestion or inhalation. The diagnosis is much more common among patients with comorbid migraine than among patients with tension-type headache or healthy controls.[20] The headache is more likely to occur with ingestion of ice water than with ice cubes and with more rapid ingestion.[21,22]

The lifetime prevalence of cold-stimulus headache is 15% in the general population.[5] Among people with migraine, 40% to 93% have cold-stimulus headache. The pathophysiology is unknown. Given the clinical association with migraine, it is notable that a cold-sensitive receptor found on trigeminal nociceptors (transient receptor potential cation channel subfamily M, member 8 [TRPM8]) has been consistently linked with migraine risk in genome-wide association studies.[23] No management is required beyond patient education and trigger avoidance.

EXTERNAL-PRESSURE HEADACHE

External-pressure headache results from nontraumatic compression or traction to the scalp, with each stimulus type recognized as a diagnostic subtype.[1] The diagnosis requires that the headache is maximal at the site of external compression or traction and that the headache resolves within 1 hour after the stimulus is removed. Examples of stimuli include swimming goggles, helmets, continuous positive airway pressure (CPAP) masks, and heavy ponytails. Further, external pressure may act as a migraine trigger among people with comorbid migraine, distinct from the cranial allodynia associated with migraine attacks. Otherwise, the headache is typically nonpulsating and not associated with nausea or environmental sensitivities.[24]

External-pressure headache has been reported to occur in 4% of the general population, although it is likely underreported.[5] In a cohort of 279 Danish military personnel, 30% reported headaches related to wearing a military helmet.[25] In a 2020 cross-sectional study of health care workers during the COVID-19 pandemic, de novo headaches related to use of personal protective

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equipment were observed in 81%.[26] The majority of these individuals met criteria for external-pressure headache related to either N95 mask or protective eyewear usage. Therefore, this headache type should be considered in occupational groups in which helmets or personal protective equipment are commonly worn. The pathophysiology presumably involves nontraumatic forces being applied to trigeminal or occipital nerve branches (or both) in the scalp.

Management requires use of a different helmet or head device to avoid the noxious exposure. In occupationally related cases, intermittent removal of the helmet or device might help mitigate the headache.[24] The value of nerve blocks or pharmacotherapy (or both) for this disorder is not known.

PRIMARY STABBING HEADACHE

Primary stabbing headache is characterized by irregular stabs, each lasting up to several seconds and ranging in daily frequency from one to many. The disorder has been previously termed *icepick headache* and *jabs and jolts syndrome*. Pain localization outside the trigeminal distribution is not uncommon and is present in an estimated 70% of patients.[27] Primary stabbing headache is distinguished from other causes of stabbing pain with an ophthalmic distribution by the lack of cutaneous triggers (characteristic of trigeminal neuralgia) and autonomic features (characteristic of short-lasting unilateral neuralgiform headache attacks with conjunctival tearing and injection [SUNCT]). Secondary causes should be pursued when the pain recurs in a fixed location, although this occurs in about one-third of patients with primary stabbing headache.[27] Routine neuroimaging for suspected primary stabbing headache is not recommended in the absence of additional red flags.

In the general population, the estimated prevalence of primary stabbing headache ranges from 0.2% to 2%, and the risk for females is 1.5 times greater than the risk for males. In adults, it is a frequent comorbidity with primary headache disorders, occurring in 42% of people with migraine; however, in children the disorder is more likely to occur independently.[28]

Primary stabbing headache may share pathophysiologic factors related to other primary headache disorders, given the common coexistence. Primary stabbing headache also appears to be associated with autoimmune disorders in highly selected case series. Therefore, neuralgic pain related to both central sensitization and immune factors has been implicated.[28]

Primary stabbing headache may improve with treatment of a coexisting primary headache disorder (eg, migraine). Independent treatment of primary stabbing headache is based on uncontrolled clinical series, in which melatonin (up to 12 mg nightly) or indomethacin has been reported as efficacious.[27]

PRIMARY THUNDERCLAP HEADACHE

Primary thunderclap headache is a tenuous diagnosis given the frequent association of a thunderclap presentation of headache with secondary causes. The diagnosis requires severe headache with abrupt onset, maximal intensity within 1 minute, and duration of at least 5 minutes. Importantly, the diagnosis requires exclusion of secondary causes, such as RCVS.[1] A diagnosis of probable primary thunderclap headache is never considered appropriate (the term *probable* is used for other disorders when one of the required criteria is not fulfilled). The diagnostic approach necessitates structural neuroimaging of the brain and arteries and often examination of the CSF. The radiographic vasospasm

KEY POINTS

- Migrainous features are not typical of nummular headache, although comorbid migraine is common.
- The temporal progression should be ascertained for all patients presenting for evaluation of a refractory chronic daily headache because the hallmark of new daily persistent headache is a daily-from-onset progression of chronic headache.
- In specialty headache practices, disorders of intracranial pressure, including idiopathic intracranial pressure with or without papilledema and spontaneous CSF leak, are relatively common; these disorders should be considered when evaluating patients for new daily persistent headache.
- New daily persistent headache is characteristically refractory to standard therapies, and empiric treatment guided by the underlying phenotype (eg, chronic migraine) is recommended.

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characteristic of RCVS is often not observed before 2 to 3 weeks, so imaging findings may be normal at initial presentation.[29]

Recurrent thunderclap headaches should be presumed to have a secondary cause. If the results of a neurodiagnostic evaluation are normal, patients with recurrent thunderclap headache should be initially presumed to have a clinical diagnosis of RCVS and asked about exposure to marijuana, stimulants, and serotonergic drugs known to precipitate vasoconstriction. Symptoms of primary thunderclap headache may improve with calcium channel blockers such as nimodipine, akin to RCVS.[30]

HYPNIC HEADACHE

Hypnic headache, also known as alarm clock headache, is a primary headache disorder characterized by headaches that begin during sleep; it typically affects older adults. The diagnosis requires that the headache occurs on at least 10 days per month over a period of at least 3 months. The headache lasts from 15 minutes to 4 hours after waking. Classically the headache arises during sleep between 2 and 4 AM.[31] To help distinguish the syndrome from cluster headache, the diagnostic criteria specify that hypnic headache is not associated with cranial autonomic symptoms or restlessness.[1] The differential diagnosis of headache arising from sleep includes intracranial hypertension, giant cell arteritis, sleep disorders (CASE 6-1), nocturnal hypertension, medication-overuse headache (analgesic withdrawal occurs during sleeping hours), and cervicogenic headache. The phenotype of hypnic headache therefore requires a diagnostic evaluation. Patients may have either tension-type or migrainous qualities with the headache.

The prevalence of hypnic headache in the general population is not known, although the general impression has been that the disorder is rare even in patients

CASE 6-1

A 63-year-old man with a history of infrequent migraine without aura presented with a 4-month history of headaches waking him from sleep. He described them as bifrontal nonpounding headaches that characteristically occurred between 2 and 3 AM that were associated with variable nausea. After 1 to 2 hours and self-treating with an over-the-counter analgesic containing caffeine, he could resume sleep. He denied daytime headaches. His wife reported that he snored during sleep. On clinical examination, the patient had an elevated body mass index of 26 and normal findings on neurologic examination. MRI of the brain showed normal findings. During a sleep study, his apnea-hypopnea index was 26.4 events per hour. Treatment of sleep apnea resolved the nocturnal headaches.

COMMENT

This patient presented with nocturnal headaches and normal findings on neurologic examination. Because of his age (>50 years) and changed headache pattern, further investigations were warranted. The case highlights that headache due to sleep apnea is a critical differential diagnosis of hypnic headache.

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at tertiary headache centers.[31] Hypnic headache appears to occur more often in females (by about 1.5 times) and typically in adults older than 50 years. However, the disorder can occur in younger patients, including children.

The pathophysiology has remained elusive, although voxel-based morphometry in age- and sex-matched controls has shown a decreased volume of the posterior hypothalamus and cortical areas involved in the central pain matrix in patients with hypnic headache.[32] Polysomnography has not shown a consistent association with sleep stage and headache onset.[33] A case-control study did not identify an association with melatonin rhythmicity.[34] Further, a trigeminal habituation deficit in response to the nociceptive blink reflex, typical of migraine, has not been replicated in patients with hypnic headache.[35] Cervicogenic headache and sleep-disordered breathing may be contributory factors in some patients.[33,36]

Hypnic headache may be prevented with caffeine or indomethacin before sleep; lithium may help if the headache is refractory.[36] Hypnic headache is unique relative to other headache disorders because frequent caffeine use is advocated as therapy. When given before sleep, various other medications, including atenolol, topiramate, and triptans, have been reported as effective, often at the level of case reports. Remission may occur after treatment, so the use of periodic trials of preventive discontinuation is justified.[37]

NUMMULAR HEADACHE

Nummular headache, also known as coin-shaped headache, is a continuous or intermittent head pain with a fixed sharply contoured shape that is typically round or elliptical and 1 cm to 6 cm in diameter (TABLE 6-1).[1] The pain is most often constant and mild to moderate but can be severe or intermittent (or both). Patients with pain in a restricted topography typically recognize whether the area of pain has a distinct boundary. The scalp area affected by the nummular headache should be examined for alopecia or a visible skin lesion, which may indicate a dermatologic condition. The area of pain, most often

***ICHD-3* Diagnostic Criteria for Nummular Headache[a]** TABLE 6-1

Nummular headache

A Continuous or intermittent head pain fulfilling criterion B

B Felt exclusively in an area of the scalp, with all of the following four characteristics:

- **1** Sharply contoured
- **2** Fixed in size and shape
- **3** Round or elliptical
- **4** 1-6 cm in diameter

C Not better accounted for by another *ICHD-3* diagnosis[b]

ICHD-3 = International Classification of Headache Disorders, Third Edition.

[a] Reprinted with permission from Headache Classification Committee of the International Headache Society, Cephalalgia.[1] © 2018 International Headache Society.

[b] Other causes, in particular structural and dermatologic lesions, have been excluded by history, physical examination, and appropriate investigations.

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parietal, is typically allodynic, and patients may report neuropathic symptoms (eg, paresthesia). Migrainous features are not typical of nummular headache, although comorbid migraine is common.[38] Secondary causes include cranial lesions, such as metastasis; Paget disease of bone; and fusiform aneurysm within the scalp.[39] Therefore, neuroimaging should be considered, although consensus is lacking.

The population-based prevalence is unknown. In a prospective study of patients in a neurology specialty clinic, 14 patients received a diagnosis of nummular headache over a 1-year period.[40] Nummular headache appears to be more common in middle-aged women.[38,40]

Nummular headache has been considered a trigeminal terminal branch neuralgia, and immune factors were implicated by the high prevalence of autoantibodies in one series of patients.[41]

Patients may not always desire treatment for nummular headache.[40] Classically, nummular headache is treated with gabapentin as a first-line therapy, although in one retrospective series gabapentin was effective in only one of seven patients.[38] In a 2019 open-label nonrandomized trial, a dose of 25 units of onabotulinumtoxinA was administered in the painful region and the primary end point of the number of headache days per month at weeks 20 to 24 was compared with the number at baseline. The 53 enrolled patients had a significant decrease of approximately seven headache days per month. The most common adverse event was injection site pain in 22.6% of patients.[42] Injections of local anesthetics in the painful region tend not to be helpful.

TABLE 6-2 ***ICHD-3* Diagnostic Criteria for New Daily Persistent Headache[a]**

New daily persistent headache	
A	Persistent headache fulfilling criteria B and C
B	Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours
C	Present for >3 months
D	Not better accounted for by another *ICHD-3* diagnosis[b-e]

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] New daily persistent headache is unique in that headache is daily from onset, and very soon unremitting, typically occurring in individuals without a prior headache history. Patients with this disorder invariably recall and can accurately describe such an onset; if they cannot do so, another diagnosis should be made. Nevertheless, patients with prior headache (migraine or tension-type headache) are not excluded from this diagnosis, but they should not describe increasing headache frequency prior to its onset. Similarly, patients with prior headache should not describe exacerbation associated with or followed by medication overuse.

[c] New daily persistent headache may have features suggestive of either migraine or tension-type headache. Even though criteria for chronic migraine and/or chronic tension-type headache may also be fulfilled, the default diagnosis is new daily persistent headache whenever the criteria for this disorder are met. In contrast, when the criteria for both new daily persistent headache and hemicrania continua are met, then the latter is the default diagnosis.

[d] Abortive drug use may exceed the limits defined as causative of medication-overuse headache. In such cases, the diagnosis of new daily persistent headache cannot be made unless the onset of daily headache clearly predates the medication overuse. When this is so, both diagnoses, new daily persistent headache and medication-overuse headache, should be given.

[e] In all cases, other secondary headaches such as acute headache attributed to traumatic injury to the head, headache attributed to increased cerebrospinal fluid pressure and headache attributed to low cerebrospinal fluid pressure should be ruled out by appropriate investigations.

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NEW DAILY PERSISTENT HEADACHE

New daily persistent headache is an important mimicker of chronic migraine and chronic tension-type headache.[43] The diagnosis requires the development of a persistent headache, distinctly becoming continuous and unremitting within a clearly remembered 24-hour period (TABLE 6-2). The headache should be present for at least 3 months.[1] Phenotypes otherwise resembling chronic migraine or chronic tension-type headache are recognized.[44] Therefore, the temporal progression should be ascertained for all patients presenting for evaluation of a refractory chronic daily headache because the hallmark of new daily persistent headache is a daily-from-onset progression of chronic headache. Approximately 50% of patients with new daily persistent headache recall a triggering event, most often a flulike illness, stressful life event, or procedure.[45]

The diagnosis of new daily persistent headache requires a review for secondary mimickers, which include cervical artery dissection, cerebral venous thrombosis, meningitis, and many other possiblities.[46] In specialty headache practices, disorders of intracranial pressure, including idiopathic intracranial hypertension with or without papilledema and spontaneous CSF leak, are relatively common and should be considered. The diagnosis of headache related to either intracranial hypertension or hypotension is often fraught with diagnostic pitfalls.[43] Symptoms of transient visual obscurations, double vision, pulsatile tinnitus, or nocturnal waking can suggest elevated intracranial pressure. Conversely, intracranial hypotension can be suggested by orthostatic headache, hypermobility, and headache improvement with the Trendelenburg position.[47]

New daily persistent headache is thought to be uncommon in the general population, but it is commonly encountered in headache subspecialty practices. In a population-based study, the 1-year prevalence of new daily persistent headache was estimated at 0.03% and included only four out of approximately 30,000 individuals (all four were 30 to 44 years old).[48] Discussing this rarity with patients may help them understand the uniqueness of the disorder, which is often impairing and life changing.[49]

The pathophysiology of new daily persistent headache is speculative. Most likely it is a heterogeneous syndrome. Immune factors have been implicated as cases may begin in the context of a presumed viral illness and tumor necrosis factor-α has been noted to be elevated in the CSF.[47] Generalized and cervical hypermobility are common in patients with new daily persistent headache, which has been associated with the syndrome developing after procedures that require intubation and prolonged neck extension.[50] The neurobiology appears to be distinct from that of other primary headache disorders because pharmacotherapies for migraine are frequently ineffective.

New daily persistent headache is characteristically refractory to standard therapies, and empiric treatment guided by the underlying phenotype (eg, chronic migraine) is recommended (CASE 6-2).[43] OnabotulinumtoxinA injections anecdotally appear to have a greater probability of being effective than many other standard therapies and should be strongly considered for patients who have a chronic migraine phenotype.[51] Early acknowledgment of a refractory course allows for early involvement of a multidisciplinary team to help bolster self-efficacy and self-management

KEY POINT

- Early acknowledgment of a refractory course allows for early involvement of a multidisciplinary team to help bolster self-efficacy and self-management strategies in patients with new daily persistent headache.

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strategies.[43,49] The use of high doses of IV methylprednisolone should be considered in patients with postinfectious new daily persistent headache, especially very early in the course.[47] Nimodipine therapy may help if the patient has a history of a thunderclap headache at onset of the new daily persistent headache.[47] In such cases, it has been speculated that the syndrome may exist on a spectrum with RCVS. Treatments directed toward suspected cervicogenic pain generators should be considered in patients with hypermobility.[47]

CONCLUSION

The category of other primary headache disorders includes a diverse group of headache disorders that are highly recognizable and have particular implications for evaluation and management. Familiarity with this group of headache disorders has immediate implications for the provision of safe and effective care of patients with headache.

CASE 6-2

A 27-year-old woman presented for evaluation of intractable chronic headache that was refractory to numerous standard preventive therapies. She reported a history of infrequent migraine without aura occurring 1 to 2 times per year; however, 4 years ago, she woke up with a severe headache that had persisted to presentation. She described the absence of thunderclap progression at onset. In the week before onset, she had been distressed about her brother's unexpected death.

The headache was holocephalic and pounding, aggravated by routine activity, and intense. She reported nausea and sensitivity to light and sound. She denied red flag features, including pulsatile tinnitus, double vision, and transient darkening of vision.

The neurologic examination findings were normal. MRI of the head with and without contrast, magnetic resonance angiography (MRA) of the head and neck, and magnetic resonance venography (MRV) of the head did not show any abnormalities.

COMMENT

New daily persistent headache, an important mimicker of chronic migraine, is often refractory to standard therapies. A daily-from-onset progression mandates a careful neurodiagnostic evaluation and a recognition that the headache is often refractory to treatment. The patient described in this case was treated with onabotulinumtoxinA injections based on her chronic migraine phenotype. Her headache continued to persist at 6 months' follow-up, but the intensity had improved by 50% with treatment. She was able to achieve improved functional status through engagement with cognitive-behavioral therapy.

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Cranial Neuralgias

By Carrie Robertson, MD, FAHS

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article discusses the differential diagnosis, evaluation, and management of trigeminal neuralgia and reviews other neuralgias of the head and neck, including those that contribute to neuralgic ear pain.**

RECENT FINDINGS: **Most cases of trigeminal neuralgia are related to vascular compression, a demyelinating plaque, or a compressive mass affecting the trigeminal nerve. However, recent studies have shown that up to 11% of patients have a family history of trigeminal neuralgia, suggesting that some patients may have a genetic predisposition to demyelination or nerve hyperexcitability. In these patients, trigeminal neuralgia may occur at a younger age, on both sides of the face, or in combination with other neuralgias.**

SUMMARY: **When a patient presents with neuralgic pain, the diagnosis is made by careful history and neurologic examination, with attention to the dermatome involved, the triggers, and the presence of any associated sensory deficit. All patients with new neuralgia or neuropathic facial pain warrant a careful evaluation for a secondary cause. The presence of sensory deficit on bedside examination is particularly concerning for an underlying secondary etiology.**

INTRODUCTION

Although most headache disorders have been attributed to pathophysiology within the brain, it is well known that irritation of individual nerves in the peripheral nervous system can contribute to head and facial pain as well. This article discusses the differential diagnosis for neuralgic pain in the face and ear, with specific attention to trigeminal neuralgia, glossopharyngeal neuralgia, nervus intermedius neuralgia, and occipital neuralgia.

BACKGROUND ON TERMINOLOGY

When discussing pain involving the cutaneous areas of the head and neck, it is important to distinguish between the terms *neuralgia* and *neuropathy*. *Neuralgia* is a term used to describe a brief paroxysmal, often triggered, lancinating pain within a specific nerve dermatome, sometimes described as sharp, stabbing, or electric shock–like. This is in contrast to *neuropathy*, in which there may be sensory deficit within the nerve distribution and a persistent pain with neuropathic features, often described as burning, tingling, or prickling, sometimes with a false sense of swelling. If the nerve is also responsible for motor function, weakness may be present in the associated muscles. Both neuralgia and

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RELATIONSHIP DISCLOSURE:
Dr Robertson serves on advisory boards for Alder BioPharmaceuticals, Inc; Biohaven Pharmaceuticals; and Impel NeuroPharma, Inc, and receives publishing royalties from UpToDate Inc.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Robertson discusses the unlabeled/investigational use of treatments for trigeminal neuralgia, none of which are US Food and Drug Administration approved for this indication, except for carbamazepine.

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painful neuropathy have been described in branches of multiple cranial nerves (trigeminal, glossopharyngeal, facial, vagus) as well as in terminal branches of the upper cervical nerves (occipital and great auricular).

When a patient experiences what seems to be nerve-related pain in the distribution of one of these nerves, it is important to evaluate for an underlying structural, inflammatory, or infectious process along the length of the nerve. If a secondary cause of neuralgia or neuropathic pain is not clear despite investigation, the neuralgia or neuropathy is termed *idiopathic* and classified with the nerve affected (eg, idiopathic glossopharyngeal neuralgia).

In some cases, the diagnostic terms may overlap, depending on the underlying pathology. For example, with a secondary neuropathy (such as a tumor infiltrating the glossopharyngeal nerve), a nerve may have components of both sharp paroxysmal stabbing pain and persistent pain. In these cases, the term that best describes the predominant pain type is used.

TRIGEMINAL NEURALGIA

Of all of the cranial nerves, classification of the pain within the trigeminal nerve distribution has been the most complex and often controversial. The *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for trigeminal neuralgia are listed in TABLE 7-1.[1]

With the current classification, if a patient presents with the symptoms listed in the criteria and has signs of neurovascular compression on imaging, including nerve root atrophy or displacement, the term *classical trigeminal neuralgia* is applied. If the trigeminal neuralgia is due to some other cause, such as a multiple sclerosis plaque or local mass compressing the nerve, the term *secondary trigeminal neuralgia* is used. If the etiology is unknown, with a normal-appearing

TABLE 7-1 **ICHD-3 Diagnostic Criteria for Trigeminal Neuralgia**[a]

Trigeminal neuralgia

Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,[b] and fulfilling criteria B and C

A Pain has all of the following characteristics:

- **1** Lasting from a fraction of a second to 2 minutes[c]
- **2** Severe intensity[d]
- **3** Electric shock–like, shooting, stabbing or sharp in quality

B Precipitated by innocuous stimuli within the affected trigeminal distribution[e]

C Not better accounted for by another *ICHD-3* diagnosis

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes.

[c] Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for >2 minutes.

[d] Pain may become more severe over time.

[e] Some attacks may be, or appear to be, spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomical location of the trigger and/or other factors.

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MRI and normal electrophysiologic tests, the diagnosis is *idiopathic trigeminal neuralgia*.[1]

Most patients with trigeminal neuralgia tend to be pain free between these paroxysmal attacks, but a subset of patients can develop continuous or near-continuous background pain between attacks in the same area as the paroxysmal pain. In these cases, the presence of this background pain is clarified at the end of the diagnosis, as in *classical trigeminal neuralgia with concomitant continuous pain*.[1] As a general rule, loss of sensation should not be present clinically with trigeminal neuralgia, although subclinical sensory deficits may be found on specialized testing.[2] The presence of numbness is more suggestive of a painful trigeminal neuropathy and requires a more detailed investigation for secondary causes.

Clinical Features

Approximately 99% of patients with trigeminal neuralgia report provocation of paroxysmal pain by some type of otherwise innocuous trigger.[3] Triggers tend to include maneuvers that activate the motor or sensory component of the trigeminal nerve, such as chewing/eating, talking, light touch over the face, shaving or applying makeup, brushing teeth, or cold wind on the face (CASE 7-1).[4,5] According to one study, cutaneous triggers tend to occur more frequently around the nose and mouth, although anywhere on the face may be described.[5]

Although each individual episode of paroxysmal pain is brief, episodes may recur as a series of attacks, especially if the trigger is still present (eg, the patient is still eating or brushing their teeth). Most of these series of attacks last less than an hour.[4] After severe paroxysmal pain attacks, some patients describe a refractory period, during which additional attacks either cannot be elicited or attack severity is diminished.[6] Patients may also experience unpredictable remissions of their pain attacks lasting weeks, months, or even years.[4]

Trigeminal neuralgia tends to affect the right trigeminal nerve slightly more than the left and involve the V2 (maxillary) and V3 (mandibular) divisions more than the V1 (ophthalmic) division.[4,5] However, a small subset of patients (<5%) may present with neuralgia isolated to the V1 division.[4] Bilateral trigeminal neuralgia is uncommon and should raise clinical concern for secondary trigeminal neuralgia, such as from multiple sclerosis.[3]

Mild autonomic symptoms, including conjunctival injection or tearing, may be present with some attacks and may be seen more frequently in patients with involvement of V1.[4] However, if autonomic symptoms are pronounced or frequent, it should raise clinical suspicion for a trigeminal autonomic cephalalgia such as short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) or short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). TABLE 7-2 lists conditions in the differential diagnosis for trigeminal neuralgia.[7]

Most patients with trigeminal neuralgia will have normal sensation on bedside examination, although careful examination in one study demonstrated mild reduction to sensation in 18% of patients with paroxysmal pain and 30% of patients with concomitant persistent pain.[8] In the absence of a history of a surgical or destructive treatment for trigeminal neuralgia, pronounced hypoesthesia or anesthesia should raise the possibility of an alternative diagnosis of painful trigeminal neuropathy and is concerning for a secondary etiology. For example, numbness in the mental nerve distribution, or numb chin syndrome, is a red flag for a neoplastic etiology.

KEY POINTS

- ***Neuralgia*** **describes sharp, stabbing, shocklike pain that is often triggered by touching within the sensory dermatome of the affected nerve, whereas *neuropathy* describes sensory deficit within the nerve distribution, sometimes with persistent neuropathic pain, such as burning, tingling, or prickling.**
- **Classical trigeminal neuralgia is trigeminal neuralgia related to neurovascular compression; nerve atrophy or displacement is required on imaging (not just vascular contact). Secondary trigeminal neuralgia is trigeminal neuralgia related to another cause, such as demyelinating plaque or local mass. Idiopathic trigeminal neuralgia is trigeminal neuralgia without a known cause.**
- **Most patients with trigeminal neuralgia are pain free between attacks, but a subset can develop near-continuous background pain.**
- **Mild sensory changes may be present in trigeminal neuralgia, but true loss of sensation should alert the clinician to look for secondary causes.**
- **Approximately 99% of patients with trigeminal neuralgia report triggers.**
- **Some patients with trigeminal neuralgia may describe a refractory period after severe attacks, during which additional attacks are diminished.**

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Pathophysiology

The complete underlying mechanism behind trigeminal neuralgia is not clear. By definition, patients with classical trigeminal neuralgia have evidence of vascular compression of the trigeminal nerve, typically by the superior cerebellar artery, but neurovascular conflict involving other vessels (anterior inferior cerebellar artery, trigeminal vein, superior petrosal vein) has been described. An area along the trigeminal nerve root within a few millimeters from where it enters the pons, called the *root entry zone*, is thought to be particularly vulnerable to injury.[9] In this area, the content of myelin transitions from the oligodendroglia of the central nervous system to the Schwann cells of the peripheral nervous system.

In patients with classical trigeminal neuralgia, it is theorized that the neurovascular compression may contribute to focal demyelination with subsequent trigeminal nerve hyperexcitability.[10,11] In support of this premise, pathologic specimens have demonstrated focal demyelination along the

CASE 7-1

A 63-year-old woman initially presented with 2 years of electrical shock–like pain that started just in front of her left ear and radiated into her upper teeth and cheek, triggered by lightly touching her face, a cool breeze on her face, chewing, and brushing her teeth. Each attack lasted only seconds, but they frequently occurred in clusters, such as when she was putting on her makeup or eating a meal. She was pain free between the attacks. Her initial neurologic examination was unremarkable, including no evidence of sensory deficit over the face. Carbamazepine was begun and had been helpful initially, but she required escalating doses and was eventually unable to tolerate the doses required for pain relief. A gadolinium-enhanced high-resolution MRI of her brain with thin slices through the posterior fossa showed the superior cerebellar artery compressing and distorting the trigeminal nerve at the root entry zone. Microvascular decompression was performed, with a synthetic pledget placed between the compressing vessel and the trigeminal nerve.

The patient was pain free for the next 11 years, then gradually noticed a return of her neuralgic pain, affecting both V2 and V3. She was subsequently treated with stereotactic radiosurgery to the trigeminal ganglion. Over the next 2 weeks, she noticed gradual numbness, with improvement in her neuralgic pain but new burning, tingling, and itching over the left V1, V2, and V3 region, with weakness of the left masseter and temporalis. She developed corneal keratitis, which was managed by an ophthalmologist. One year after her radiosurgery, the persistent neuropathic pain was still present, requiring gabapentin and opiates for pain relief.

COMMENT

The patient's initial symptoms were consistent with classical trigeminal neuralgia that improved after microvascular decompression. When her pain returned, she was treated with a neuroablative procedure, leading to a painful posttraumatic trigeminal neuropathy (also known as anesthesia dolorosa).

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trigeminal root in the area of compression.[10,12] It is theorized that in the region of compression, ectopic impulses arise from the demyelinated axons and the close apposition of groups of demyelinated axons facilitates ephaptic cross talk between fibers mediating light touch and those mediating pain.[10,11,13] When pain significantly outlasts the trigger, it may be because of injury-induced changes at the trigeminal ganglia, creating ectopic pacemakers with self-sustained firing.[13] It is thought that during a burst of firing, calcium-activated potassium channels open, allowing potassium ions to flow out of these channels. It is only after enough potassium exits the neuron to cause membrane hyperpolarization that the firing stops. If the hyperpolarization is significant enough, it will prohibit additional firing, leading to the clinically described refractory period.[13]

Some patients may have a genetic predisposition to demyelination or nerve hyperexcitability, contributing to earlier or more frequent compressive neuralgia. In these patients, trigeminal neuralgia may occur at a younger age, on both sides of the face, or in combination with other neuralgias.

The theory that compression of the trigeminal nerve at the root entry zone can contribute to symptoms of trigeminal neuralgia is supported by the fact that most patients show improvement in symptoms following microvascular decompression.[12] However, this does not explain the subset of trigeminal neuralgia patients without evidence of compression on imaging or posterior fossa exploration.[14,15] It is also noteworthy that neurovascular compression can occur without symptoms. In one study examining 3T MRI of 200 trigeminal nerves in 100 asymptomatic individuals, 175 (87.5%) of the nerves showed neurovascular compression.[16] The authors did not grade the neurovascular contact, however, and others have argued that severe compression with displacement or atrophy is rare in asymptomatic individuals.[9]

Epidemiology

Trigeminal neuralgia is a rare condition, with a prevalence of 0.03% to 0.3%[17] and an annual incidence of 4 per 100,000 to 13 per 100,000 people.[11] It is more common in women, with a ratio of approximately 1.5:1 to 1.7:1.[4,18] The average age of onset is older than 50 years.[4] However, trigeminal neuralgia can occur at any age, including in children.[19] Patients with secondary and idiopathic trigeminal neuralgia tend to present at a younger age than patients with neurovascular compression.[14,20]

Trigeminal neuralgia is typically sporadic, although a positive family history may be present in up to 11% of patients.[21] In reported familial cases, both autosomal dominant and autosomal recessive inheritance patterns have been described.[22] Some of the reported familial trigeminal neuralgia cases have been in the setting of hereditary peripheral neuropathy, such as Charcot-Marie-Tooth disease, raising the possibility that patients' abnormal myelin might have contributed to an underlying vulnerability to nerve compression.[23,24] Other cases may show a genetic predisposition to peripheral nerve hyperexcitability, with mutations similar to other disorders of neuropathic pain. For example, a gain-of-function mutation in $Na_V1.6$ has been described in one patient with classical trigeminal neuralgia, and more recently, whole-exome sequencing of familial cases demonstrated multiple genetic variants in ion channels, including sodium channels, potassium channels, chloride channels, calcium channels, and transient receptor potential (TRP) channels.[21] It has been suggested that familial cases may have an earlier onset and may be associated with additional neuralgias, such as glossopharyngeal neuralgia or hemifacial spasm.[25]

KEY POINTS

- Bilateral trigeminal neuralgia can occur but is uncommon and should raise suspicion for secondary trigeminal neuralgia, such as from multiple sclerosis.
- Trigeminal neuralgia associated with pronounced autonomic symptoms should raise clinical suspicion for a trigeminal autonomic cephalalgia.
- Unexplained numbness isolated to the chin is a red flag for potential malignancy.
- Neurovascular contact of the trigeminal nerve is common even in people without symptoms. Therefore, the severity of compression on imaging may be more relevant, including nerve displacement or atrophy.
- A family history of trigeminal neuralgia may be present in up to 11% of patients. Familial cases may have an earlier onset and may be associated with additional neuralgias, such as glossopharyngeal neuralgia or hemifacial spasm.

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Causes of Secondary Trigeminal Neuralgia

Red flags for a secondary cause of trigeminal neuralgia include bilateral trigeminal neuralgia, pronounced sensory changes, and a younger age at onset. The most common causes of secondary trigeminal neuralgia include multiple sclerosis or a tumor at the cerebellopontine angle. In one series of patients with both trigeminal neuralgia and multiple sclerosis, the diagnosis of trigeminal neuralgia preceded the diagnosis of multiple sclerosis in about 10% of patients by an average of 5 years.[26] Although patients with multiple sclerosis often have a demyelinating plaque near the trigeminal nerve root entry zone, they can have neurovascular compression ipsilateral to these plaques as well.[27] It is theorized that in these cases, a "double crush" mechanism may be present, in which both the neurovascular compression and the

TABLE 7-2 **Conditions That May Mimic Trigeminal Neuralgia**[a]

Condition	Location	Branch commonly mimicked	Pain characteristics	Aggravating factors	Things to look for or consider
Cracked tooth	Affected tooth	V2, V3	Dull or sharp shooting	Biting/chewing; hot or cold	Difficult to visualize
Caries/pulpitis	Affected tooth	V2, V3	Dull or sharp; minutes to hours	Sweet foods, hot or cold	Visible decay
Dry socket	Affected tooth	V2, V3	Continuous deep or sharp	Hot or cold	Loss of clot, exposed bone
Temporomandibular joint disorder	Jaw, ear, temple	V3	Tender, aching or sharp	Opening mouth, chewing	Jaw locking/popping
Giant cell arteritis	Jaw or temple	V3 more than V2	Cramping in jaw muscle, tender or sharp at temple	Eating can increase jaw muscle cramping; touching over temple/scalp	May have fever/chills, night sweats, weight loss, increased erythrocyte sedimentation rate/C-reactive protein
Sialadenitis/salivary stone	Submandibular or parotid	V3 more than V2	Continuous with tenderness to palpation	Salivation (eating or smelling foods)	Erythema, swelling over gland, dry mouth; may have fever
First bite syndrome	Submandibular or parotid	V3 more than V2	Paroxysmal sharp or cramping	Salivation (eating or smelling foods)	Improves after a few bites; history of head/neck surgery common
SUNA/SUNCT	Orbital, supraorbital, or temporal	V1 more than V2	Paroxysmal sharp, stabbing with ipsilateral autonomic symptoms	Spontaneous or cutaneous triggers	Generally no refractory period

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demyelinating plaque contribute to trigeminal neuralgia.[27,28] Less common causes of secondary trigeminal neuralgia include arteriovenous malformations, epidermoid cysts, aneurysms, small infarcts in the pons or medulla, and bony compression of the nerve such as from an osteoma or osteogenesis imperfecta.[10,29] In patients without evidence of neurovascular compression or an obvious secondary cause of trigeminal neuralgia, arachnoid thickening and adhesion with the trigeminal nerve and surrounding structures has been proposed as an alternative etiology.[30]

Differential Diagnosis and Evaluation

A number of different causes of facial pain can potentially be confused with trigeminal neuralgia (TABLE 7-2). Prominent autonomic symptoms, such as

CONTINUED FROM PAGE 670

Condition	Location	Branch commonly mimicked	Pain characteristics	Aggravating factors	Things to look for or consider
Primary stabbing headache	Orbital or temporal	V1	Paroxysmal sharp, stabbing; typically low attack frequency	Spontaneous	May move from one area of the head to another; no autonomic symptoms
Painful trigeminal neuropathy	Trigeminal nerve	V1, V2, or V3	May have persistent neuropathic pain (burning, tingling, throbbing) with numbness and sometimes sharp/stabbing pain	Touch may worsen pain	If no history of trauma to nerve, requires evaluation for neoplastic or inflammatory causes
Postherpetic neuralgia	Typically single nerve dermatome	V1, V2, or V3	Neuropathic pain (burning, itching, tingling); can be deep/boring or lancinating	Touch may worsen pain	History of vesicles/rash at onset
Glossopharyngeal neuralgia (cranial nerve IX)	Ear, throat, jaw	V3	Paroxysmal sharp, stabbing	Swallowing, yawning, coughing	10% associated with arrhythmia/syncope; consider ambulatory ECG monitor
Nervus intermedius neuralgia (cranial nerve VII)	Deep in ear more than jaw	V3	Paroxysmal sharp, stabbing	Touch within ear canal	May have Bell's palsy at onset
Great auricular neuralgia (branch of C2/C3)	Ear, periauricular, jaw	V3	Paroxysmal sharp, stabbing	Turning head/neck position	May have tenderness/Tinel sign over lateral neck

SUNA = short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

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conjunctival injection, periorbital edema, tearing, or rhinorrhea, should raise suspicion for a trigeminal autonomic cephalalgia such as SUNCT. If the pain is predominantly triggered by eating/chewing, hot/cold foods, or brushing teeth (without cutaneous triggers), a dental etiology should be considered. Often the pain remains intraoral in patients with dental pathology, but rarely a local associated abscess or cellulitis can cause pain that seems to radiate through the affected jaw or ear. If the patient has any history of erythema or rash in the affected painful area at the onset of pain, postherpetic neuralgia should be considered. If the pain is persistent or neuropathic in nature with associated sensory deficit, trigeminal neuropathy should be considered. If the pain is outside the area of the trigeminal nerve, it may be neuralgia related to a different nerve, such as glossopharyngeal neuralgia or nervus intermedius neuralgia, as discussed below.

During a thorough neurologic examination for focal deficits, including testing of all 12 cranial nerves, the clinician should test for sensory loss in all three trigeminal nerve divisions (V1, V2, and V3). Because of overlap from cervical nerve branches over the jaw and lower cheek, the most reliable area to test V3 is over the chin. Masseter and temporalis muscles should be tested for symmetry of muscle bulk and strength.

MRI of the brain, ideally with IV contrast and high-resolution thin cuts through the posterior fossa, is the preferred imaging if no contraindications are present. Three-dimensional time-of-flight magnetic resonance angiogram (MRA) can add additional visualization of arteries.[31] Although not required for diagnosis, trigeminal reflex testing can be particularly useful for evaluating trigeminal nerve impairment in patients with secondary trigeminal neuralgia, with a reported sensitivity and specificity close to 90%.[28] ECG and laboratory testing, including complete blood cell count and electrolytes with kidney and liver function, should be performed to guide medication options. Erythrocyte sedimentation rate should be added if giant cell arteritis is a possibility. A dental evaluation is usually recommended if pain involves predominantly V2 and V3.[12]

Medical Treatment

The initial treatment for trigeminal neuralgia is generally pharmacologic, and either carbamazepine (200 mg/d to 1200 mg/d) or oxcarbazepine (300 mg/d to 1800 mg/d) is generally considered first line. These anticonvulsants block sodium channels, contributing to stabilization of the membrane and likely suppressing the ectopic hyperexcitability of the trigeminal nerve root and ganglion.[13] Carbamazepine has the best evidence as a long-term treatment for trigeminal neuralgia, but a significant number of patients have difficulty tolerating the side effects, which include dizziness, hyponatremia, drowsiness, cognitive symptoms, rash, ataxia, liver damage, and bone marrow suppression; carbamazepine may also potentially interact with a number of other drugs.[31,32] Oxcarbazepine is reportedly better tolerated and has fewer potential drug interactions but may have a higher risk of causing hyponatremia.[11,31,32] In one study, side effects eventually led to withdrawal of medication in 27% of patients on carbamazepine and 18% of patients on oxcarbazepine.[32] Alternatives to carbamazepine and oxcarbazepine with weak evidence include lamotrigine, gabapentin, or onabotulinumtoxinA injections,[31] followed by eslicarbazepine acetate, baclofen, topiramate, valproate, levetiracetam, and phenytoin.[31,33] Studies are also investigating a new voltage- and use-dependent Nav1.7 channel blocker called vixotrigine for trigeminal neuralgia.[11,33]

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RESCUE TREATMENT. Patients with an acute exacerbation of trigeminal neuralgia that is refractory to medication may present to an urgent care setting. Depending on the clinic and the time of day, a surgeon or specialized proceduralist may not be available for immediate invasive procedures. Pain may be so severe that patients are unable to eat or drink and may require in-hospital treatment. In these cases, IV fosphenytoin or possibly even IV lidocaine (5 mg/kg over 60 minutes) combined with rehydration may be required.[33] Either of these therapies should be delivered under specialist supervision with cardiac monitoring.[33] Another option may be subcutaneous or nasal sumatriptan, which has been reported as possibly effective in small series of patients with refractory trigeminal neuralgia.[34,35] Acute pain relief might also be achieved with peripheral blocks (bupivacaine with lidocaine) of the most affected trigeminal nerve branches, such as the supraorbital, infraorbital, auriculotemporal, or mental nerve.[36] Requiring slightly more experience, ultrasound-guided trigeminal nerve block via the pterygopalatine fossa has been shown to provide pain relief in a small series.[37]

Surgical and Procedural Management

If a patient with trigeminal neuralgia tries one of the sodium channel blockers and has either insufficient pain relief or intolerable side effects, the patient should be referred for a neurosurgical consultation.[11,31] If the patient has evidence of neurovascular compression on imaging and no contraindications to surgery, microvascular decompression is considered first line.[12,31] In patients without neurovascular decompression visible on imaging, typically a neuroablative procedure is considered first.[31] Neuroablative procedures include stereotactic radiosurgery or percutaneous procedures (eg, balloon compression, glycerol injection, or radiofrequency thermocoagulation). The goal of these procedures is to injure the trigeminal nerve enough that the pain is reduced. Partial sensory rhizotomy, internal neurolysis, and peripheral stimulation of trigeminal branches are alternative procedural options for patients with refractory trigeminal neuralgia or patients without neurovascular compression.

MICROVASCULAR DECOMPRESSION. Microvascular decompression involves a retromastoid craniotomy and posterior fossa exploration to identify both the affected trigeminal nerve and the compressive vessel. The vessel is then relocated away from the nerve, with most surgeons using a piece of synthetic material to create a barrier between the vessel and the nerve (FIGURE 7-1). Compared with other treatments for classical trigeminal neuralgia, microvascular decompression is reported to have the greatest probability of pain relief, with 68% to 88% of patients reporting pain freedom at 1 to 2 years postoperatively[31] and approximately 64% of patients still pain free 10 years after surgery.[38] Factors that may increase the risk of pain recurrence include female sex, symptoms lasting longer than 8 years, venous compression rather than arterial compression, the presence of arachnoiditis, the lack of immediate postoperative pain relief, and the presence of persistent pain between attacks.[38,39]

Patients with more severe neurovascular compression on imaging (especially with distortion of the nerve or atrophy) seem to have a better outcome after microvascular decompression,[40,41] possibly because it increases the likelihood that the neurovascular contact was not simply an incidental imaging finding.

Side effects of microvascular decompression include CSF leak (1.5%), ipsilateral hearing loss (1.2%), facial palsy (0.9%), severe facial numbness (1.6%), aseptic

KEY POINTS

- Patients with multiple sclerosis may have both a demyelinating plaque and neurovascular compression near the trigeminal nerve root entry zone, causing neuralgia through a "double crush" mechanism.
- Postherpetic neuralgia should be considered in patients presenting with trigeminal neuralgia who have a history of erythema or rash in the affected area at the onset of pain.
- Because of overlap from cervical cutaneous branches over the jawline, the most reliable area to test the mandibular (V3) division is over the chin.
- If the patient's pain is predominantly in V2 and V3 and without cutaneous triggers, a dental evaluation should be considered.
- Carbamazepine is considered first-line treatment for trigeminal neuralgia.
- For urgent treatment of refractory trigeminal neuralgia, IV fosphenytoin, IV lidocaine, or peripheral blocks can be considered.
- A patient with trigeminal neuralgia that is refractory to medical therapy should be referred to a neurosurgeon. If neurovascular compression is present on imaging, microvascular decompression is typically considered first. If not, a neuroablative procedure (with injury to the nerve) is typically considered first.

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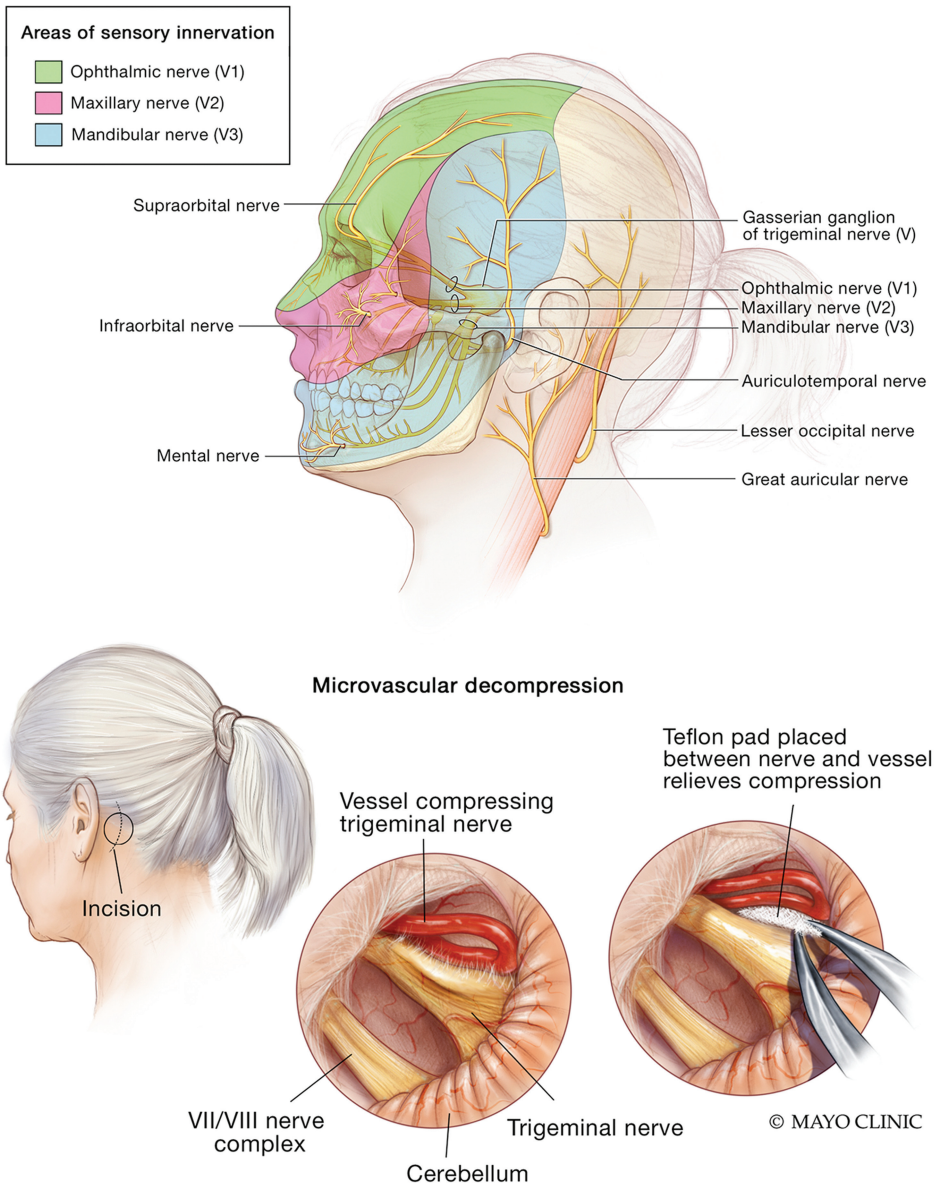

FIGURE 7-1

Trigeminal nerve branches and dermatomal innervation. Lower image shows vascular compression of the trigeminal nerve and subsequent microvascular decompression.

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meningitis (16.8%), trochlear or abducens palsy (1.1%), brainstem infarct (0.1%), and death (0.2%).[38]

When patients have recurrence of trigeminal neuralgia after microvascular decompression, sometimes a repeat posterior fossa exploration is performed. This exploration may identify a new or previously missed compressing vessel, compression with the synthetic material used in decompression, a foreign body inflammatory giant cell granulomatous reaction around the synthetic material (eg, "Teflon granuloma"), or formation of arachnoid adhesions/arachnoiditis.[42,43] Repeat microvascular decompression has a lower

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chance of pain relief and a higher risk of complications but may be an option in select patients.[44]

STEREOTACTIC RADIOSURGERY. Stereotactic radiosurgery involves aiming a carefully targeted external beam of radiation to part of the trigeminal nerve root during a single session, with a goal of inducing focal axonal degeneration. Techniques vary slightly, with a variety of technologies (eg, Gamma Knife, CyberKnife) used. Lower doses of radiation are felt to have very little impact on the trigeminal nerve structure and higher doses can potentially cause necrosis of neurons.[45,46] Because the targeting is precise, the radiation can be directed anywhere along the nerve root, with some surgeons favoring targeting the root entry zone close to the brainstem (sometimes overlapping with the brainstem)[46] and others favoring just proximal to the trigeminal ganglion or the ganglion itself.[47,48] One large systematic review found that both targets had similar efficacy initially, but the more anterior retrogasserian target was slightly better tolerated.[48] Of the approximately 85% of patients with trigeminal neuralgia who achieve pain relief with stereotactic radiosurgery, most start feeling the relief within 2 weeks to 2 months (general consensus is the maximum interval for pain relief is 180 days).[45] By 4 to 5 years after surgery, about 33% to 56% of patients remain pain free.[31] Decreased sensation is common and may develop an average of 6 to 36 months after radiation.[45] Sensory loss is only severe or bothersome in about 3% of patients; however, select patients may experience corneal numbness with neurotrophic keratopathy, dysesthesia, anesthesia dolorosa (painful numbness), and associated weakness of masticatory muscles.[45,48]

PERCUTANEOUS LESIONING OF THE TRIGEMINAL NERVE. Percutaneous ablative procedures are performed under fluoroscopic guidance and involve passing a long cannula into the cheek and through the foramen ovale, then lesioning the trigeminal nerve branches or ganglion. Radiofrequency thermocoagulation involves destruction of nerve fibers with heat, and patients are typically required to be awake briefly in the middle of the procedure to make sure the sensation of paresthesia matches the painful area. With chemical destruction (ie, glycerol rhizotomy) or mechanical destruction of nerve fibers (ie, balloon compression), patients are typically anesthetized the entire time. Initial pain relief rates with percutaneous procedures are high (>90% of patients), but the relief falls to 53% to 69% by 3 years.[45,49] About 20% of patients will have severe numbness, and, similar to other neuroablative procedures, some patients may experience additional complications, such as anesthesia dolorosa, exposure keratitis (damage to the cornea due to dryness), troublesome dysesthesia, and weakness of the masticatory muscles.[31,45]

PARTIAL SENSORY RHIZOTOMY OR INTERNAL NEUROLYSIS. Partial sensory rhizotomy involves surgical section of the sensory root of the trigeminal nerve; it has a reported clinical response in 70% to 88% of patients.[50] As in other destructive procedures, an increased risk exists of numbness, exposure keratitis, and difficulty with chewing. Internal neurolysis consists of dissecting sensory and motor roots of the trigeminal nerve into 5 to 10 fasciculi from the root entry zone to the Meckel cave.[50] In one series, improvement in pain was reported in 77% of patients at 1 year and in 72% at 5 years postoperative.[51]

KEY POINTS

- Recurrence of trigeminal neuralgia after microvascular decompression may be because of a new or previously missed vessel, compression with the synthetic material used in decompression, or arachnoid adhesions.
- Repeat microvascular decompression has a lower chance of pain relief and higher risk of complications.
- The best dosing and location of radiosurgery (where to aim along the trigeminal root) for trigeminal neuralgia is still being studied.
- Pain relief from radiosurgery may start 2 weeks to 2 months after treatment, whereas decreased sensation may start an average of 6 to 36 months after treatment.

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PAINFUL TRIGEMINAL NEUROPATHY

Trigeminal neuropathy typically manifests as numbness in one or more branches of the trigeminal nerve, sometimes associated with paresthesia or continuous or near-continuous neuropathic pain (ie, burning, prickling, itching, or pins-and-needles sensation). Patients may have superimposed brief paroxysms of pain resembling neuralgia, but they are not the predominant type of pain.[1] Similarly, large areas of mechanical allodynia or hyperalgesia may be present within the painful territory, but they are different than the small trigger zones in trigeminal neuralgia.[1]

Like other neuropathies, trigeminal neuropathy can be secondary to injury from a multitude of traumatic, metabolic, inflammatory, neoplastic, or infectious causes.[52] Sometimes local trauma may affect only one branch of a nerve, such as following a dental procedure, salivary gland biopsy, or face-lift (eg, mental neuropathy, inferior alveolar neuropathy, infraorbital neuropathy). Other times, painful posttraumatic trigeminal neuropathy may involve the entire nerve with injury to the nerve root or ganglion, such as after neuroablative procedures for trigeminal neuralgia, surgical trauma, or avulsion injuries.

Postherpetic Neuralgia

Acute herpes zoster (shingles) can cause a painful trigeminal neuropathy involving pain in the distribution of one or more trigeminal branches, with herpetic vesicles in the same distribution as pain. In rare cases in which no rash is present (zoster sine herpete), the diagnosis can be confirmed with a positive varicella-zoster virus polymerase chain reaction (PCR) in the CSF.[1] After the rash has healed, some patients may be left with continued debilitating neuropathic pain in the affected area. If this pain lasts more than 3 months, it is diagnosed as postherpetic neuralgia. Postherpetic neuralgia is more common in older adults, and it is often quite difficult to treat. First-line treatment includes tricyclic antidepressants (eg, amitriptyline or nortriptyline), antiepileptic drugs (eg, gabapentin or pregabalin), or topical medicines (eg, lidocaine or capsaicin).[53,54] Multiple medicines may be required to achieve pain relief, and some patients require long-term pain management with a specialized pain physician. Botulinum toxin A shows promise as a treatment for postherpetic neuralgia, but larger randomized trials are still needed.[53,55]

Numb Chin Syndrome

In the absence of a temporally associated dental procedure, numbness with or without neuropathic pain isolated to the chin and lip on one side (ie, numb chin syndrome) can be an ominous sign. This is because neuropathy isolated to the mental or inferior alveolar nerve may be the presenting symptom of an orofacial or systemic malignancy.[56] The neuropathy may be due to direct invasion of the nerve or mandible, such as from squamous cell carcinoma, leptomeningeal metastases, or mandibular metastases of distant neoplasms. In one systematic review of 136 patients with malignancy-related numb chin syndrome, breast cancer was the most commonly associated malignancy, followed by lymphoma, prostate cancer, and leukemia.[57]

It is common for patients presenting to neurologists with facial numbness to be evaluated for trigeminal neuropathy with a gadolinium-enhanced MRI of the brain, and in cases of numb chin syndrome, this may help with evaluation for demyelinating or leptomeningeal disease. However, a typical brain MRI may not

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extend inferiorly enough to view the mandible and may therefore miss a focal mass or osseous lesion. In cases of numb chin syndrome, additional facial MRI with gadolinium and special attention to the inferior alveolar canal may be helpful. If suspicion is high for neoplasm, a CT of the chest, abdomen, and pelvis; fludeoxyglucose positron emission tomography (FDG-PET)/CT; or CSF testing for malignant cells may also be helpful.[56]

NEURALGIC EAR PAIN

Patients presenting with ear pain should be evaluated by an otolaryngologist for underlying ear pathology. If the evaluation is negative, the pain may be referred to the ear from surrounding structures, such as the throat, teeth, parotid gland, lateral neck including vessels, or upper cervical roots. Neuralgic pain can be referred along six different nerves that innervate the ear, often with overlapping dermatomes (FIGURE 7-2).[58] Local structural irritation or trauma of these nerves, infection, inflammation, or neoplasm could contribute to pain within the nerve territories (TABLE 7-3). The first test after evaluation by an otolaryngologist is often a brain MRI with gadolinium, because it can visualize the internal auditory canal and the root entry zones of the cranial nerves. However, an MRI of the brain cannot visualize many of the structures that refer pain to the ear, so patients with neuralgic ear pain of unclear etiology may also require an MRI of the face and soft tissues of the neck with gadolinium. To remember the

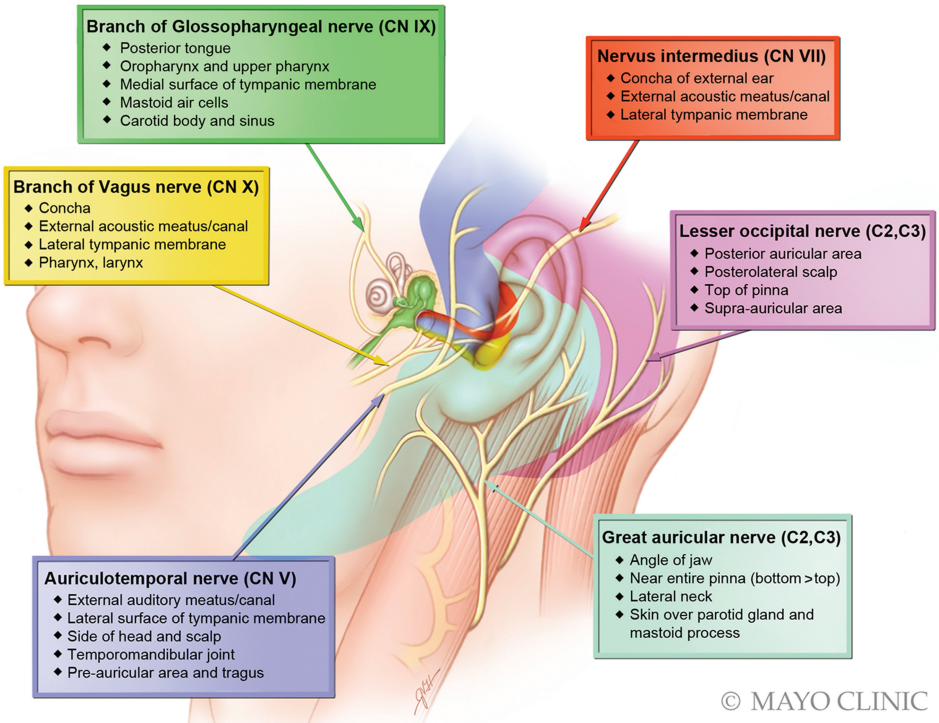

FIGURE 7-2

Innervation of the ear and surrounding anatomy. Depiction of the sensory nerves shows the innervation of the ear and surrounding anatomy. The boxes with their corresponding colors illustrate each nerve's distribution. Sensory distributions may overlap.

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KEY POINTS

- Trigeminal neuropathy following a neuroablative procedure for trigeminal neuralgia is called *painful posttraumatic trigeminal neuropathy*.
- By convention, the term *postherpetic neuralgia* is used for either neuralgic or neuropathic facial pain starting in an area with active herpes zoster rash and persisting for more than 3 months.
- Brain MRI is not adequate for numb chin syndrome as it may not visualize the mandible and may miss a malignancy located there.
- Stabbing ear pain may be referred along six nerves with overlapping dermatomes: the auriculotemporal nerve, lesser occipital nerve, great auricular nerve, nervus intermedius, glossopharyngeal nerve, and vagus nerve.
- Brain MRI is not adequate for unexplained ear pain, as it cannot visualize many structures that radiate pain to the ear, such as the throat, cervical vessels, and thyroid.

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TABLE 7-3

Secondary (Referred) Causes of Otalgia[a]

Cranial nerve VII (nervus intermedius)

- Cerebellopontine angle tumors
- Herpes zoster
- Nervus intermedius neuralgia

Cranial nerve V (auriculotemporal)

- Temporomandibular joint disease
- Dental pathology
- Parotiditis
- Parotid tumor
- Oral cavity cancer (squamous cell carcinoma)
- Acute sinusitis
- Trigeminal neuralgia

Cranial nerve IX

- Pharyngitis
- Tonsillitis/peritonsillar abscess
- Posttonsillectomy
- Pharyngeal tumor (squamous cell carcinoma)
- Retropharyngeal/parapharyngeal abscess
- Laryngopharyngeal reflux (gastroesophageal reflux disease)
- Eagle syndrome
- Glossopharyngeal neuralgia

Cranial nerve X

- Laryngopharyngeal reflux (gastroesophageal reflux disease)
- Laryngeal tumor/cancer (squamous cell carcinoma)
- Thyroid tumor/inflammation
- Intrathoracic mass lesion
- Laryngitis

C2, C3 (lesser occipital and great auricular nerve)

- Cervical degenerative disease/arthritis
- Whiplash/trauma
- Cervical lymphadenitis
- Great auricular or lesser occipital neuralgia

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various structures that can cause stabbing pain in the ear, the mnemonic ENT may be helpful:

- Ear pathology (intrinsic to the ear)
- Neuralgia of one of the nerves to the ear (cranial nerves V, VII, IX, X; lesser occipital nerve; and great auricular nerve)
- Throat, tonsils, tongue, thyroid, trachea, teeth, temporomandibular joint, and tunnels for vessels (jugular foramen and carotid sheath)[58]

GLOSSOPHARYNGEAL NEURALGIA

Glossopharyngeal neuralgia is described as unilateral paroxysmal electrical shock–like pain affecting the posterior tongue, pharynx, tonsillar fossa, deep in the ear, and/or beneath the angle of the jaw. It is typically provoked by swallowing, yawning, coughing, or sometimes talking.[1] Attacks last 2 seconds to 2 minutes on average.[59] Given that it is quite rare (with an estimated incidence of 0.2 per 100,000 to 0.7 per 100,000[60]) and the fact that it can co-occur with other neuralgias, such as trigeminal neuralgia, diagnosis is often complicated.

Approximately 2% of patients have associated symptoms of syncope with their pain.[61] Some have hypothesized that this is related to irritation of the afferent branches of the glossopharyngeal nerve, whereas others feel this is more likely spillover of impulses from the glossopharyngeal nerve via the tractus solitarius to the dorsal motor nucleus of the vagus nerve.[61,62] Bradycardia, hypotension, seizures, and even cardiac arrest have been described with excessive vagal involvement during an attack of glossopharyngeal neuralgia (ie, vagoglossopharyngeal neuralgia).[59] For this reason, patients with lightheadedness, palpitations, or syncope with their pain may require ambulatory ECG monitoring to look for associated bradyarrhythmia.

Similar to trigeminal neuralgia, glossopharyngeal neuralgia may be caused by neurovascular compression of the glossopharyngeal-vagal complex, typically by the posterior inferior cerebellar artery or less commonly by the anterior inferior cerebellar artery or vertebral artery.[60,63] Secondary causes can be related to compression, irritation, or infiltration of the nerve anywhere along the glossopharyngeal pathway, such as from demyelinating lesions; laryngeal, oropharyngeal, or skull base tumors (CASE 7-2); inflammation or infection (ie, parapharyngeal abscess); carotid sheath trauma; or elongated/calcified styloid processes (referred to as *Eagle syndrome*).[59] Pharmacologic treatment is similar to treatment of trigeminal neuralgia and includes carbamazepine, oxcarbazepine, or other membrane-stabilizing agents.[59] A topical anesthetic on the pharynx/tonsillar pillars or injected anesthetic as an extraoral glossopharyngeal nerve block can be helpful diagnostically and provide temporary pain relief.[60]

In cases refractory to medical therapy, surgery may be considered, typically either microvascular decompression or direct sectioning of the glossopharyngeal nerve and upper rootlets of the vagus nerve, or both.[63] Both have good short- and long-term success, and both have potential complications, including long-term dysphagia and hoarseness.[59,63,64] In patients in whom neurovascular compression is visible on imaging, microvascular decompression may be preferred,[59,63] although this is more technically difficult than microvascular decompression of the trigeminal nerve. In one systematic review comparing microvascular decompression, nerve section, and stereotactic radiosurgery, the authors concluded that nerve sectioning might provide the most favorable treatment

KEY POINTS

- Glossopharyngeal neuralgia is provoked by swallowing, yawning, or coughing.
- Patients with lightheadedness, palpitations, or syncope with their glossopharyngeal neuralgia pain may require ambulatory ECG monitoring to look for an associated bradyarrhythmia.
- Similar to trigeminal neuralgia, glossopharyngeal neuralgia may be related to neurovascular compression or other lesions along the nerve path.
- Either microvascular decompression or sectioning of the glossopharyngeal nerve (and sometimes vagus nerve rootlets) is considered a reasonable first-line treatment for medically refractory glossopharyngeal neuralgia.

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response for pain relief and postoperative outcome.[64] Stereotactic radiosurgery, radiofrequency nerve ablation, balloon compression, and other neuroablative procedures have also been described.[59]

NERVUS INTERMEDIUS NEURALGIA

The nervus intermedius is a branch of the facial nerve that carries parasympathetic fibers to the lacrimal and nasopalatine glands as well as sensory information from the tongue and concha of the ear.[65] Nervus intermedius neuralgia, also known as *geniculate neuralgia*, is characterized by paroxysmal deep ear pain (sometimes described as being stabbed in the ear with an ice pick), with possible radiation to just behind the ear.[65-67] Pain can be triggered by light touch (eg, with a cotton swab) or cold wind over the posterior wall of the auditory canal or periauricular region and may be accompanied by a disorder of lacrimation, salivation, or taste.[1,65]

Nervus intermedius neuralgia may follow infection or inflammation of the facial nerve and may therefore develop during or just after Ramsay Hunt syndrome or Bell's palsy.[58] When the neuralgic pain is related to varicella-zoster

CASE 7-2

A 73-year-old woman presented for a neurologic consultation with a 7-month history of sharp, electrical shock–like shooting pain in her left throat and deep into her left ear. The pain was triggered by swallowing and yawning. Talking, chewing, and touching her face did not affect the pain. She could not recall any rash in her throat or ear. The back of her throat felt very sensitive, and this tenderness, along with the triggered sharp pains, had been so severe that she had not been able to eat much. Because of this, she had lost 3.6 kg (8 lb) in the previous 4 months. An MRI of the brain with gadolinium 4 months into her symptoms showed no pathology along the glossopharyngeal nerve root entry zone. Erythrocyte sedimentation rate had been normal. At a local clinic, an otolaryngologist had performed a topical lidocaine block over the pharyngeal region. This provided significant relief, and she was able to swallow pain free until it wore off. Carbamazepine and gabapentin at low doses had not helped with her pain, and she had been unable to tolerate higher doses.

Neurologic examination was normal; however the patient had a hard palpable mass along the lateral neck that she said she had started noticing in the past 2 months. A gadolinium-enhanced MRI of the face and soft tissues of the neck showed findings suspicious for a left palatine tonsillar carcinoma, with a pathologic-appearing level 2/3 lymph node consistent with possible lymphatic metastasis.

COMMENT

This patient's symptoms were consistent with glossopharyngeal neuralgia. In this case, she had secondary glossopharyngeal neuralgia related to a palatine tonsillar carcinoma. It is important to note that a typical MRI of the brain may not provide adequate visualization of the throat. Patients with pain in the throat or deep in the ear may need additional imaging with a gadolinium-enhanced MRI of the face or soft tissues of the neck.

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virus, the *ICHD-3* recommends using the term *painful nervus intermedius neuropathy*; if the pain persists longer than 3 months, the term *postherpetic neuralgia of nervus intermedius* is used.[1] Medical therapy is similar to that used for trigeminal neuralgia, with carbamazepine or other antiepileptic drugs.[58] Rare cases of vascular compression have been described, and both microvascular decompression and sectioning of the nervus intermedius may be considered in cases that do not respond to pharmacologic treatment.[65-67]

OCCIPITAL NEURALGIA

The greater occipital nerve derives from the dorsal ramus of the C2 spinal nerve emerging at the posterior skull base and ascending to the vertex (FIGURE 7-3[68]). The lesser occipital nerve originates from branches of C2 and C3 in the cervical plexus and wraps around the sternocleidomastoid to innervate the lateral scalp, including the top of the external ear. The third occipital nerve is supplied by the medial branch of the C3 dorsal ramus and provides innervation to the lower occipital scalp and upper medial neck.[69,70]

Occipital neuralgia refers to paroxysmal shooting or stabbing pain in the posterior scalp in the dermatome of the greater occipital, lesser occipital, or third occipital nerves.[1] Patients may describe the pain as starting in the posterior skull base and radiating toward the vertex (greater occipital nerve) or over the ear toward the temple (lesser occipital nerve). By *ICHD-3* criteria, the pain is associated with dysesthesia and/or allodynia apparent during innocuous stimulation of the scalp and is associated with tenderness or a painful trigger point over the emergence of the affected nerve. Also by criteria, the pain is improved temporarily by a local anesthetic block of the affected nerve.[1]

Similar to other neuralgias, the patient should have a neurologic examination that includes looking for a sensory deficit in the distribution of the painful area. Rarely, occipital neuralgia can be secondary to lesions in the upper cervical cord, including cavernous malformations and demyelinating lesions.[71,72] Neuralgia with associated mild sensory deficit in the occipital nerve dermatomes has been described with occipital nerve schwannomas.[73,74] Irritation of the upper cervical nerve roots by blood vessels or Chiari malformation may also present with neuralgic pain in the occipital nerve distributions.[75] Given the possibility of secondary etiologies, it may be

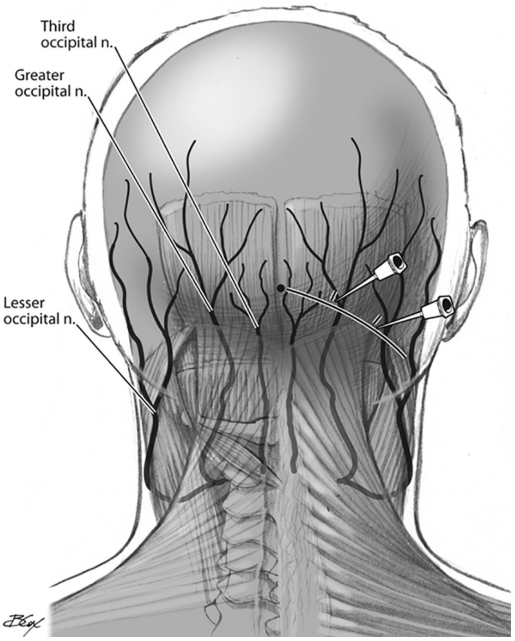

FIGURE 7-3
Location of greater occipital, lesser occipital, and third occipital nerves with location of greater and lesser occipital nerve blocks.
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KEY POINTS

- **Nervus intermedius neuralgia may present with stabbing pain deep in the ear triggered by cold wind or using a cotton swab in the ear canal.**
- **Nervus intermedius neuralgia may develop in the setting of classic Bell's palsy or Ramsay Hunt syndrome (herpes zoster affecting the ear and facial nerve).**
- **Occipital neuralgia is typically described as shooting or stabbing pain that starts at the posterior skull base and radiates either to the vertex (greater occipital nerve) or over the ear toward the temple (lesser occipital nerve).**

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KEY POINT

● If loss of sensation is present with occipital neuralgia, a secondary cause of pain should be considered.

prudent to consider imaging with an MRI of the brain and cervical spine in patients with new and unexplained occipital neuralgia.[70]

In most patients with occipital neuralgia, physical therapy and treatment with antiepileptic drugs or tricyclic antidepressants is often effective.[70,75,76] For flares of pain, nerve blocks can be performed by injecting anesthetic, sometimes combined with a corticosteroid, near the emergence of the occipital nerves at the skull base. This treatment can provide pain relief for a few weeks and in a small subset of patients may last several months.[75,76] Patients with occipital neuralgia not responding adequately to medical therapies or repeated blocks may benefit from pulsed radiofrequency treatment, neurolysis, onabotulinumtoxinA, or occipital nerve stimulation.[69,75]

Patients with severe pain refractory to medication or nerve blocks should be reevaluated for alternative diagnoses, such as referred pain from the atlantoaxial or upper zygapophysial joints. Primary headache disorders (eg, migraine) can sometimes be difficult to distinguish from occipital neuralgia, as they may have tenderness over the posterior skull base and may sometimes respond well to occipital nerve blocks.[67]

CONCLUSION

When evaluating a patient with neuralgic pain in the face or head, the diagnosis is made by careful history and examination, with attention to the dermatome involved, the triggers, and any associated sensory deficit. Patients with sensory deficit are particularly concerning for a secondary etiology, although all patients with new facial pain warrant additional evaluation for an underlying cause.

When evaluating neuralgic pain in the head and neck, a reasonable first image would be an MRI of the brain with contrast and specific views of the suspected nerve involved. However, this image is limited in scope and may miss pathology along the distal branches of V3 (mental or inferior alveolar nerves) as well as many structures in the neck that can radiate pain to the ear. For this reason, depending on the affected nerve, if the MRI brain is unremarkable, additional imaging with an MRI face or MRI soft tissues of the neck may be necessary. In the case of neuralgic pain in the distribution of the occipital nerves, if concern exists for a secondary etiology, an MRI of the cervical spine might also be considered.

Treatment of neuralgias includes antiepileptic medicines, baclofen, and tricyclic antidepressants. Cases refractory or intolerant to medication may benefit from surgical procedures, such as microvascular decompression, stereotactic radiosurgery, or percutaneous procedures. Occipital neuralgia may respond to injections with local anesthetic, sometimes combined with a corticosteroid.

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REVIEW ARTICLE

Headache in Women

By Jelena M. Pavlović, MD, PhD

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RELATIONSHIP DISCLOSURE:
Dr Pavlović serves on advisory boards for Alder BioPharmaceuticals, Inc/Lundbeck and Amgen Inc/Novartis AG and as a consultant for Alder BioPharmaceuticals, Inc/Lundbeck. Dr Pavlović receives research/grant support from the National Institute on Aging/National Institutes of Health (K23 AG049466).

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr. Pavlović discusses the unlabeled/investigational use of medications for the treatment of menstrually related migraine and migraine and other headaches in pregnancy and lactation, none of which are approved by the US Food and Drug Administration for this indication.

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ABSTRACT

PURPOSE OF REVIEW: **Women are greatly overrepresented among patients seeking treatment for symptoms of headache pain in general and migraine in particular. Understanding the presentation of headache in women in relation to hormonal changes both during the menstrual cycle and throughout the life span is essential for appropriate diagnosis and treatment.**

RECENT FINDINGS: **Although perimenstrual migraine attacks are generally without aura, the diagnosis of migraine with aura has been added to the headache classification for menstrual migraine to account for women with the diagnosis of migraine with aura who experience menstrual migraine attacks. Emerging knowledge regarding the differences between menstrual and nonmenstrual attacks, the variability of attack triggering within and between women, and the response of women with menstrually related migraine to new migraine drug classes is contributing to better understanding and more effective treatment of these particularly burdensome and refractory attacks. Given the burden of migraine, almost one-fourth of women with migraine avoid or delay pregnancy. Women who experience migraine during pregnancy are more likely to have a hypertensive disorder and stroke during pregnancy and/or delivery and the postpartum period. Treatment of headache in general and migraine in particular in pregnancy is challenging because of fetal and maternal risks; however, a 2021 systematic review suggests that triptans and low-dose aspirin may not be associated with fetal/child adverse effects and could be more strongly considered for headache treatment in pregnancy.**

SUMMARY: **Headache in general and migraine in particular are extraordinarily common in women of reproductive age and fluctuate with hormonal changes and phases of life. Improved knowledge of the epidemiology, pathophysiology, and response to treatment of perimenstrual attacks is essential for more effective response to this most burdensome headache type. Treatment of headache in pregnancy remains challenging.**

INTRODUCTION

It has long been recognized that headache disproportionately affects women and that female biology affects migraine across the life cycle, with implications for migraine triggering and migraine manifestations across the menstrual cycle in women. Hormonal fluctuations can have a significant impact on the occurrence of both migraine and tension-type headache. As other types of headache are not typically recognized as being hormonally influenced, the focus in this article is on migraine as the most common headache

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type in women affected by hormonal change. The perimenstrual attacks of migraine thought to be precipitated by falling estrogen levels before the onset of menstruation have been shown to be more severe and refractory to treatment in clinic- and population-based studies.[1,2] Tension-type headaches have also been observed to increase in frequency during this time period. Given the increased burden of perimenstrual headache attacks, they present a treatment challenge but also an opportunity because of their predictable nature. As migraine frequency tends to increase with fluctuating hormones, perimenopause can be particularly challenging for women with migraine. Although headache and migraine generally improve during pregnancy, treatment during this time is challenging given the inherent risk to fetus and mother. A great need remains for additional evidence regarding the safety of both acute and preventive treatments for headache in general and migraine specifically in women who are pregnant and lactating. Data on the safety of new drug classes in these groups are lacking. Neuromodulation devices and biobehavioral approaches present a great opportunity for nonpharmacologic treatment of migraine in pregnancy and lactation without evidence of adverse effects and are an emerging new venue for migraine treatment.

KEY POINT

- Migraine is predominantly a disorder of women that is affected by fluctuations in ovarian hormones, affecting women throughout their lifetime by varying in frequency and burden with hormonal changes.

MIGRAINE IN WOMEN

Migraine is predominantly a disorder of women. It is 3 times more prevalent in women than men and is the leading cause of years lived with disability for women of reproductive age.[3,4] Migraine disproportionately affects women of reproductive age, interfering with their work, social, and family life and leading to a significant burden to both the individual and society.

Although the annual migraine prevalence in US women is 18%, the migraine prevalence for women in their thirties approaches 30%.[5,6] The increased prevalence in women begins at menarche, increases until the early forties, and then rapidly declines following the final menstrual period around age 52.[5] Early menarche appears to be a risk factor for developing migraine independent of family history and weight.[7] As migraine is triggered by fluctuation in ovarian hormones, migraine attacks affect women throughout their lifetime, varying in frequency and burden with hormonal changes. Migraine attacks most commonly abate during the second and third trimesters of pregnancy when hormonal levels are stable and often suddenly worsen in the peripartum period and perimenopause when hormonal levels fluctuate.

Ovarian hormone variability throughout the menstrual cycle also affects migraine occurrence on a monthly basis (FIGURE 8-1[8]). Menstruation and the resulting hormonal change are considered one of the most common migraine triggers. More than 60% of women of reproductive age report an association between their migraine attacks and menses.[1,7] Estrogen withdrawal before menstruation has long been implicated in the triggering of migraine, and estrogen replacement has been used in migraine treatment, although it can exacerbate migraine in some women.[9,10]

PATHOPHYSIOLOGY OF THE EFFECTS OF OVARIAN HORMONES ON MIGRAINE

It has been suggested that migraine is a "brain state," with a potential multitude of alterations in the activity of brain networks that may be affected by hormonal changes. The influence of hormones on migraine has long-standing recognition,

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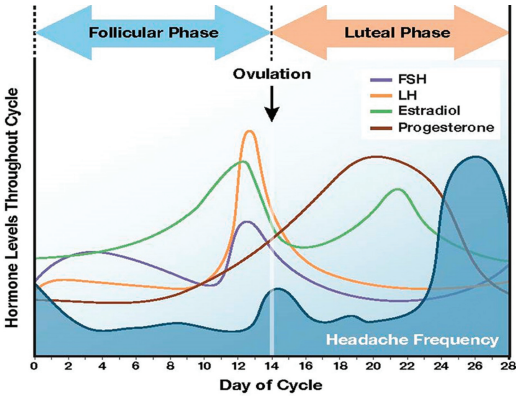

FIGURE 8-1

Migraine occurrence in relation to hormonal changes through the menstrual cycle. Changes in headache frequency with hormonal changes seen in a typical ovulatory cycle are shown. Sex hormones related to the menstrual cycle are indicated as follows: follicle-stimulating hormone (FSH, *purple*), luteinizing hormone (LH, *orange*), estradiol (*green*), progesterone (*brown*). The frequency of headache days through the menstrual cycle is presented under the *blue curve*. Migraine attacks tend to peak during estrogen "withdrawal" in the late luteal phase, leading to perimenstrual migraine.

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and the role of estrogen in particular has been implicated since the 1970s.[9] Multiple studies have observed that migraine most frequently occurs in conjunction with the rapid drop in estrogen in the late luteal phase and early subsequent follicular phase when estrogen and progesterone levels are at their lowest (2 days before menses and the first 3 days of menses) (FIGURE 8-1).[11,12] This presumed association between the increased occurrence of migraine relative to menses has been referred to as the *estrogen withdrawal hypothesis*.[9] Although progesterone withdrawal does not affect migraine occurrence, progesterone likely plays a modifying role in the headache-promoting effects of estrogen fluctuation.

Both estrogen and progesterone have complex and dynamic effects on multiple aspects of the hypothalamic-pituitary axis. They feature synergistic and opposing roles on pain in migraine, depending on their concentration and timing. The opposing effects of sex hormones and the differing effects of their absolute and relative levels make for complex interactions. Estrogen mainly increases neuronal hyperexcitability by stimulating excitatory glutamatergic conductance and by decreasing inhibitory γ-aminobutyric acid–mediated (GABA-ergic) activity.[13] Progesterone and its metabolites, in contrast to estrogen, display neuroinhibitory effects via pro–GABA-ergic and anti-inflammatory effects.[7,13] It is of interest that although neuroexcitatory, estrogen appears to have a protective role in migraine. This protective role is likely to be mediated through estrone stimulation of the antinociceptive serotonergic and opioidergic systems. Estrogen has complex interactions with the serotonergic system but, overall, appears to increase serotonergic tone in the trigeminal system, thereby contributing to antinociceptive mechanisms in migraine.[7,13] It also potentiates the endogenous opioidergic system by stimulating the production of endorphins. These mechanisms may play an important role in estrogen's effect on the pathophysiology of migraine and are likely to be further modulated by loss of GABA-ergic tone because of progesterone decline in the late luteal phase. Also, calcitonin gene-related peptide (CGRP) levels are higher in women of reproductive age than in men and are influenced by cyclic hormonal fluctuations; CGRP release appears to be primarily associated with the higher estrogenic state, a somewhat controversial finding that requires further examination.[13,14]

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Furthermore, specific hormonal changes can have different effects at different stages of a woman's reproductive life. For example, although progesterone supplementation has been observed to prevent migraine in premenopausal women, it can provoke migraine in postmenopausal women.[15]

MIGRAINE IN RELATION TO THE MENSTRUAL CYCLE—MENSTRUAL MIGRAINE

The increased risk of perimenstrual migraine attacks has long been recognized. The pathophysiology of these attacks has for the past 50 years been related to the estrogen withdrawal hypothesis coined by Somerville,[9] in which migraine "triggering" was observed because of the decrease of supplemental estrogen (estradiol) and not in the setting of decreasing progesterone. Menstruation has been repeatedly conceptualized as one of the most common triggers of migraine in women,[7] although in comparison with other common triggers that are exogenous (such as stress and alcohol), it represents an endogenous change that may be a biological trait as women with migraine appear to have accelerated estrogen decline in the first 2 days of the late luteal phase compared to women without a history of migraine.[8] Perimenstrual attacks tend to be particularly burdensome and refractory to treatment.[1,7] However, the predictable nature of hormonal influences on migraine presents an opportunity for targeted therapy for these attacks.[2]

Perimenstrual attacks typically occur 2 days before the onset of bleeding and can last through the first 3 days of bleeding. This perimenstrual interval is commonly referred to in the literature as –2 to +3, with the first day of menstrual bleeding being the day +1 (there is no day 0). The *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) groups the phenomenon of increased susceptibility to migraine attacks around the time of menstruation into two diagnoses: (1) pure menstrual migraine, a rare disorder affecting less than 10% of women with migraine in which attacks are limited to the perimenstrual window of –2 to +3, and (2) menstrually related migraine, a common disorder affecting more than 50% of women with migraine, who experience attacks during the –2 to +3 days around menstruation as well as during other times of the menstrual cycle.[16] The perimenstrual attacks are commonly referred to as menstrual migraine, leading to some confusion in the literature about whether the reference is to the migraine attacks or to the group of women experiencing the perimenstrual attacks (either pure menstrual migraine or menstrually related migraine). Although this confusion is not of significant consequence to clinical practice, it is essential to be mindful of it in the research setting and evaluation of literature. Perimenstrual attacks are commonly migraine without aura, even in women who otherwise have attacks with aura.[1] This propensity for migraine without aura was reflected in the *ICHD* criteria, in which, until recently, the pure menstrual migraine and menstrually related migraine diagnoses were explicitly associated with migraine without aura (TABLE 8-1 and TABLE 8-2); a recent change in the diagnostic classification has added migraine with aura as a potential subtype to both pure menstrual migraine and menstrually related migraine (TABLE 8-3 and TABLE 8-4).

For the diagnosis of both pure menstrual migraine and menstrually related migraine to be fulfilled, perimenstrual attacks must have occurred with at least two out of the last three menstrual cycles.[16] Although the diagnosis in clinical

KEY POINTS

- Perimenstrual migraine attacks are thought to be due to estrogen withdrawal before menstruation.
- Although generally neuroexcitatory, estrogen appears to have a protective role in migraine, with migraine occurrence being related to low estrogen levels.
- Perimenstrual migraine attacks are more intense, more burdensome, and more refractory to treatment than nonmenstrual attacks, requiring a proactive approach. The predictive nature of perimenstrual attacks provides an opportunity for treatment.
- Perimenstrual migraine attacks are commonly migraine without aura, even in women who otherwise have attacks with aura.

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practice is commonly based on retrospective information (ie, interview of the patient), the *ICHD-3* diagnostic criteria recommend that diary data be used for diagnostic determination, particularly for research purposes. Of clinical relevance is that patients should be asked whether they experience migraine attacks "around their period" and not only "with their period," as women often do not recognize the days before bleeding as associated with the perimenstrual window of hormonal change.

Variation in the menstrual cycle length in women can create potential challenges, depending on the sampling time and the length of sampling interval (women with long cycles may need several months to record three cycles). Furthermore, a 2020 study using electronic diaries over 3 months in women with migraine observed that the effect of menstruation on migraine varies more within an individual woman (ie, a woman who experiences perimenstrual attacks in one cycle may not do so in the next) than between women.[17] Although many women with migraine intuitively recognize that not all of their cycles carry equal risk of perimenstrual attacks, this confirmation of patients' intuition using intense diary data is highly relevant information that may influence clinical practice with the recognition that women need to record more than three cycles for diagnosis based on temporal sampling.

TREATMENT OF MIGRAINE RELATED TO MENSTRUATION

No treatments currently available are specifically approved for perimenstrual attacks in either pure menstrual migraine or menstrually related migraine. Treatment of acute migraine attacks is generally the same whether perimenstrual or not menstrually related. However, perimenstrual attacks tend to be more refractory to treatment than nonmenstrual attacks.[2]

The predictability of perimenstrual migraine and a limited time interval of attacks (no more than 7 days) allows for a treatment strategy commonly referred to as *mini-prevention*, in which patients are instructed to start treating their perimenstrual headache (with nonsteroidal anti-inflammatory drugs [NSAIDs] or triptans) 2 times a day for the length of the time they would typically have headache (5 days on average); treatment typically begins at the onset of

TABLE 8-1 ***ICHD-3* Diagnostic Criteria for Pure Menstrual Migraine Without Aura[a]**

Pure menstrual migraine without aura	
A	Attacks, in a menstruating woman,[b] fulfilling criteria for migraine without aura and criterion B below
B	Occurring exclusively on day 1 ± 2 (ie, days −2 to +3)[c] of menstruation[b] in at least two out of three menstrual cycles and at no other times of the cycle[d]

ICHD-3 = International Classification of Headache Disorders, Third Edition.

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[b] For the purposes of *ICHD-3*, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy.

[c] The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0.

[d] For research purposes a prospective diary is recommended, but this is not mandatory for clinical diagnosis of pure menstrual migraine without aura.

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perimenstrual headache (although recommendations vary from the onset of headache to a few hours to 2 days before) in those who have very predictable attacks. Triptans are generally recommended as first-line treatment. The best evidence available is for frovatriptan 5 mg 2 times a day started 1 to 2 days before a predicted menstrual migraine, with 2.5 mg 2 times a day for an additional 5 days. If frovatriptan is not available, naratriptan 2.5 mg 2 times a day for 5 days is commonly used. Naproxen 500 mg 2 times a day can also be prescribed and is particularly useful for women who also experience dysmenorrhea. Although bridging with perimenstrual estrogen was initially recommended as it was shown to significantly reduce the occurrence of menstrual attacks, it is currently not recommended as migraine tends to be delayed to later in the cycle following treatment withdrawal.[10]

If the response to mini-prevention is inadequate, nonhormonal preventive strategies used for migraine in general should be used. For more information on preventive strategies, refer to the article "Preventive Migraine Treatment" by Rebecca Burch, MD, FAHS,[18] in this issue of *Continuum*. This preventive treatment can be tailored based on the patient's accompanying symptoms and comorbidities. Evidence of the effect of preventive agents on menstrual migraine has until recently been limited to an open-label study of topiramate showing a reduction in menstrual attack frequency but not the duration or severity of attacks.[2] In a post hoc analysis of erenumab (a monoclonal antibody targeting the CGRP receptor) for preventing episodic migraine, women with self-reported menstrual migraine had efficacy and safety profiles comparable to those without menstrual migraine.[19] Further studies are ongoing to examine the use of both acute and preventive agents targeting the CGRP pathway in menstrual migraine.

MIGRAINE IN PERIMENOPAUSE AND MENOPAUSE

As migraine is affected by hormonal fluctuations, perimenopause and menopause present an often-eventful time for women with migraine, who may experience an increase in both attack frequency and symptoms of perimenopause.[20] It is essential to recognize that the menopausal transition takes

ICHD-3 Diagnostic Criteria for Menstrually Related Migraine Without Aura[a]

TABLE 8-2

Menstrually related migraine without aura

A Attacks, in a menstruating woman,[b] fulfilling criteria for migraine without aura and criterion B below

B Occurring on day 1 ± 2 (ie, days −2 to +3)[c] of menstruation[b] in at least two out of three menstrual cycles, and additionally at other times of the cycle[d]

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[b] For the purposes of *ICHD-3*, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy.

[c] The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0.

[d] For research purposes a prospective diary is recommended, but this is not mandatory for clinical diagnosis of menstrually related migraine without aura.

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10 years on average and has several stages, each characterized by specific hormonal changes[21]:

- **Premenopause: no menstrual irregularity in the past 12 months**
- **Early perimenopause: menses in the past 3 months, with less predictable periods**
- **Late perimenopause: two or more skipped periods and interval of amenorrhea for more than 60 days**
- **Early postmenopause: 12 months following the final menstrual period**

Consistent cyclical hormone patterns characterize premenopause and early perimenopause. Late perimenopause and early postmenopause are characterized by irregular hormone patterns with widely fluctuating hormonal levels. In contrast, late postmenopause is characterized by quiescent hormonal patterns with low and blunted hormone levels. Although the effect of these menopausal transition phases on migraine remains underexplored in the literature, considerable anecdotal and experiential evidence indicates that headache frequency worsens as the menopausal transition progresses and finally becomes quiescent in menopause.[15,20]

Women with a history of premenstrual syndrome typically have more pronounced worsening of migraine symptoms during the menopausal transition and more pronounced resolution after the menopausal transition.[20] During the menopausal transition, worsening migraine severity is manifested as unpredictable attacks that last longer and are more severe and less responsive to treatment compared to premenopausal attacks. Women who are perimenopausal have a 50% increased risk of having high-frequency migraine compared to women who are premenopausal.[22] Women who undergo surgical menopause often experience worsening rather than improvement of migraine, suggesting that the hormonal levels and timing of hormonal interactions are not easily explained by simple withdrawal mechanisms. Furthermore, women with migraine are more likely to experience the vasomotor symptoms of menopausal transition, which are associated with less favorable cardiovascular profiles as is migraine, suggesting a shared physiologic pathway between migraine and vasomotor symptoms.[23,24] For further discussion on the association of migraine

TABLE 8-3 ***ICHD-3* Diagnostic Criteria for Pure Menstrual Migraine With Aura[a]**

Pure menstrual migraine with aura	
A	Attacks, in a menstruating woman,[b] fulfilling criteria for migraine with aura and criterion B below
B	Occurring exclusively on day 1 ± 2 (ie, days −2 to +3)[c] of menstruation[b] in at least two out of three menstrual cycles and at no other times of the cycle[d]

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[b] For the purposes of *ICHD-3*, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy.

[c] The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0.

[d] For research purposes a prospective diary is recommended, but this is not mandatory for clinical diagnosis of pure menstrual migraine with aura.

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with cardiovascular risk in women, refer to the excellent 2020 narrative review by Tietjen and colleagues.[24]

HEADACHE AND PREGNANCY

Given that the prevalence of headache in general and migraine in particular is highest in women during childbearing years, the diagnosis and management of headache during pregnancy present a common clinical challenge. Although primary headache disorders occurring in pregnancy tend to be preexisting, headaches can also happen de novo during pregnancy or the peripartum and postpartum periods or while breastfeeding. The stress of pregnancy planning and challenges of infant care can often exacerbate preexisting headaches. Most women with primary headaches experience improvement during pregnancy, presumably because of steadily rising hormone levels. This phenomenon is particularly well understood in migraine, the primary headache for which women most often seek care, but has also been observed in tension-type and other headaches. Although this article primarily focuses on the presentation and treatment of common primary headaches during pregnancy (with emphasis on migraine), it is important to recognize that the emergence of new headache or a change in the characteristics of preexisting headache disorders during pregnancy and the peripartum period should be viewed with a high index of caution given the prothrombotic state that puts women at risk for secondary headache. For more information on secondary headaches, refer to the article "Diagnosing Secondary and Primary Headache Disorders" by David W. Dodick, MD, FAAN, FAHS,[25] in this issue of *Continuum*. Furthermore, the treatment of headache in pregnancy presents unique challenges of balancing the risks and benefits of the treatment with the health of the mother and the fetus. As evidence on the overall safety of acute and preventive treatments in headache remains very limited,[26] it is not surprising that even many headache specialists have discomfort with this area of headache treatment.[27]

Tension-type Headache in Pregnancy

Compared to migraine, studies of tension-type headache during pregnancy are greatly limited; the evaluation of tension-type headache during pregnancy

***ICHD-3* Diagnostic Criteria for Menstrually Related Migraine With Aura[a]** TABLE 8-4

Menstrually related migraine with aura

A Attacks, in a menstruating woman,[b] fulfilling criteria for migraine without aura and criterion B below

B Occurring on day 1 ± 2 (ie, days −2 to +3)[c] of menstruation[b] in at least two out of three menstrual cycles, and additionally at other times of the cycle[d]

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[b] For the purposes of *ICHD-3*, menstruation is considered to be endometrial bleeding resulting either from the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy.

[c] The first day of menstruation is day 1 and the preceding day is day −1; there is no day 0.

[d] For research purposes a prospective diary is recommended, but this is not mandatory for clinical diagnosis of menstrually related migraine with aura.

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without the knowledge of prepregnancy diagnosis presents a challenge for research, given that the migraine phenotype is known to improve in later stages of pregnancy and can therefore be misdiagnosed as tension-type headache. In the few studies to date, women with tension-type headache had fewer changes during pregnancy than those with migraine, with about 20% of women improving compared to only 2% worsening.[28] A relationship of nonmigraine headache with parity has been suggested by the Norwegian population-based Head-HUNT study, in which the association between headache and pregnancy was significant for women pregnant with their first child but not for multiparous women.[29] Tension-type headaches have not been demonstrated to cause adverse effects in pregnancy. Treatment of tension-type headache is often not needed as symptoms tend to be mild and are easily treated with nonpharmacologic approaches and acetaminophen. In patients with severe tension-type headache, acute and preventive treatments for migraine can be used.

Migraine in Pregnancy and the Peripartum Period and During Lactation

The majority of studies of women with migraine support the clinical notion that migraine improves over the course of pregnancy. However, pregnancy planning and the first trimester of pregnancy can still present a significant challenge for women with migraine in terms of both headache frequency and intensity and treatment options. Given the recommendation to discontinue preventive and minimize acute treatments before conception, women often experience ambivalence about pregnancy planning, with almost 20% (121 of 607) of women in the American Registry for Migraine Research reporting that they avoided pregnancy because of fears that their migraine would worsen or complicate pregnancy or that the medications would have deleterious effects on the fetus.[30] These women were, on average, younger and more likely to have menstrually related and chronic migraine. However, about 50% to 80% of women with migraine experience a reduction in headache frequency or even complete remission of migraine during the second and third trimesters.[31] Less is known about the first trimester given the methodologic challenges involved in studying an interval during which women may not be aware that they are pregnant. Clinical experience suggests that headaches tend to be worst leading up to conception (presumably because of the discontinuation of treatment) and during the first several weeks postconception, a period of time when hormonal fluctuations and other symptoms of pregnancy can exacerbate migraine. With rising estrogen and endogenous opioid levels, migraine stabilizes as the pregnancy progresses, with up to 83% of women having improvement or complete resolution of migraine symptomatology by the third trimester.[32] This improvement appears to be more common in women who have migraine without aura compared to those with aura,[32] but this effect has not been replicated in all studies.[33] Those who have aura may not have such a remission.

Many studies have shown that women with a history of menstrually related migraine experience the most benefit during pregnancy.[31] The majority of these studies have been retrospective, whereas a 2018 prospective study did not confirm the benefit in women with a self-reported history of menstrually related migraine. Although both the menstrually related migraine and non–menstrually related migraine groups improved as expected during the second and third trimesters, they also experienced high headache frequency before pregnancy, during early pregnancy, and in the postpartum period, with the menstrually

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related migraine group having higher frequency and more severe headaches.[34] As perimenstrual attacks are known to be more intense, burdensome, and refractory to treatment, these results are not entirely surprising given that women with menstrually related migraine are known to be more susceptible to hormonal fluctuations and may therefore experience worse attacks at times that are hormonally influenced.

A 2017 systematic review of migraine in pregnancy reported worsening of migraine without aura in 8% of cases during the first trimester, primarily associated with persistent hyperemesis gravidarum.[35] Of note is that when new migraine phenomena appear during pregnancy, they are more likely to be migraine with aura than migraine without aura, and new auras and isolated aura may occur.[31] This phenomenon is thought to be due to the high estrogen to progesterone ratio, which is known to decrease the threshold for cortical spreading depression in animal models.[7] Overall, a systematic review concluded that about one-fourth of patients with migraine without aura will continue to have attacks during pregnancy, with hyperemesis, pathologic pregnancy course, and pregestation menstrually related migraine occurring more commonly in these women.[32,35]

The peripartum period is characterized by sudden drop in estrogen immediately following delivery, leading to a number of symptoms, including headache. More than one-third of women will experience the reappearance of migraine within 1 week postdelivery, and almost two-thirds will have an attack within a month.[31] The attacks have been described as worse than those experienced during pregnancy, with reports of attacks both similar to or worse than prepregnancy attacks.

The exacerbating effects of rapid estrogen drop can be ameliorated by breastfeeding. Lactating mothers experience ovulatory suppression because of elevated levels of prolactin, thereby limiting fluctuations in estradiol and resulting migraine. In a longitudinal prospective study, breastfeeding caused a delayed effect on migraine recurrence, with lactating women having recurrence rates of 50% at 1 month, 65.8% at 3 months, and 71.1% at 6 months compared to nonlactating women, whose recurrence rates were 86.4% at 1 month, 90.9% at 3 months, and 95.5% at 6 months.[36] Furthermore, lactation is associated with secretion of vasopressin and oxytocin, which have antinociceptive properties likely to play a role in migraine inhibition. As women with migraine may be hesitant to breastfeed given further limitations of migraine treatment, special efforts should be taken to educate women regarding the benefits of lactation on migraine suppression. Sleep deprivation and other stressors of early motherhood and infant care should be addressed and patients educated on biobehavioral approaches to this challenging time of a woman's life.

IMPACT OF MIGRAINE ON PREGNANCY. Migraine is associated with higher rates of both medical and obstetric events; pregnant women with a history of migraine, particularly those with frequent attacks, should be considered at higher risk of adverse outcomes and should be educated and monitored for potential complications. Migraine has been associated with increased risk of vascular disorders of pregnancy, particularly gestational hypertension and preeclampsia.[37] Women who have migraine with aura appear to be at higher risk for preeclampsia than those without aura (5.9% compared to 2.9%),[38] whereas the presence of aura appears to have no association with elevated risk of

KEY POINTS

- Clinicians and patients must recognize that menstruation can affect migraine in women in many different ways. To get a better sense of how menstruation and migraine are related in a given woman, a diary should be kept for a longer period of time than the currently recommended 3 months.
- Perimenstrual migraine can be treated with routine acute migraine treatment agents or with mini-prevention approaches in which triptans or nonsteroidal anti-inflammatory drugs are taken 2 times a day for about 5 days starting at the onset of perimenstrual migraine, typically 2 days before onset of menstruation.
- Perimenopause and the menopausal transition are marked by hormonal fluctuations and present an often-eventful time for women with migraine, who may experience an increase in both attack frequency and symptoms of perimenopause.
- Migraine is the most common primary headache disorder for which women seek help during pregnancy.
- Migraine frequency and symptomatology typically improve as pregnancy progresses, yet many women delay pregnancy for fear of migraine worsening or potential complications to themselves or the fetus. Education of women on the natural course of migraine in pregnancy is essential.

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gestational hypertension. The prothrombotic state of pregnancy adds additional risk to pregnant women with migraine, who may already be prone to often-undiagnosed hypercoagulabilities. Migraine during the peripartum period has been associated with increased risk of ischemic stroke, cerebral hemorrhage, myocardial infarct, venous thromboembolism, pulmonary embolism, and thrombophilia.[37] A 2020 study of 3 million births in California found that women who experienced migraine during pregnancy were more likely to have a hypertensive disorder and stroke during pregnancy and/or delivery and the postpartum period, with the highest adjusted risk ratio during the pregnancy/delivery period. After adjustment for potential mediators, only about one-fourth of the excess cases of maternal stroke associated with migraine were attributable to hypertensive disorders, suggesting other mechanisms that play a role in stroke risk in migraine during pregnancy and the peripartum period.[39] As a hypercoagulable state is most likely to contribute to additional risk of stroke and cardiovascular events in migraine during pregnancy, treatment with low-dose aspirin can be considered, particularly in migraine with aura, as it is safe and effective for both hypercoagulability and treatment of headache pain,[40] although no outcome studies regarding migraine have been reported.

TREATMENT OF MIGRAINE IN PREGNANCY. Treatment of migraine during pregnancy and lactation presents a significant challenge as potential benefit and harm to both the mother and the fetus must be considered, often without sufficient data. Given the episodic nature of attacks in the majority of women, the strategy is often to delay or avoid treatment or to use nonpharmacologic treatments, such as relaxation, mindfulness, and biofeedback. Based on current US Food and Drug Administration (FDA) classifications of medications, acetaminophen and metoclopramide are the recommended first-line treatments for migraine in pregnancy, and NSAIDs could be used in the second trimester (but before 30 weeks of gestation). Triptans, which are the mainstay of acute headache treatment in nonpregnant and nonlactating women, are currently not recommended during pregnancy, although studies of teratogenicity have long suggested that they are safe. Their safety was confirmed in a 2021 systematic review that noted that triptans and low-dose aspirin may not be associated with fetal/child adverse effects and should likely be much more readily used for treatment of migraine in pregnancy.[26] It should be noted that because of the widespread use of opioids for pain treatment, a greater amount of data exists regarding opioid use during pregnancy than for other commonly used migraine acute medications. This often still leads to preferential prescribing of opioids for the treatment of migraine in pregnant women. Transitioning from prescribing opioids to triptans for women who are pregnant or lactating is a priority. For women who require preventive treatment during pregnancy, calcium channel blockers may be the drugs of choice as Saldanha and colleagues[26] reported they "may not be associated with fetal/child adverse effects."

Women who had medication exposures during pregnancy should be encouraged to register with the pertinent pregnancy medication registry. The US FDA does not maintain any pregnancy registries but posts the registries at the request of investigators/manufacturers (www.fda.gov/science-research/womens-health-research/pregnancy-registries).[41] No first-line migraine treatments are currently listed on the FDA pregnancy registry website. Most pregnancy registries are maintained by the medication manufacturers and thus

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may not be available for real-time access. The majority of drugs currently used as first-line acute migraine treatment have not been associated with deleterious effects to the fetus during pregnancy exposure. As most women with migraine experience improvement in their headache during pregnancy, preventive treatments are generally not needed.

For patients who require additional treatment, interventional therapies such as nerve blocks, trigger point injections, and onabotulinumtoxinA injections provide alternative treatment options. Peripheral nerve blocks with lidocaine or ropivacaine as the anesthetic agent of choice are increasingly being used for treatment of and prophylaxis against headaches in pregnancy and lactation.[42] OnabotulinumtoxinA, a preventive therapy for chronic migraine with long-term action, has been shown to have the same rate of birth defects (3%) as in the general population.[43] Finally, neuromodulation devices present a great opportunity for nonpharmacologic treatment of migraine in pregnancy without evidence of adverse effects and are an emerging new option for migraine treatment in pregnancy.[44]

Overall, a great need remains for additional evidence regarding the safety of both acute and preventive treatments of headache broadly and migraine specifically in women who are pregnant and lactating. No specific maternal toxicities, major birth defects, or increased reporting of spontaneous abortion were reported in a recent evaluation of 94 cases of the use monoclonal antibodies targeting CGRP or its receptor in pregnancy.[45] Although the lack of evidence for novel drug classes (gepants, ditans, monoclonal antibodies) is expected, the knowledge deficit for therapies that have been available for decades at this time speaks to the great need for further research and patient advocacy in this area. The need for better evidence is startling given that the majority of women going through this very demanding phase of life opt not to treat migraine because of fears of harm to themselves and their fetuses.

Cluster Headache in Pregnancy

As cluster headache is rare in women, a significant knowledge gap exists regarding the prevalence in and impact of cluster headache on pregnancy. Unlike migraine, cluster headache does not seem to be affected by hormonal fluctuations during the menstrual cycle and is not believed to be affected by pregnancy.[46]

The approach to cluster headache during pregnancy is similar to all other primary headaches, with the main goal to be as conservative as possible to avoid harm to the fetus. Although nonpharmacologic approaches are generally not effective in acute cluster treatment, the predictability of cycles of cluster attacks can be used to counsel patients on the timing of pregnancy, with potentially planning pregnancy proximal to the resolution of the most recent cycle of cluster headache. Women who use tobacco or alcohol should be encouraged to abstain during pregnancy planning and clearly during pregnancy itself, because they can lower the threshold for cluster outbreaks.

High-flow oxygen should be used as the first-line abortive treatment for cluster headache in pregnancy. Sumatriptan is a reasonable choice given the severe intensity of pain during a cluster attack and increasing support for use of triptans in pregnancy.[26] Occipital nerve injections or intranasal lidocaine can also be effective in breaking a cluster cycle. Steroids, which are relatively safe in pregnancy, can also be used in an attempt to break a cluster cycle. When

KEY POINTS

- New migraine phenomena during pregnancy are more likely to be migraine with aura than migraine without aura. Isolated auras can also occur. This is likely due to a high estrogen to progesterone ratio, which decreases the threshold for cortical spreading depression.
- Sleep deprivation and other stressors of early motherhood and infant care should be addressed and patients educated on biobehavioral approaches to this challenging time of a woman's life.
- Migraine is associated with higher rates of both medical and obstetric events; pregnant women with a history of migraine, particularly those with frequent attacks, should be considered at higher risk of adverse outcomes and should be monitored with a heightened index of suspicion.
- The prothrombotic state of pregnancy adds additional risk to pregnant women with migraine who may already be prone to often-undiagnosed hypercoagulabilities. Women with migraine with aura should be followed by their obstetricians with extra caution.
- Triptans, which are the mainstay of acute headache treatment in nonpregnant and nonlactating women, have recent reassuring safety data, and select medications in this category may be considered in these populations.

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TABLE 8-5 **Clinical Clues in the Diagnosis of Secondary Headache Disorders in Women Who Are Pregnant or Postpartum**[a]

Clinical clue	Diagnosis	Timing
Orthostatic headache pattern	Post-dural puncture headache	Post-epidural anesthesia (hours to days)
Relapsing thunderclap headaches	Reversible cerebral vasoconstriction syndrome (RCVS)	Postpartum more often than antepartum
Single thunderclap headache	Aneurysmal subarachnoid hemorrhage	Antepartum and postpartum
	RCVS	Postpartum more often than antepartum
	Cerebral venous thrombosis	Antepartum and postpartum
	Cervical artery dissection	Postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Pneumocephalus	Post-epidural anesthesia (immediate)
Hypertension	Preeclampsia/eclampsia	Antepartum more often than postpartum
	Posterior reversible encephalopathy syndrome (PRES)	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Visual loss	Preeclampsia/eclampsia	Antepartum more often than postpartum
	PRES	Antepartum more often than postpartum
	Pituitary apoplexy	Antepartum more often than postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
Seizures	Eclampsia	Antepartum more often than postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum
Horner syndrome	Cervical artery dissection	Postpartum
Papilledema	Cerebral venous thrombosis	Antepartum and postpartum
	Idiopathic intracranial hypertension	Antepartum more often than postpartum
	Space-occupying lesion (eg, neoplasm)	Antepartum and postpartum
Focal neurologic findings	Ischemic stroke	Antepartum and postpartum
	Intracranial hemorrhage	Antepartum and postpartum
	Cerebral venous thrombosis	Antepartum and postpartum
	PRES	Antepartum more often than postpartum
	RCVS	Postpartum more often than antepartum

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preventive therapy is required, verapamil should be used at the lowest effective dose. The recent FDA clearance of a vagus nerve stimulator device for cluster headache provides a promising noninvasive drug-free option for women who are pregnant or lactating.[47]

Other Primary Headaches in Pregnancy

A significant knowledge gap exists regarding the course of other primary headaches during pregnancy. Anecdotal reports suggest that non–hormonally regulated headaches are likely to stay the same or worsen during pregnancy. It is thought that the additional symptoms and burden of pregnancy lead to the worsening of preexisting headaches when they occur. Of note, it may be useful to screen for sleep disturbances and sleep apnea in all pregnant women presenting with headache, as sleep disorders can increase headache frequency and the risk of complications during pregnancy, including preeclampsia.

Secondary Headaches

For more information on secondary headaches, refer to the article "Diagnosing Secondary and Primary Headache Disorders" by David W. Dodick, MD, FAAN, FAHS,[25] in this issue of *Continuum*. Briefly, the secondary headaches likely to present in pregnancy are generally due to a prothrombotic state (stroke and thrombosis) and states of elevated blood pressure (preeclampsia).[40] New-onset headache in pregnancy and the peripartum period, new-onset aura, a change in prior headache, and elevated blood pressure accompanying headache should all be considered as potential red flags for secondary headache. The evaluation of headache in the setting of pregnancy is similar to that in nonpregnant women, starting with a thorough history and physical examination for signs and symptoms that may point toward a secondary cause. TABLE 8-5 lists clinical clues that should raise the suspicion for secondary headache in pregnancy and the peripartum period.[40]

If imaging is required, MRI is preferred over CT to avoid the risk of radiation to the fetus. Iodinated contrast can potentially decrease thyroid function; if used, the infant's thyroid function should be checked in the first week after birth. Although use of MRI is preferred over CT, gadolinium contrast should be avoided during pregnancy if possible. Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) can be performed without contrast with time-of-flight sequences. If gadolinium is necessary to guide treatment, the mother should be counseled on potential risks to the fetus. No contraindication exists to the use of gadolinium after delivery in lactating women.[48]

CONCLUSION

Despite the magnitude of the public health impact of headache and migraine in women and the widespread understanding of its association with hormones, knowledge gaps remain regarding the hormonal underpinnings of migraine. A better understanding of the effects of daily hormonal fluctuations on migraine occurrence over the course of the menstrual cycle and over the menopausal transition is needed for improved parsing of migraine subtypes. This improved awareness will lead to more effective and appropriate treatment of women with migraine. The diagnosis and treatment of headache in pregnancy and lactation continue to be a clinical challenge and are likely to remain so given the

KEY POINTS

- The majority of drugs currently used as first-line acute migraine treatment have not been associated with deleterious effects to the fetus during pregnancy exposure. As most women with migraine experience improvement in their headache during pregnancy, preventive treatments are generally not needed.
- Secondary headaches likely to present in pregnancy are generally due to a prothrombotic state (stroke and thrombosis) and states of elevated blood pressure (preeclampsia).

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methodologic challenges and safety concerns in this time of life. Neuromodulation and behavioral treatments present a promising venue for migraine treatment of women in all phases of life, particularly in pregnancy and lactation.

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Headache in Children and Adolescents

By Christina Szperka, MD, MSCE, FAHS

REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **This article reviews the approach to a child or adolescent with headache, the criteria for common diagnoses, and the evidence base for treatments.**

RECENT FINDINGS: **The guidelines for acute and preventive treatment of migraine were updated in 2019. These guidelines summarize the available evidence and outline the questions that should be addressed in future research. The US Food and Drug Administration (FDA) approval of several new classes of drugs and devices to treat adult migraine in the past few years has resulted in ongoing or planned pediatric trials.**

SUMMARY: **Headache is a common symptom in children, and it is important to take a detailed history and perform a thorough physical examination to make the diagnosis. Nearly 1 in 10 children experience recurrent headaches due to migraine, which cause significant impairment in school performance and quality of life. The acute and preventive treatments that are currently available will help at least two-thirds of children with migraine, and several trials of new therapies offer hope for the future.**

INTRODUCTION

Headaches are a very common and disabling problem for children and adolescents. Globally, nearly 60% of children and adolescents experience significant headache, and 7.7% to 9.1% have migraine.[1,2] If the criteria are expanded to include probable migraine, the prevalence is much higher. Children with migraine miss more school than their peers[3] and have impaired school performance[4] and impaired quality of life, similar to that of children with rheumatoid arthritis or cancer.[5] This disability is complicated by the fact that migraine is a silent disease; no outward findings are visible, so the child's report of pain may be doubted, leading to shame and frustration.

In addition to the problems of disability in childhood, up to three-fourths of children with migraine will continue to have symptoms into adulthood.[6] Migraine is the leading cause of disability worldwide for older adolescents and young adults.[7] However, there is reason to hope: at least two-thirds of children will respond to currently available therapies,[8,9] and children who benefit from preventive therapy are likely to maintain better headache control into adulthood.

This article is organized to mirror the clinical encounter: history and physical examination, differential diagnosis, and treatment of migraine. Treatment

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RELATIONSHIP DISCLOSURE:
Dr Szperka serves as an associate editor for *Pain Medicine* and has received research/grant support from Amgen Inc, Miles for Migraine, Pfizer Inc, the National Institutes of Health/National Institute of Neurological Disorders and Stroke (K23 NS102521), and the US Food and Drug Administration
Continued on page 731

UNLABELED USE OF PRODUCTS/ INVESTIGATIONAL USE DISCLOSURE:
Dr Spzerka discusses the use of various medications and devices for the prevention of migraine in children and adolescents. The only medications approved by the US Food and Drug Administration (FDA) for migraine in children and adolescents are topiramate for prevention of migraine (ages 12+); rizatriptan (ages 6+) and almotriptan, zolmitriptan nasal, and sumatriptan/naproxen (ages 12+) for acute treatment of migraine. The external vagus nerve stimulator, remote electrical neuromodulation, and single-pulse transcranial magnetic stimulation devices are FDA cleared for use in adolescents. All other medications and devices discussed in this article are unlabeled/investigational in children and adolescents.

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includes both a summary of guideline-recommended acute and preventive therapies and practical recommendations to cover areas where evidence is insufficient.

HISTORY TAKING

With a young child, the history will come from both the child and the parent(s)/guardian(s), so it is important to make both child and parent(s)/guardian(s) comfortable. The child should be kept as calm as possible, so the clinician's actions may need to vary a bit based on the child's temperament. The child should be approached in a nonthreatening way; the clinician may crouch down to the child's eye level, wave hello, and introduce themselves to the child. If the child looks frightened or recoils into their parent/guardian, the clinician may need to physically back away and give the child space. If the child is comfortable, they may be asked if they know why they have come for the visit. The child should be given an overview of what to expect, with an explanation that they will begin by talking for a while. The child can keep playing initially while the parent/guardian is asked many questions, but the child should be asked a few questions also, since they are the expert on how their head feels. The clinician may explain that the examination is just like the one that the pediatrician does and that then the clinician and child will decide together how to help the child feel better. Young children often associate the doctor's office with painful procedures, so once enough of a history has been taken to clarify, the child can be reassured that no shots are planned that day. It is often helpful to have paper and crayons available so the child can color whatever they want in the beginning. Once the child is comfortable, they can be asked to draw a picture of how they feel when they get a headache, as drawings with migraine features have high concordance with migraine diagnosis.[10]

The style for older children and teenagers is different. Teenagers can be directly questioned, then the parent/guardian later given the opportunity to relay perceived differences or additional details. To prepare teenagers to transition to adult care, it is important to coach them to take increasing independence with medical care.

The author recommends starting the history taking with an open-ended question, such as, "What brings you here today?" Parents/guardians usually state their worries and ideas about etiology right away, but if they do not offer that information up front, they should be asked more explicitly at the end of the history. After starting with a few open-ended questions, the author explains that she is going to ask a lot of detailed questions to make sure that she understands what is happening, keeping a paper and pen nearby to scribble a note if the parent/guardian mentions something that is out of the usual order to remember to return to it to clarify later. A headache questionnaire can be integrated into the electronic health record, so that the parent(s)/guardian(s) may have answered a lot of questions about the child's headaches before the visit. This increases the efficiency of history taking because it has asked the patient and parent(s)/guardian(s) to think about the pattern of headache, recent changes, and current frequency before the conversation starts. Those answers should be reviewed in a semistructured interview, making sure that all the questions were understood, paying particular attention to the following:

- **Headache frequency: Ask about both bad and mild headaches. Many parents/guardians are surprised to realize that the child has unreported frequent mild headaches or even constant pain.**

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- Headache pattern: Ask if the headaches have been intermittent for several months or if this is a new or escalating problem.
- Headache location: Ask the child to point to the places on the head that hurt with headache.
- Headache quality: Ask about the quality of the pain. For young children, ask if the pain feels like someone squeezing their head (while squeezing the hands together), like someone knocking on their head (while pounding one fist gently into the other), or like their head is exploding (moving the hands outward).
- Headache severity: Ask about headache severity using the Faces Pain Scale,[11] or clarify whether the pain is little, medium-sized, or really bad. Teenagers can be asked to rate their headache on a numeric 0 to 10 scale. Children may report a severity number larger than expected by the observer. Remember that pain is subjective and relative to the child's own history of pain.
- Associated features: Ask the parent/guardian whether the child's behavior or appearance changes before or during a headache. The author explicitly reviews the following:
  - Premonitory symptoms: Before pain onset, about one-third of young children and two-thirds of older children and adolescents with migraine experience premonitory symptoms such as facial pallor, fatigue, irritability, mood changes, and yawning.[12]
  - Migraine aura: Visual aura is most common in children, sometimes accompanied by sensory, speech, or motor symptoms.[13] Children may not volunteer other symptoms that come with headache, so they should be explicitly and concretely asked. Ask the child if they see any extra spots, lights, or lines; if anything is missing from their vision before or during a headache; and whether they have associated numbness or tingling. The time course should be clarified, as sometimes children will report that they see spots in their vision upon standing during migraine from orthostasis, which does not fit the criteria for aura. If a child reports weakness, clarify whether it is a feeling of all-over muscle fatigue, numbness resulting in clumsy movements, or focal weakness. The latter is uncommon but raises the possibility of familial hemiplegic migraine, which can be caused by mutations in *CACNA1A, ATP1A2, or SCN1A*.
  - Migraine symptoms: Sensitivity to light and sound and nausea and vomiting are diagnostic criteria for migraine. Pallor and anorexia are also common in young children,[14] as are difficulty thinking, lightheadedness, fatigue,[15] and osmophobia in older children. These symptoms may be observed by parent(s)/guardian(s) rather than reported by the child (CASE 9-1).
  - Cranial autonomic symptoms: These symptoms include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, ear pressure, and facial flushing and are common in children with migraine and usually bilateral.[16] Unilateral autonomic symptoms can be present with migraine but may suggest a trigeminal autonomic cephalalgia.
  - Postdromal symptoms: Nonpain symptoms such as fatigue, cognitive difficulties, and nausea often persist for hours after the pain has resolved. More than 80% of children develop new symptoms, including thirst, somnolence, visual disturbances, and food cravings, after the pain has resolved.[17]
- Red flags for secondary headache: Screening for secondary headache is discussed below in the section on diagnostic considerations.
- Headache-related disability: Ask both the child and the parent/guardian how headaches affect their lives, both at home and at school, using the Pediatric Migraine Disability Assessment (PedMIDAS) (cincinnatichildrens.org/service/h/headache-center/pedmidas).[18,19]
- Medical and psychological history: Pay particular attention to comorbidities, which may include the following
  - Related syndromes: Ask whether the child currently has or previously had episodes of recurrent vomiting (cyclic vomiting), disabling abdominal pain (abdominal migraine), head tilt (benign paroxysmal torticollis), "drunk" gait or inability to stand upright sometimes with nystagmus (benign paroxysmal vertigo), or persistent crying as a baby (colic). These childhood periodic syndromes often occur at a younger age and may be migraine precursors in the developing brain, although cyclic vomiting and abdominal migraine often persist into teenage years.[20]

KEY POINTS

- Headaches are a very common and disabling problem for children and adolescents. Globally, nearly 60% of children and adolescents experience significant headache, and 7.7% to 9.1% have migraine.
- Children with migraine miss more school than their peers and have impaired school performance and impaired quality of life, similar to that of children with rheumatoid arthritis or cancer. This disability is complicated by the fact that migraine is a silent disease; no outward findings are visible, so the child's report of pain may be doubted, leading to shame and frustration.
- Migraine is the leading cause of disability worldwide for older adolescents and young adults.
- Children may not volunteer other symptoms that come with headache, so they should be explicitly and concretely asked.

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- Obesity: A high body mass index has been correlated with migraine frequency and disability in children and adolescents.[21]
- Epilepsy: Patients with epilepsy have an increased rate of migraine and vice versa.[22]
- Atopic disorders: Children with allergic rhinitis or conjunctivitis have a higher incidence of migraine,[23] and those with migraine, especially migraine with aura, have higher rates of atopic disorders.[24]
- Anxiety/depression: Adolescents with depression and migraine experience higher rates of disability than those without depression, even after controlling for frequency and severity of migraine attacks.[25]
- Attention problems and cognitive differences: Studies have demonstrated an association between migraine and attention deficit hyperactivity disorder[26] as well as both within-attack[27] and between-attack[28] cognitive differences. Attention and learning difficulties can cause stress in school, which can, in turn, trigger migraine. Simultaneously, stimulant medications can cause headache as a side effect.
- Sleep disorders: Migraine is associated with narcolepsy[29] and restless legs syndrome[30] in children.

- Social history: Ask about sources of emotional stress on both the child and the family. Studies have demonstrated that adverse experiences in childhood (eg, financial stress; physical, emotional, or sexual abuse; parental divorce; death; mental illness; or addiction) predispose to headache in childhood as well as later in life.[31] Give teenagers a moment away from parent(s)/guardian(s) to discuss safety, sexuality, and substance use.

PHYSICAL EXAMINATION

For all new patients with headache, a detailed general and neurologic examination should be performed, specifically looking for any facial asymmetry, visual or eye movement abnormalities, papilledema, or motor asymmetry. Vital signs

CASE 9-1

A 6-year-old boy with a history of mild intermittent asthma presented with headaches. Upon questioning, his mother reported that the headaches had started a couple of years earlier but had increased in frequency to every other week. With each episode he became quiet, withdrew from play, and asked to lie down with the lights off. His parents had tried treating with acetaminophen, but they were not sure it was helping. Sometimes he vomited the medicine back up and then fell asleep. The entire episode seemed to resolve within a couple of hours. They came to clinic because he had an episode at school the previous week. The school nurse mentioned that he might have migraine and needed a better plan, but the boy's mother asked whether he could have a brain tumor. His general and neurologic examinations were normal.

After assessment, he was diagnosed with migraine, and his mother was reassured that imaging was not indicated. A migraine action plan was written, which included an appropriate dose of ibuprofen at onset, noting that an antiemetic or triptan could be used if needed.

COMMENT

This case demonstrates that primary headache disorders including migraine are more common than serious secondary headaches and that a thorough history and examination are usually sufficient for diagnosis.

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should be noted, looking for hypertension or tachycardia; growth parameters should also be noted, especially changes in or disproportionate head circumference (which should be measured in all pediatric patients with headache). As part of the neurologic examination, eye alignment and convergence and saccadic eye movements should be checked; these are often abnormal after concussion, but in the author's experience, saccadic eye movements can also be abnormal when headache is present. In addition, thinking about specific causes for headache, a "headache examination" should be performed[32]:

- Examine the neck (looking for limitations in range or pain with motion) and the spine (looking for scoliosis).
- Palpate over the sinuses to assess for focal tenderness.
- Examine the jaw for tenderness or clicking to suggest temporomandibular joint dysfunction, which can be comorbid with migraine.
- Listen over the eyes and temples for bruits, which can signal vascular abnormalities.
- Rub lightly over the forehead and scalp to test for significant allodynia and palpate over the bilateral greater and lesser occipital nerves and supraorbital and supratrochlear nerves to assess for tenderness. The presence of allodynia or nerve tenderness do not guide the differential diagnosis but demonstrate the presence of sensitization as part of underlying pathophysiology.
- For patients with continuous or positional headache, assess for an orthostatic change in pulse rate. A significant pulse change (usually defined as ≥40 beats/min) when going from lying to standing and persisting over several minutes is consistent with postural tachycardia syndrome.[33] In addition, the Beighton scale for hypermobility can be used, which can signify Ehlers-Danlos syndrome, associated with both postural tachycardia syndrome and spontaneous intracranial hypotension.[34]

KEY POINTS

- Studies have demonstrated that adverse experiences in childhood (financial stress; physical, emotional, or sexual abuse; parental divorce; death; mental illness; or addiction) predispose to headache in childhood as well as later in life.
- It is important to know what the child does not have as well as what the child does have. Life-threatening causes such as brain tumors occur in approximately 2% to 3% of children who present to the emergency department for headache and in about 1% of children with headache seen in primary care.

DIAGNOSTIC CONSIDERATIONS

When approaching a child or teenager with headache, it is important to consider the full differential diagnosis of secondary and primary headache disorders.

Step 1: Screening for Secondary Headache

It is important to know what the child does not have as well as what the child does have. Life-threatening causes, such as brain tumors, occur in approximately 2% to 3%[35] of children who present to the emergency department for headache and in about 1% of children with headache seen in primary care.[36] Potential concerning features indicating a serious cause for headache are described in TABLE 9-1,[37–46] organized by the mnemonic SNOOP4Y (**s**ystemic signs/symptoms, **n**eurologic signs/symptoms; **o**nset sudden; **o**nset in sleep/early morning; **p**ositional exacerbation, **p**recipitated by Valsalva, **p**arents [lack of family history], **p**rogressive or new; **y**oung age), adapted from the SNOOP4 mnemonic for signs and symptoms of secondary headache in adults.[37]

Studies that have tried to identify signs and symptoms to predict a serious cause for headache have been limited by the very low rate of cases. For example, an occipital location or inability to describe the location of headache were previously thought to be risk factors for serious secondary headache,[45] but all of the children with concerning lesions also had objective neurologic signs. More recent work has questioned the idea that location alone is concerning.[47] The most worrisome features are an abnormal neurologic examination, significant systemic illness, and new or worsening pattern of headaches.

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TABLE 9-1 **Potential Red Flags for Serious Causes of Headache Organized by the Mnemonic SNOOP4Y[a]**

Red Flag	Significance
Systemic signs/symptoms	
Fever, acute symptoms	Infections ranging from minor to serious[35] are the most common cause of headache in children in the emergency department
Head trauma	Relatively common cause for headache in the emergency department
Vomiting	Consistent with migraine[38] but also a risk factor for brain tumors[39]
Weight loss	Can be a symptom of malignancy
Comorbidities	Many systemic illnesses, including rheumatologic, oncologic, vascular, and hematologic conditions; genetic syndromes; and abnormalities of the immune system predispose to other serious causes for headache
Medications	Headache can be a medication side effect[40]
Neurologic signs/ symptoms	Abnormal gait, ataxia, papilledema, changes in personality/behavior/cognition, visual disturbances/eye movement abnormalities, and seizure[39] are red flags for serious secondary headache
Onset sudden	Thunderclap onset of headache in which pain peaks instantly is rare in children but can signal serious causes such as cerebral hemorrhage or reversible cerebral vasoconstriction syndrome; the full range of differential diagnosis from adults with thunderclap headache should be considered, and imaging should be pursued
Onset in sleep/early morning	Headache causing a child to awaken from sleep or occurring early in the morning has been associated with intracranial lesions[41] and can be suggestive of sleep apnea and other sleep disorders[42]; however, this diurnal pattern is also common in primary headache disorders[43]
Positional exacerbation	
Worse upright	Headache that resolves when supine and worsens immediately upon standing or slowly throughout the day can suggest spontaneous intracranial hypotension or postural tachycardia syndrome[33]
Worse supine	Consider increased intracranial pressure from tumor or idiopathic intracranial hypertension
Precipitated by Valsalva	Brief headaches triggered by Valsalva maneuvers can signal intracranial abnormalities; headache triggered by cough along with signs/symptoms of brainstem/cerebellum/cervical spinal cord dysfunction[38] may suggest Chiari malformation (although Chiari malformation may be found incidentally with other headaches and is of varying significance)
Parents (lack of family history)	Several studies have found that lack of family history of headaches is associated with higher odds of having a serious cause of headache in children[39]; most children with migraine have a family history of migraine, although the parent(s)/guardian(s) may not be aware of the diagnosis
Progressive or new	Significant change in the headache pattern, new headache, or progressively escalating headache raises the level of concern for secondary cause[44]; however, many new-onset headaches are not caused by structural brain abnormalities[44] and may be attributed to relatively benign causes such as viral infections; furthermore, studies have used different cutoff points from days to months[45] when trying to determine when a "recent-onset" headache is worrisome, so the newness of the headache must be interpreted with the presence or absence of other headache features
Young age	Some studies have found that children of younger age (defined as either ≤5 years[45,46] or ≤7 years[39]) were more likely to be diagnosed with a life-threatening headache, whereas other studies have refuted that concern[44]

[a] The mnemonic SNOOP4Y is adapted from the SNOOP4 used in adults.[37]

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Several studies support that neuroimaging is unnecessary for children with stable frequency of headaches, the absence of concerning features, and normal neurologic examination, such as the child in CASE 9-1.[48] From a health economics perspective, unnecessary imaging results in significant cost.[49] If red flags are present, brain imaging is indicated.[48] The specific study will be dictated by the urgency of the situation, the need for/availability of sedation, and the differential diagnosis suggested by the headache features.[49] If the child has fever and nuchal rigidity or papilledema without evidence of tumor or thrombosis, lumbar puncture should be performed. Laboratory studies also depend on clinical symptoms, and infectious testing will vary by geographic location and season.[48]

Step 2: Identifying the Primary Headache Diagnosis

The majority of children who present to the neurologist will have a primary headache disorder, the features of which are described in this section.

MIGRAINE. Migraine is a primary headache disorder characterized by recurrent (at least five) episodes of moderate to severe pulsating head pain lasting hours and accompanied by nausea/vomiting and sensitivity to light and sound.[38] In children, migraine attacks can be brief; the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria define a minimum of 2 hours for children,[38] although experts have proposed that this should be lowered to a minimum of 30 minutes in children 5 and younger[20] or to a minimum of 1 hour for all children.[15] The sensitivity to light and sound can be inferred through behavior.[38] Unilateral pain is part of the diagnostic criteria of migraine in adults, but more than 80% of children report bilateral pain,[15] so the diagnostic criteria allow for this difference.

Migraine prevalence and features vary from childhood to adolescence and from boys to girls. Migraine affects approximately 5% of boys and girls by the age of 10,[50] 7% of girls and 5% of boys up to age 15, and 10% of girls and 6% of boys by the age of 20.[1] Evidence indicates that the prevalence of migraine is rising, at least in some populations.[2] Migraine frequency is lower in children younger than 7 years of age,[51] although they tend to vomit more compared to older children. Headaches in very young children may also have more symptomatic overlap between migraine and tension-type headache.[52] The presence of aura and associated dizziness increases with age.[53]

Genetic and epigenetic factors likely play a role in the age of onset. Children with a parental history of migraine develop the condition an average of 11 to 12 years earlier than their affected parents[54] and 2 to 3 years earlier than children who do not have a migraine family history.[55] Younger age of onset may portend worse prognosis: children seen in pediatric neurology clinics whose headaches begin before age 6 are more likely than those whose headaches begin at age 6 to 10 years to need preventive therapy in the next 2 years.[56] Migraine peak incidence occurs at least 4 years earlier in boys than girls. Those who develop migraine with visual aura report onset of migraine 3 to 5 years before those who have migraine without aura.[57] Among children without a family history of migraine, lower household income is associated with higher odds of migraine.[58]

Hormones also play a role. Early menarche (≤12 years of age) is associated with increased odds of migraine and other headaches in adolescent girls.[59] A large population-based study found that girls who have reached menarche within the past 2 years are more likely to report recurrent headaches compared to girls who

KEY POINTS

- Several studies support that neuroimaging is unnecessary for children with stable frequency of headaches, the absence of concerning features, and a normal neurologic examination.
- Migraine is a primary headache disorder characterized by recurrent (at least five) episodes of moderate to severe pulsating head pain lasting hours and accompanied by nausea/vomiting and sensitivity to light and sound.
- Migraine prevalence and features vary from childhood to adolescence and from boys to girls. Migraine affects approximately 5% of boys and girls by the age of 10, 7% of girls and 5% of boys up to age 15, and 10% of girls and 6% of boys by the age of 20.

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have not reached menarche, but longitudinal analysis of individuals did not demonstrate an increased frequency of migraine after menarche.[60]

TENSION-TYPE HEADACHE. Tension-type headache describes headaches that are mild to moderate, nondisabling, and without notable associated symptoms such as vomiting. Tension-type headache occurs in 10% to 24% of children and adolescents[52] but does not usually bring the child to medical attention because the attacks are mild and cause little disability.

TRIGEMINAL AUTONOMIC CEPHALGIAS. Trigeminal autonomic cephalgias, including cluster headache, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks (SUNHA), have been reported very rarely in young children. Typical adult criteria are used for diagnosis, largely because pediatric cases are so rare. Cluster headache prevalence is believed to be low at 0.1% in adolescents,[61] but many adult patients with cluster headache retrospectively report that their headaches began during adolescence or even childhood. Cluster episodes may increase in frequency and duration from adolescence to adulthood,[62] and restlessness may be less pronounced at younger ages.[20] Substantial clinical overlap exists between paroxysmal hemicrania and cluster headache, and children with paroxysmal hemicrania may not fulfill all *ICHD-3* criteria.[20]

PRIMARY STABBING HEADACHE. Primary stabbing headache describes very brief episodes of stabbing pain without associated autonomic features. These are often

CASE 9-2

A 13-year-old girl presented for a neurologic consultation reporting a history of headache attacks, some with nausea, since the age of 9. The headaches had slowly increased in frequency over the past 2 years. She recalled that she had about 4 days of headache each week the previous spring. Headaches were a bit better over the summer. One week after the start of the school year and around her menses, she developed a migraine attack, and the pain and associated symptoms had waxed and waned for 2 weeks since then without going away completely despite twice-daily ibuprofen. She had missed 4 days of school. Physical and neurologic examination were normal.

Based on the history and normal physical examination, chronic migraine with status migrainosus was diagnosed. She was sent to the emergency department for IV prochlorperazine and ketorolac to break the current attack, and she was given a note requesting flexibility so that she could return to school even before she had caught up on the work. She returned for a follow-up visit the next week to discuss options for preventive therapies to decrease the frequency and severity of attacks over time.

COMMENT

This case demonstrates that escalating frequency of migraine attacks can be insidious but often comes to attention when the severity or persistence of headache causes more disability. It is important to consider both acute and preventive treatments and to set realistic expectations that improvement may take time and multiple therapeutic trials.

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severe and scary to the child and parent(s)/guardian(s) but do not usually require treatment unless they are frequent.[14] They tend to occur in children with other primary headache disorders such as migraine.

FREQUENT OR DAILY HEADACHES. In population-based self-report studies, at least 1.5% of children report headaches several times per week or daily. Girls are more likely to report daily headache than boys.[63,64] Overuse of acute medications is less common than in adults with daily headache.[65] In the past the umbrella term *chronic daily headache* was used, but it is preferable to use the more specific term (chronic migraine, chronic tension-type headache, new daily persistent headache, or hemicrania continua) as some differences exist in treatment and prognosis.

Chronic migraine, defined in *ICHD-3* as headache on at least 15 days per month for at least 3 months with at least 8 days of migraine per month,[38] is more common in girls than boys,[63] and the prevalence increases through the adolescent years.[64] The proportion of children with daily headache who meet the criteria for chronic migraine has changed as the definitions have evolved, but most have some headaches that meet the criteria for migraine.[63] Adolescents may progress from a relatively low to a high frequency of headache attacks, sometimes having features of migraine, over weeks to months (CASE 9-2), whereas adults typically progress over years. Migraine features may remain prominent in adolescents even when the headaches are daily or nearly daily.[66] Not surprisingly, adolescents with chronic migraine have high rates of disability.[64]

Children who did not previously have significant headaches but develop a new-onset headache that persists for 3 months or longer may be diagnosed with new daily persistent headache after an appropriate workup has ruled out sinister causes. Clinic-based cohort studies of adolescents with the umbrella term *chronic daily headache* have found that at least one in five have new daily persistent headache.[65] Population-based studies have found a very low prevalence of new daily persistent headache.[63]

Hemicrania continua is rare in the population,[65] but much less rare when considering the population of patients with refractory continuous headache. Hemicrania continua classically causes side-locked continuous headache with ipsilateral autonomic features. Sometimes patients report pain on both sides with words but point to only one side. In these cases, they often clarify that one side always hurts, but the pain spreads bilaterally when severity increases. Similarly, autonomic features are not universal, so a trial of indomethacin is appropriate for any patient with continuous side-locked headache.[67]

It is particularly important to consider comorbidities in children with frequent headaches. Physical and sexual abuse is more common in children with daily headache than in the general population.[68] Studies have found that the majority of children with chronic daily headache have anxiety related to academics,[69] and a subset have significant psychiatric disease and school phobia,[70] which may contribute to the seasonal pattern of new daily persistent headache onset. Similarly, acute family financial distress was found to be a risk for incident chronic daily headache.[71] Depression and anxiety are associated with higher disability,[72] and poor sleep may be a risk factor for poor response to therapy.[73]

TREATMENT

The majority of children and adolescents who seek care in outpatient neurology and headache clinics have migraine.[46] New daily persistent headache or posttraumatic

KEY POINTS

- **Tension-type headache occurs in 10% to 24% of children and adolescents but does not usually bring the child to medical attention because the attacks are mild and cause little disability.**
- **In population-based self-report studies, at least 1.5% of children report headaches several times per week or daily.**

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headache with a migrainous phenotype may be treated similarly. Treatment specifics for other headache conditions are discussed elsewhere in this issue.

First-line Acute Treatment

All children with migraine should receive an acute treatment plan to be used at the start of an episode (CASE 9-1)[8] that includes a school note permitting the child to be excused from class at symptom onset to hydrate, take an acute medication, and rest before returning to class. A Pediatric Migraine Action Plan, modeled after the commonly used Asthma Action Plan, organizes treatment recommendations in a format familiar to school nurses (available directly at headachejournal.onlinelibrary.wiley.com/doi/epdf/10.1111/head.13681).[74] Updated guidelines for acute pharmacologic treatment for children were released in 2019 (TABLE 9-2).

TABLE 9-2

Recommendations of the AAN and AHS 2019 Practice Guideline Update: Acute Treatment of Migraine in Children and Adolescents[a]

Establish a specific headache diagnosis

- When evaluating children and adolescents with headache, clinicians should diagnose a specific headache type (primary, secondary, or other headache syndrome).
- When evaluating children and adolescents with headache, clinicians should ask about premonitory and aura symptoms, headache semiology (onset, location, quality, severity, frequency, duration, and aggravating and alleviating factors), associated symptoms (nausea, vomiting, phonophobia, and photophobia), and pain-related disability in order to improve diagnostic accuracy for migraine and appropriately counsel the patient.

Acute headache treatment

- Clinicians should counsel that acute migraine treatments are more likely to be effective when used earlier in the migraine attack, when pain is still mild.
- Clinicians should prescribe ibuprofen oral suspension (10 mg/kg) as an initial treatment option to reduce pain in children and adolescents with migraine.
- For adolescents with migraine, clinicians should prescribe sumatriptan/naproxen oral tablets (10/60 mg, 30/180 mg, 85/500 mg), zolmitriptan nasal spray (5 mg), sumatriptan nasal spray (20 mg), rizatriptan orally disintegrating tablets (5 mg or 10 mg), or almotriptan oral tablet (6.25 mg or 12.5 mg) to reduce headache pain.
- Clinicians should counsel patients and families that a series of medications may need to be used to find treatments that most benefit the patient.
- Clinicians should instruct patients and families to use the medication that best treats the characteristics of each migraine to provide the best balance of efficacy, side effects, and patient preference.
- Clinicians should offer an alternate triptan, if one triptan fails to provide pain relief, to find the most effective agent to reduce migraine symptoms.
- Clinicians may prescribe a nonoral route when headache peaks in severity quickly, is accompanied by nausea or vomiting, or oral formulations fail to provide pain relief.
- Clinicians should counsel patients and families that if their headache is successfully treated by their acute migraine medication but headache recurs within 24 hours of the initial treatment, taking a second dose of acute migraine medication can treat the recurrent headache.
- In adolescents whose migraine is incompletely responsive to a triptan, clinicians should offer ibuprofen or naproxen in addition to a triptan to improve migraine relief.

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NONSTEROIDAL ANTI-INFLAMMATORY DRUGS. The guidelines recommend ibuprofen 7.5 mg/kg to 10 mg/kg be used as first-line treatment for all children and adolescents.[8] Sometimes other nonsteroidal anti-inflammatory drugs (NSAIDs) that have evidence of efficacy in adults, including naproxen, diclofenac, ketoprofen, and flurbiprofen,[75] may be used.

TRIPTANS. If ibuprofen is insufficient, a triptan can be considered. Guideline-recommended triptans for adolescents include sumatriptan/naproxen, rizatriptan, and almotriptan oral and zolmitriptan and sumatriptan nasal.[8] This list mostly reflects the triptans that were studied later with novel trial designs to lower placebo response, which enabled the demonstration of both efficacy and safety. Triptans that were tested in parallel-design studies (straight randomization

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Treatment of associated symptoms

- For children and adolescents with migraine who experience prominent nausea or vomiting, clinicians should offer additional antiemetic treatments.

Counseling

- Clinicians should counsel children and adolescents with migraine and their families about migraine-healthy habits, including lifestyle modification, identification/disproof/resolution of migraine triggers/aggravating factors, and avoidance of medication overuse.
- Clinicians should make collaborative agreements with children and adolescents with migraine and their families on treatment goals that are individualized to the patient.
- Clinicians may counsel children and adolescents with migraine and their families to maintain a headache diary to monitor their response to treatments.
- Clinicians should counsel patients and families to use no more than 14 days of ibuprofen or acetaminophen per month, no more than 9 days of triptans per month, and no more than 9 days per month of any combination of triptans, analgesics, or opioids for more than 3 months to avoid medication-overuse headache. (No evidence supports the use of opioids in children with migraine.)

Contraindications and precautions to triptan use

- Clinicians must not prescribe triptans to those with a history of ischemic vascular disease or accessory conduction pathway disorders to avoid the morbidity and mortality associated with aggravating these conditions.
- Clinicians should counsel adolescent patients with migraine with aura that taking their triptan during a typical aura is safe, but that the triptan may be more effective if taken at the onset of head pain.
- Clinicians may consider referral of children and adolescents with hemiplegic migraine or migraine with brainstem aura who do not respond to other treatments to a headache specialist to find effective treatment.

AAN = American Academy of Neurology; AHS = American Headache Society.
[a] Data from Oskoui M, et al, Neurology.[8]

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into active versus placebo) were affected by high rates of placebo response. As a result, those trials demonstrated safety but not efficacy for sumatriptan, zolmitriptan, and eletriptan oral.[76] Pharmacokinetic data are also available for frovatriptan[77] and naratriptan[78] in adolescents. Although the guidelines did not specifically recommend triptans for younger children, rizatriptan is US Food and Drug Administration (FDA)–approved for children 6 years of age and older, and many triptans have been studied in this age group with evidence of safety. In practice, the choice of triptan for adolescents is guided substantially by insurance coverage, formulation, and onset and duration of specific medications. For example, adolescents with rapid escalation of pain or with significant nausea may benefit from nasal triptans.[8] If a child is unable to swallow pills, dissolvable tablets or nasal formulations can be considered, with the latter being particularly helpful if the child has significant nausea or rapid rise in headache severity.

ANTINAUSEA MEDICATIONS. If the child has significant nausea/vomiting, adding an antiemetic medication should be considered. Medications that block dopamine, including metoclopramide, promethazine, and prochlorperazine, may help both the nausea and the migraine pain, but specific antiemetics (including ondansetron) may also be used.

LIMITATION OF ACUTE MEDICATIONS. Concern exists that very frequent use of acute medications could predispose patients to more frequent headaches, termed *medication-overuse headache*.[38] The guidelines recommend counseling families to limit simple analgesics (eg, NSAIDs, acetaminophen) to 14 or fewer days per month and triptans or combination analgesics (containing caffeine) to 9 or fewer days per month.[8]

TABLE 9-3 **Strategies for Perimenstrual Migraine Prophylaxis**

Class	Specifics
Nonsteroidal anti-inflammatory drugs	Naproxen 550 mg 2 times a day for 5-6 days, ideally starting 1 day before expected headache onset[81]
	Mefenamic acid up to 500 mg 3 times a day from the start of headache through menses[82]
	The cyclooxygenase-2 (COX-2) inhibitor celecoxib has shown promise[83] in pilot studies
Triptans[81]	Frovatriptan 2.5 mg 2 times a day for up to 6 days, ideally beginning 1 day before expected headache onset
	Naratriptan 1 mg 2 times a day for 5-6 days, ideally beginning 1 day before expected headache onset
	Zolmitriptan 2.5 mg 2 to 3 times a day for up to 7 days, ideally beginning 1 day before expected headache onset
Magnesium[81]	Specific formulation studied is not available in the United States, but it is reasonable to use available forms perimenstrually; can also help with perimenstrual syndrome
Vitamin E	400 IU/d for 5 days beginning 2 days before menses[84]
Estrogen	Supplementation ("add back") via patch or gel in teenagers who have migraine without aura[83]

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OPIOIDS. Opioids are not recommended for acute treatment of migraine in children.

DEVICES. All four of the devices with FDA clearance for treatment of migraine in adults (external trigeminal nerve stimulation, external vagus nerve stimulation, single-pulse transcranial magnetic stimulation, and remote electrical neuromodulation) can be used acutely. The latter two devices have been beneficial in case series of youth.[79,80]

Acute Treatment of Menstrual Migraine

Treatment of menstrual migraine deserves special attention. If migraine with menses is infrequent and short in duration, then the usual acute medications may be used. However, menstrual migraine can be particularly disabling and difficult to treat,[81] with the added difficulty of irregular menstrual cycles making prediction more difficult for adolescents. Borrowing evidence from adult studies, adolescents with status migrainosus around menses may benefit from short-term prophylaxis. Several medications and supplements have been studied for relatively long durations of time (TABLE 9-3[82-84]), but in reality these therapies are often prescribed for 3 days to avoid concerns about medication overuse and dispensed quantity limitations.

If these strategies are insufficient, hormonal contraceptives may be considered. Progesterone-only and combined progesterone-estrogen oral contraceptives, especially with continuous formulation, have both demonstrated benefit for the prevention of menstrual migraine.[83] Use of high-dose estrogen increases the relative risk of thrombosis, including stroke, in women with migraine with aura. Therefore, the progesterone-only contraceptives may be a safer option. Low-dose and ultra-low-dose combined oral contraceptives may reduce aura frequency but still should be avoided in women who have migraine with aura unless no other options are available and after a discussion of potential risks.[85]

Acute Treatment of Status Migrainosus

An intractable migraine attack is a common clinical scenario (CASE 9-2), yet a paucity of evidence is available to guide treatment. Home strategies may be used to treat a severe or continuous headache cycle, especially when IV or procedural treatments are not feasible. Borrowing from menstrual migraine, treatment options include scheduled NSAIDs and/or triptans 2 to 3 times daily (depending on the specific medication), usually for 3 to 5 days. Neuroleptics may also be used to treat pain, nausea, and related insomnia. Short-term oral valproic acid is important to avoid in female adolescents given its teratogenicity. Similarly, short-term oral steroids, including dexamethasone, prednisone, and methylprednisolone, may be used. Alternative formulations of medications with demonstrated effectiveness in IV form, such as prochlorperazine given rectally, intramuscular injection of ketorolac, or intranasal dihydroergotamine, can be tried. These anecdotal recommendations are included given that status migrainosus is a common clinical scenario and situational barriers to the use of IV and procedural treatments may be present.

If treatments at home are insufficient to treat an acute migraine attack, more aggressive therapeutic options, such as IV medications or procedures, can be considered. A crossover trial of IV ketorolac and prochlorperazine in the

KEY POINTS

- All children with migraine should receive an acute treatment plan to be used at the start of an episode that includes a school note permitting the child to be excused from class at symptom onset to hydrate, take an acute medication, and rest before returning to class.
- Menstrual migraine can be particularly disabling and difficult to treat, with the added difficulty of irregular menstrual cycles making prediction more difficult for adolescents.

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TABLE 9-4 **SMART (Sleep, Meals, Activity, Relaxation, Triggers) Lifestyle Considerations**[a]

Factor	Advice
Sleep: consistent and sufficient	
Bedtime and wake-up time	Maintain a consistent bedtime routine and avoid daytime napping to prevent disruptions to the sleep-wake cycle[99]; children 3-5 years of age should sleep 10-13 hours per day (including naps), children 6-12 years of age should sleep 9-12 hours per day, and teenagers should sleep 8-10 hours per day[100]
Problems falling asleep	Use bed only for sleep, turn off screens at least 1-2 hours before bed to limit blue light exposure[101]
Problems staying asleep	Consider causes such as sleep apnea, depression
Daytime somnolence	Consider causes such as sleep apnea, depression
Meals and hydration: consistent and sufficient	
Missed meals	Recognize that fasting can be a trigger
Well-balanced diet	Eat a variety of fruits and vegetables, protein, and dairy (or another source of vitamin D)
Access problems or limited time	Address time limitations and food insecurity with individualized solutions; consider social work consult
Water consumption	≥8 cups per day for children older than 9 years of age (more for teenage boys and extra at times of high exertion)[102]
Other beverage consumption	Limit to avoid weight gain as obesity is associated with worsened migraine frequency and disability[21]
Caffeine consumption	High caffeine consumption is associated with increased odds of headache in adolescents,[95] probably because of caffeine withdrawal[103]
Activity: consistent and sufficient	
Address inactivity	Inactivity in adolescents is associated with higher odds of migraine[95]; weight loss in overweight teenagers can contribute to headache improvement[21]
Exercise	Meta-analyses in adults have concluded that exercise may be a beneficial and safe treatment for migraine[104]
Relaxation: cope with stress and prevent migraines	
Sources of stress	Home-related stressors (eg, arguments with siblings, observing parental disagreements) or school-related stressors (eg, difficulty in school, fear of doing poorly) can be triggers for headache
Help cope with stressors	Validate the normalcy and commonality of stressors and discuss coping strategies
Relaxation strategies	Cognitive-behavioral therapy can help migraine in children[105]; mindfulness-based stress reduction looks promising[106]
Triggers: avoidance/management	
Weather	Changes in weather patterns are commonly reported as headache triggers; use of long-acting triptans may help to prevent migraine attacks around storms[107]
Specific foods	Little evidence shows that foods other than alcohol and caffeine are consistent headache triggers, although many patients report avoiding specific foods
Menses	Refer to the section on menstrual migraine

[a] Modified with permission from Blume HK, Szperka CL, Pediatr Ann.[40] © 2010 SLACK Incorporated.

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emergency department demonstrated 50% pain reduction in 55% of those who received ketorolac and 85% of those who received prochlorperazine. After nonresponders received the other medication, the overall success rate was 93%.[86] As a result, many institutions use IV fluids, ketorolac, and prochlorperazine or another neuroleptic as their first-line IV therapies. Although not yet widely used, a 2018 trial demonstrated that low-dose propofol was equivalent to standard-of-care therapy with decreased rate of return to the emergency department.[87] If initial IV treatment is not sufficient, open-label case series have described benefit for status migrainosus with repeated doses of dihydroergotamine or magnesium[88] as well as with continuous infusions of valproic acid.[89] Similarly, case series have reported improvement with peripheral nerve blocks as both acute and preventive treatments for migraine in adolescents.[88] Several trials of therapies for severe headache flares are listed at clinicaltrials.gov, including occipital nerve block,[90] intranasal ketorolac,[91] intranasal lidocaine,[92] sphenopalatine ganglion block,[93] and auricular acupuncture.[94]

Preventive Healthy Habits

Consistent lifestyle habits may help to minimize migraine triggers and should be discussed with all patients. Some evidence indicates that poor sleep, inactivity, and skipping breakfast are associated with increased likelihood of headache in adolescents.[95] Changing these behaviors is practical, and consistent education about lifestyle habits may have acted as an effective cointervention in at least one migraine preventive trial.[96] However, factors outside the child's control may preclude change, including school start time,[97] homework, and work schedules of parent(s)/guardian(s). Even when children intend to follow the advice, adherence is difficult.[98] Furthermore, little evidence is available to guide which specific changes actually impact headache frequency. A way to begin is by gathering information organized by the mnemonic SMART (**s**leep, **m**eals, **a**ctivity, **r**elaxation, **t**riggers) (TABLE 9-4[99-107]).[40]

While reviewing these lifestyle details, areas of concern and possible remedies can be discussed with the patient and parent/guardian. These may need to be addressed in a letter to the school to ensure access to water and permission to use the bathroom as needed, access to a snack if lunch is unusually early or late in the day, and flexibility with homework when possible to avoid inconsistency of sleep. However, it should be emphasized to the child and parent(s)/guardian(s) that the goal is a healthy lifestyle, not an overly regimented or headache-focused one. It is helpful to know whether staying up late brings on a headache, but it is not helpful if occasionally staying up late brings on significant anxiety (for child or parent[s]/guardian[s]) about the expected headache. These strategies are ways to help the child "be the boss of migraine."

Preventive Treatment

Preventive treatment should be considered in all children who have frequent headaches or significant headache-related disability, or both (CASE 9-2). In adults, headache on 6 or more days per month is a risk factor for progression to chronic migraine.[108] Most studies of preventive treatment in pediatrics have used a minimum of 4 headache days per month and/or three to four migraine attacks per month.[9] Children with continuous headaches and very high levels of disability have been excluded from these treatment trials, but in clinical practice the treatment approach is the same.

KEY POINTS

- Consistent lifestyle habits may help to minimize migraine triggers and should be discussed with all patients.
- Factors outside the child's control may preclude the development of healthy lifestyle habits, including school start time, homework, and work schedules of parent(s)/guardian(s). Even when children intend to follow the advice, adherence is difficult. Furthermore, little evidence is available to guide which specific changes actually impact headache frequency.
- Preventive treatment should be considered in all children who have frequent headaches or significant headache-related disability, or both.

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The 2019 American Academy of Neurology/American Headache Society guideline for pharmacologic treatment for pediatric migraine prevention (TABLE 9-5) recommends shared decision making between providers and families, with an open discussion about the fact that many children/adolescents with migraine who received placebo in trials improved and that most preventive medications have not been proven superior to placebo.[9] High placebo response in trials limits the ability to demonstrate efficacy of a medication, and this must be addressed in future trials (perhaps with novel trial designs, change in patient selection, and timing of trials) to increase the number of evidence-based insurance-approved therapies. However, in clinical practice, placebo response can be beneficial, as the goal is patient improvement without harm. The guidelines do recommend consideration of topiramate, propranolol, and amitriptyline combined with cognitive-behavioral therapy, which was demonstrated to be superior to amitriptyline plus headache education. The guidelines also recommend warning

TABLE 9-5

Recommendations of the AAN and AHS 2019 Practice Guideline Update: Pharmacologic Treatment for Pediatric Migraine Prevention[a,b]

Counseling and education for children and adolescents with migraine and their families

- Clinicians should counsel patients and families that lifestyle and behavioral factors influence headache frequency
- Clinicians should educate patients and families to identify and modify migraine contributors that are potentially modifiable (ie, being overweight, caffeine and alcohol use, lack of physical activity, poor sleep habits, tobacco exposure, depression)
- Clinicians should discuss the potential role of preventive treatments in children and adolescents with frequent headache (defined in trials as a minimum of 4 headache days per month and three to four migraine attacks per month for at least 3 months) or migraine-related disability (PedMIDAS score >30) or both
- Clinicians should discuss the potential role of preventive treatments in children and adolescents in medication overuse (taking triptans, ergotamines, opioids, and combination analgesics >9 days in a month or taking over-the-counter analgesics on >14 days in a month)

Starting preventive treatment

- Clinicians should inform patients and caregivers that in clinical trials of preventive treatments for pediatric migraine, placebo was effective and the majority of preventive medications were not superior to placebo
- Acknowledging the limitations of currently available evidence, clinicians should engage in shared decision making regarding the use of short-term trials (a minimum of 2 months) for those who could benefit from preventive treatment
- Clinicians should discuss the evidence for amitriptyline combined with cognitive-behavioral therapy for migraine prevention, inform patients and families of the potential side effects of amitriptyline including risk of suicide, and work with families to identify providers who can offer this type of treatment
- Clinicians should discuss the evidence for topiramate for pediatric migraine prevention and its side effects
- Clinicians should discuss the evidence for propranolol for pediatric migraine prevention and its side effects

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patients and parent(s)/guardian(s) about the risk of suicidality with amitriptyline and of teratogenicity and risk of decreased effectiveness of hormonal contraception with topiramate (and advise supplementation with folic acid).[9]

Acknowledging that trial design may have affected the outcome of several pediatric preventive studies, in clinical practice headache specialists often use medications not included in the guideline recommendations (TABLE 9-6[109-116]). Other pharmacologic treatments without pediatric data but with evidence of benefit in adults, such as candesartan and lisinopril, may be tried. Knowing that full evidence is several years away, the Pediatric-Adolescent Headache Section of the American Headache Society put together recommendations for off-label use of the monoclonal antibodies against calcitonin gene-related peptide.[117]

Alternatively, if one interprets that the trials demonstrated the benefit of pill-taking behavior regardless of the content of the pill, it seems prudent to consider other treatments that may have fewer side effects (TABLE 9-6). Nutraceuticals

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Counseling for patients of childbearing potential

- Clinicians must consider the teratogenic effect of topiramate and valproate in their choice of migraine prevention therapy recommendations to patients of childbearing potential
- Clinicians who offer topiramate or valproate for migraine prevention to patients of childbearing potential must counsel these patients about potential effects on fetal/childhood development
- Clinicians who prescribe topiramate for migraine prevention to patients of childbearing potential must counsel these patients about the potential of this medication to decrease the efficacy of oral combined hormonal contraceptives, particularly at doses over 200 mg daily
- Clinicians who prescribe topiramate or valproate for migraine prevention to patients of childbearing potential should counsel patients to discuss optimal contraception methods with their health care provider during treatment
- Clinicians must recommend daily folic acid supplementation to patients of childbearing potential who take topiramate or valproate

Monitoring and stopping medication

- Clinicians must periodically monitor medication effectiveness and adverse events when prescribing migraine preventive treatment
- Clinicians should counsel patients and families about the risks and benefits of stopping preventive medication once good migraine control is established[b]

Mental illness in children and adolescents with migraine

- Children and adolescents with migraine should be screened for mood and anxiety disorders because of the increased risk of headache persistence
- In children and adolescents with migraine who have comorbid mood and anxiety disorders, clinicians should discuss management options for these disorders

AAN = American Academy of Neurology; AHS = American Headache Society; PedMIDAS = Pediatric Migraine Disability Assessment.

[a] Data from Oskoui M, et al, Neurology.[9]

[b] These statements are verbatim from the 2019 Guidelines. The author and editors of this manuscript would like to emphasize concern about teratogenicity of valproic acid and its use in females of childbearing age.

[c] "Good migraine control" is not well defined.

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TABLE 9-6 **Preventive Treatments Studied for Pediatric Migraine Prevention**

Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Antiepileptics[9]				
Topiramate	2-3 mg/kg/d; typical dose 100 mg/d; maximum dose 200 mg/d	Paresthesia, anorexia, weight loss, fatigue, cognitive impairment, decreased perspiration Serious side effects: renal stones, depression, teratogenicity, angle closure glaucoma	Lowers potency of oral contraceptive pill, especially when more than 200 mg/d; recommend folic acid supplementation	Probably more likely than placebo to decrease frequency of headache days
Divalproex sodium	15-30 mg/kg/d up to 1000 mg/d	Nausea, weight gain, dizziness, somnolence, tremor, alopecia; monitor for thrombocytopenia, lymphopenia, elevated liver enzymes Serious side effects: pancreatitis, hyperammonemia, hepatotoxicity, teratogenicity	Recommend folic acid supplementation Not recommended for females of child-bearing age due to teratogenicity	Insufficient evidence
Zonisamide[109]	4-10 mg/kg/d, usual maximum 200 mg/d	Somnolence, anorexia, weight loss, paresthesia, dizziness, fatigue	Sometimes used if topiramate side effects intolerable	Not reviewed (no pediatric trials)
Levetiracetam[110]	20-40 mg/kg/d divided into twice daily dosing (usual maximum 3000 mg/d)	Somnolence, fatigue, irritability, behavior/mood change		Not reviewed (no pediatric trials)
Antidepressants[9]				
Amitriptyline	0.25-1 mg/kg/d (at bedtime)	Sedation, dizziness, dry mouth, weight gain; may cause prolonged QTc		Insufficient evidence when used alone; refer to entry for cognitive-behavioral therapy
Antihypertensives[9]				
Propranolol	20-40 mg 3 times a day	Sedation, hypotension, bradycardia, weight gain; may worsen depression and exercise-induced asthma		Possibly more likely than placebo to cause 50% reduction in headache frequency
Flunarizine[111]	5-10 mg at bedtime	Sedation, weight gain	Not available in the United States	Insufficient evidence

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Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Cinnarizine	1.5 mg/kg/d for <30 kg; 50 mg/d for >30 kg	Sedation, weight gain	Not available in the United States	Probably more likely than placebo to decrease headache frequency
Nimodipine	10-20 mg 3 times a day	Abdominal discomfort		Insufficient evidence
Antihistamine[9]				
Cyproheptadine[112]	0.25-0.5 mg/kg/d, maximum 16 mg given either at bedtime or divided 2 times a day	Sedation, increased appetite, weight gain	Liquid dosing option, can also treat cyclic vomiting and gastrointestinal pain	Not reviewed (no pediatric migraine trials)
Toxin[9]				
OnabotulinumtoxinA	74 units or 155 units injected per PREEMPT protocol[113] every 12 weeks	Injection site pain, weakness, worsened headache		Insufficient evidence
Nutraceuticals[114]				
Riboflavin	50-400 mg/d either once daily or divided into two doses	Urine discoloration	Limited studies	Not included
Magnesium	Elemental magnesium 9 mg/kg/d with food (magnesium oxide divided 3 times a day; others used)	Diarrhea	Limited studies, some positive	Not included
Coenzyme Q10	1-3 mg/kg/d in the morning with food	Insomnia, gastrointestinal upset	Limited studies, some positive	Not included
Vitamin D	Studies have used 400 IU/d for children with normal blood level of Vitamin D; 800 IU/d for mild and 5000 IU/d for moderate Vitamin D deficiency	Well tolerated	Limited studies	Not included
Melatonin[115]	2-3 mg every day at bedtime	Sedation	Limited studies, some positive	Not included
Polyunsaturated fatty acids	Fish oil compound	Nausea	Limited studies	Not included

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Treatment	Dose	Side effects	Comments	2019 AAN-AHS Guideline Comment[9]
Devices				
Single-pulse transcranial magnetic stimulation[80]	Twice daily as preventive therapy; additional pulses may be used as needed for headache attacks	Mild discomfort	Open-label pilot study led to US Food and Drug Administration (FDA) clearance in adolescents	Not included
Other				
Cognitive-behavioral therapy	10 sessions		Multiple barriers to implementation; biofeedback can be integrated with cognitive-behavioral therapy or is sometimes done separately	Cognitive-behavioral therapy plus amitriptyline more likely than headache education plus amitriptyline to decrease frequency
Acupuncture[116]	Variable	Discomfort, needle phobia	Safe and effective	Not included

AAN = American Academy of Neurology; AHS = American Headache Society.

CASE 9-3

A 17-year-old girl presented for a follow-up visit for treatment-refractory new daily persistent headache that had started in the setting of an upper respiratory illness at age 15. After appropriate trials of three oral preventive medications and cognitive-behavioral therapy, she still had continuous headache. She reported attending school consistently, with positive mood overall, but expressed frustration about her pain. Her history, normal physical examination, and past workup were reviewed to consider diagnoses such as spontaneous intracranial hypotension or postural tachycardia syndrome.

The diagnosis of new daily persistent headache was confirmed, and no additional testing was ordered. The risks and benefits of different treatment options were discussed, and she ultimately decided to try an off-label injectable anti–calcitonin gene-related peptide monoclonal antibody.

COMMENT

New daily persistent headache, as the name suggests, can cause persistent, difficult-to-treat headaches, but it is also important to ensure that relevant secondary headaches have been ruled out. New daily persistent headache often has a migrainous phenotype, so treatments for migraine can be used.

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were not reviewed in the guidelines, but some have evidence of benefit and safety and are commonly used by patients even before they are recommended by clinicians. Preliminary data support the use of magnesium and coenzyme Q10 for headache prevention in children. Vitamin D_3 and riboflavin also have evidence of safety in children but mixed or inconclusive data on efficacy.[114] *Petasites* (butterbur) also has evidence of benefit[118,119] but is not recommended because of concerns about liver toxicity.[120] This illustrates that supplements are not always benign, and the lack of regulation and out-of-pocket cost are significant disadvantages.

No current evidence guides the decision of which therapy is first line. For any pill-based therapy, adherence data favor once-daily over twice-daily dosing when appropriate.[98] Response to medication should be monitored, and preventive therapy should be withdrawn once the headaches are infrequent and no longer disabling. Cognitive-behavioral therapy is an appropriate second-line therapy, as it demonstrated added benefit with amitriptyline.[105]

If patients have tried multiple therapies without benefit, it is prudent to reexamine diagnosis and consider comorbidities (**CASE 9-3**). Sometimes at this juncture patients prefer to try an alternative therapy such as intensive exercise or dietary changes. Given that so many unknowns exist about migraine treatment in youth, clinicians should discuss these ideas openly with patients, encouraging self-efficacy but discouraging therapies with large risk of harm.

PROGNOSIS

How do headaches change in the short-term? A large population-based study with 1-year follow-up found that headache frequency in those 8 to 15 years of age remained the same for about half of respondents, increased in about one-fourth, and decreased in about one-fourth.[121] Over 6-year follow-up, approximately half of children with migraine have persistent migraine, one-fourth have headaches most consistent with the diagnosis of tension-type headache, and headaches have resolved in one-fourth.[122] Girls were more likely than boys to have persistent headache. Among those with continued headaches, many experience a decrease in frequency over the years. Migrainous headaches, parental history of migraine, depression/anxiety, and poor stress coping skills were associated with higher headache frequency over 4- and 5-year follow-up.[123]

What happens to headaches as children grow into adults? Children with recurrent headaches have approximately double the likelihood of recurrent headaches in adulthood and also have increased likelihood of having other physical symptoms and psychiatric comorbidities.[124] These likely compound each other. Long-term follow-up data from a population-based study in Sweden found that among the adolescents who had reported frequent headache at the start of the study, approximately one-fifth still had frequent headaches at 14-year follow-up.[125] Children with higher headache frequency, higher levels of disability, comorbid depression, and female sex were more likely to report headaches at least once per week at long-term follow-up.[125] Children with migraine are more likely to report continued headaches into adulthood compared to children with tension-type headache, and, similarly, higher pain severity increases the odds of continued headache into adulthood.[6] A long-term study of Swedish schoolchildren with migraine found that 60% had a migraine-free period of at least 2 years (average 6 years) by their twenties, although one-third relapsed by their thirties. Boys were much more likely than girls to experience a sustained migraine remission. At the 40-year follow-up,

KEY POINTS

- High placebo response in trials limits the ability to demonstrate efficacy of a medication. However, in clinical practice, placebo response can be beneficial, as the goal is patient improvement without harm. The guidelines recommend consideration of topiramate, propranolol, and amitriptyline combined with cognitive-behavioral therapy, which was demonstrated to be superior to amitriptyline plus headache education.
- Nutraceuticals were not reviewed in the current guidelines for pediatric migraine prevention, but some have evidence of benefit and safety and are commonly used by patients even before they are recommended by clinicians.
- Children with recurrent headaches have approximately double the likelihood of recurrent headaches in adulthood and also have increased likelihood of having other physical symptoms and psychiatric comorbidities.

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approximately half reported migraine freedom, about one-fourth had migraine at least yearly, and one-fourth had migraine less than once per year. About 34% of male participants but only 15% of female participants had become migraine-free by their early twenties and continued without migraine throughout the 40-year follow-up.[126]

What is the prognosis for children who have very frequent headaches? A follow-up of a school-based study in Taiwan demonstrated that among children who had chronic daily headache at the time of initial interview, one-fourth had significant disability from headaches 8 years later and about one-eighth still had chronic daily headache. The presence of migraine features, onset of chronic daily headache before age 13, duration of chronic daily headache for 2 or more years at the time of the initial interview, and medication overuse predicted higher headache frequency at follow-up.[127] However, this was a population-based sample in which the rate of consultation and treatment was very low, so the chances of continued disability and high headache frequency are likely higher for patients who present to clinic like the patient in CASE 9-3.

ADDRESSING BARRIERS TO CARE

Children with migraine who seek care, receive a diagnosis, and take appropriate treatments have at least a two-thirds chance of significant and sustained improvement. However, three major challenges must be overcome for the delivery of appropriate care.[128]

The first challenge is consulting a health care provider. Population-based studies have demonstrated that despite reporting significant disability from their headaches, only 5% to 40% of adolescents with chronic migraine had visited a health care provider for their headaches within the preceding year.[63,64] Approximately three-fourths of outpatient care for migraine in children is delivered by pediatricians or family physicians and one-fourth by neurologists.[129] For children whose migraine is not helped by the intervention of their primary care provider, prompt referral to a specialist is advised. Delay between the onset of migraine and the first visit to a multidisciplinary pediatric headache clinic predicts higher risk of chronic migraine at 10-year follow-up.[130]

How could consultation rates for children with migraine be increased so that they receive the appropriate care? Given that children must attend school and school-related disability is a major effect of migraine, school is the logical place to intervene. School-based interventions have demonstrated improvements in consultation rates in asthma, a condition with similar prevalence and effect on school attendance.[131] The Headache Action Plan Project for Youth (HAPPY) was a large multipronged educational intervention that asked school nurses to identify children with frequent headaches and explicitly recommend that they seek evaluation for the headaches from their primary care provider.[132] The effect of the intervention on consultation rates in that study was not able to be measured, but additional work is planned.

The next challenge to care is receiving a migraine diagnosis.[128] A large database study from the United Kingdom found that only one in five children who present to their general practitioner for headache were given a diagnosis of migraine.[36] One percent were given a diagnosis of secondary headache, whereas almost four-fifths were not given a specific diagnosis. A study using electronic health record data from a health system in the midwestern United States similarly found that among children who either had a chief complaint of headache/migraine

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or were given an *International Classification of Diseases* diagnostic code for headache/migraine, only 17.7% were diagnosed with migraine. The nonspecific diagnosis "headache" was made for 36.6%, and 45.7% reported headache or migraine as the reason for the visit but received no diagnosis related to headache.[133] A large portion of those diagnosed with headache likely have migraine. The odds of prescribing evidence-based treatment increased when migraine was diagnosed compared to either headache or no diagnosis.[133]

The third major challenge is prescription use of the appropriate treatment.[128] Even when a diagnosis of migraine has been made, prescription of appropriate therapies by primary care providers is low.[36] A 2019 neurology clinic–based study demonstrated that only 5% of children with migraine who met criteria for use of preventive medication were started on one while awaiting referral to neurology, and no children were prescribed a triptan by their primary care provider.[134] Population-based studies have similarly reported low rates (varying from 1% to 20%) of preventive medication use among adolescents with chronic migraine.[63,64] Prescription of acute treatments is also imperfect. In a study of prescribing practices by primary care providers in a large health system, White youth were more likely than youth of color to receive any acute medication to treat their headaches, but White youth were also more likely to receive a prescription for an opioid or butalbital than youth of color.[133]

Evidence-based solutions are available to improve the rate of appropriate prescriptions. One center demonstrated that headache specialists were more than twice as likely to prescribe triptans as child neurologists who were not headache specialists, indicating that education and awareness will help.[134] Use of a headache questionnaire integrated into the electronic health record at a large academic pediatric neurology practice increased the likelihood of making a specific diagnosis, which, in turn, substantially increased the odds of appropriate treatment.[135] The HAPPY school-based intervention paired with online clinician decision support led to a modest improvement in the rate of prescription of evidence-based acute and preventive headache therapies by primary care providers.[132]

KEY POINTS

- **Children with migraine who seek care, receive a diagnosis, and take appropriate treatments have at least a two-thirds chance of significant and sustained improvement.**
- **Recurrent headaches are common in children and adolescents. The most common cause, migraine, is underdiagnosed and undertreated. Many unanswered questions about the "correct" approach to migraine treatment for children and adolescents remain.**

CONCLUSION

Recurrent headaches are common in children and adolescents. The most common cause, migraine, is underdiagnosed and undertreated. Many unanswered questions about the "correct" approach to migraine treatment for children and adolescents remain. Clarifying the best algorithm of first-, second-, and third-line therapies and whether these should vary depending on the particular headache characteristics would make establishing a treatment strategy more efficient and decrease patient disability. In the future, it would be ideal if there were markers to predict individual treatment responsiveness to avoid the current trial-and-error approach. In addition, the appropriate treatment for children with continuous headache and very high levels of disability, who have been excluded from most treatment trials, must be clarified. We must reach the children who are not reaching us, either because their parent(s)/guardian(s) and teachers do not recognize that headache is a treatable problem or because they lack insurance or have not traversed the sometimes-insurmountable barriers to care. Care must not only be evidence-based but must also truly meet the needs of patients and be culturally sensitive.[136]

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USEFUL WEBSITES

AMERICAN MIGRAINE FOUNDATION: UNDERSTANDING PEDIATRIC MIGRAINE
This website includes information about migraine in children from the American Migraine Foundation, which seeks to mobilize a community for patient support and advocacy as well as drive and support impactful research that translates into advances for patients with migraine and other disabling diseases that cause severe head pain.

americanmigrainefoundation.org/resource-library/pediatric-migraine/

HEADACHE RELIEF GUIDE
This website was created as part of the Headache Action Plan Project for Youth (HAPPY) to help teens and their families to gain better control of headaches, get appropriate medical care, and limit the disability caused by headaches.

headachereliefguide.com

MIGRAINE AT SCHOOL
This website was developed by the Coalition for Headache and Migraine Patients and is a collection of the resources for students, parents, and educators.

migraineatschool.org

THE AMERICAN ACADEMY OF PEDIATRICS PARENTING WEBSITE
This website provides recommendations on lifestyle behaviors from the American Academy of Pediatrics.

healthychildren.org

CENTERS FOR DISEASE CONTROL AND PREVENTION HEADS UP
This website provides concussion resources from the Centers for Disease Control and Prevention.

cdc.gov/headsup

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DISCLOSURE

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Clinic-based Procedures for Headache

By Matthew S. Robbins, MD, FAAN, FAHS

ABSTRACT

PURPOSE OF REVIEW: Headache disorders are common and disabling, and many therapies that are effective and safe are procedural.

RECENT FINDINGS: After pivotal clinical trials, onabotulinumtoxinA has become an established preventive therapy for chronic migraine; it is better tolerated than many other treatments and may be useful for other headache disorders. Peripheral nerve blocks, especially greater occipital nerve blocks, have amassed evidence from randomized trials in the acute and short-term preventive treatment of migraine and cluster headache. Trigger point injections and sphenopalatine ganglion blocks have recent trials suggesting efficacy and safety in properly selected patients. Medical education initiatives are needed to train neurologists in these procedures to help manage the large population of patients with headache disorders who need them.

SUMMARY: Evidence exists for the efficacy and safety of procedural therapies to be incorporated into neurology practice for the management of patients with migraine, cluster headache, and other headache disorders.

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Dr Robbins serves on the board of directors of the American Headache Society and the New York State Neurological Society, as an associate editor for *Headache*, and as a section editor for *Current Pain and Headache Reports*.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Robbins discusses the unlabeled/investigational use of onabotulinumtoxinA for new daily persistent headache and chronic posttraumatic headache.

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INTRODUCTION

The management of headache disorders has increasingly featured the incorporation of procedures into clinical practice. In a 2011 survey of practicing neurologists by the American Academy of Neurology, onabotulinumtoxinA injections and nerve blocks were the only procedures demonstrating an increase in use by neurologists over the preceding decade.[1] OnabotulinumtoxinA received regulatory approval by the US Food and Drug Administration (FDA) for chronic migraine in 2010 after two pivotal clinical trials,[2,3] and in recent years an accumulation of evidence for the use of other procedures for headache, most notably peripheral nerve blocks[4-9] and, to an extent, trigger point injections[10,11] and sphenopalatine ganglion blocks, has mounted.

Although headache practice has diversified substantially with the advance of migraine-specific drug therapies and neuromodulation, it is challenging to practice contemporary headache medicine comprehensively without the capability of performing or access to such procedures (TABLE 10-1).[12-25]

ONABOTULINUMTOXINA

Peripheral administration of onabotulinumtoxinA is an important treatment option for chronic migraine and remains the only specific therapy approved for

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this particular indication, largely because the evidence supports its use for chronic but not episodic migraine. After several years of study for migraine of varying frequency and with different treatment protocols, two large clinical trials were conducted for chronic migraine and form the basis of the use of onabotulinumtoxinA today.[2,3]

The PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) trials took place in Europe and the United States and cumulatively randomly assigned 1384 patients. The pooled data from the PREEMPT trials demonstrated a significant reduction of headache days per month over placebo at week 24 (−8.4 versus −6.6, $P<.001$).[26] The benefit from placebo was substantial, which generates consideration that the treatment effect may not be just from the biological action of onabotulinumtoxinA but also from any neuromodulation related to mechanical factors such as the needle insertion and the injected solution volume or lack of blinding resulting from effacement of brow wrinkles.[27] Longer-term studies have demonstrated a durable benefit of onabotulinumtoxinA for at least 2 years.[28] Evidence from a 2019 post hoc analyses of the PREEMPT data suggests that pain relief in many patients develops within the first few weeks of onabotulinumtoxinA administration.[29]

Summary of the Procedures for Headache Disorders Most Commonly Performed by Neurologists TABLE 10-1

Procedure	Treatment type	Injection frequency	Evidence highlights
OnabotulinumtoxinA	Preventive	12-week intervals	Randomized controlled trials for chronic migraine[2,3] Randomized controlled trial for sleep-related bruxism[12] Observational studies for new daily persistent headache,[13] chronic posttraumatic headache,[14] nummular headache,[15] trigeminal neuralgia[16]
Peripheral nerve blocks	Acute, short-term preventive	Single or repeated at 2-week or longer intervals as needed	Randomized controlled trials for migraine (short-term prevention)[6–9,17] Randomized controlled trials for migraine in emergency department[18,19] Randomized controlled trials for cluster headache (short-term prevention)[4,5] Observational studies in pediatric,[20] pregnant,[21] and geriatric[22] populations
Trigger point injections	Acute, short-term preventive	Single or repeated at 2-week or longer intervals as needed	Randomized controlled trials for tension-type headache[10,11]
Sphenopalatine ganglion blocks	Acute, short-term preventive	Single or repeated twice weekly or longer intervals as needed	Randomized controlled trial for acute and preventive treatment of chronic migraine[23,24] Randomized controlled trial for acute headache in emergency department[25]

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After internalization of its light chain within neurons, onabotulinumtoxinA cleaves proteins of the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which are responsible for fusing synaptic vesicles to the neuronal membrane. Such proteins include synaptosomal associated protein of 25 kDa (SNAP-25), syntaxin, and synaptobrevin.[30] In the periphery, the inhibitory effect of onabotulinumtoxinA may prevent the release of inflammatory substances important in migraine and pain, such as calcitonin gene-related peptide. Anatomically, extracranial administration of onabotulinumtoxinA to the scalp may prevent activation of C-type meningeal nociceptors that cross skull suture lines[31]; conversely, dural trigeminal branches may also cross suture lines and receive sensory information from extracranial structures.[32] Therefore, extracranial administration of onabotulinumtoxinA may directly impact intracranial dural afferent signaling.

After reconstitution of the toxin in saline, onabotulinumtoxinA is administered in small equal doses totaling 155 units distributed throughout the head, neck, and shoulder musculature, including the corrugator, procerus, frontalis, temporalis, occipitalis, cervical paraspinal, and trapezius muscles (FIGURE 10-1).[33] An additional 40 units in total can be injected into the temporalis, occipitalis, and trapezius muscles depending on the location of the pain, although no clear evidence has shown that the addition of other units aside from the initial 155 units is superior for durable pain relief. The injections are generally performed with the patient in the sitting position. However, in the phase 3 clinical trials, patients were positioned supine for the anterior and lateral injections and sitting for posterior injections. Injections are repeated every 12 weeks, with recommendations to attempt at least two injection cycles to assess for efficacy.

One of the major benefits of onabotulinumtoxinA relative to other preventive therapies, particularly oral drugs, is its tolerability, which has been verified in

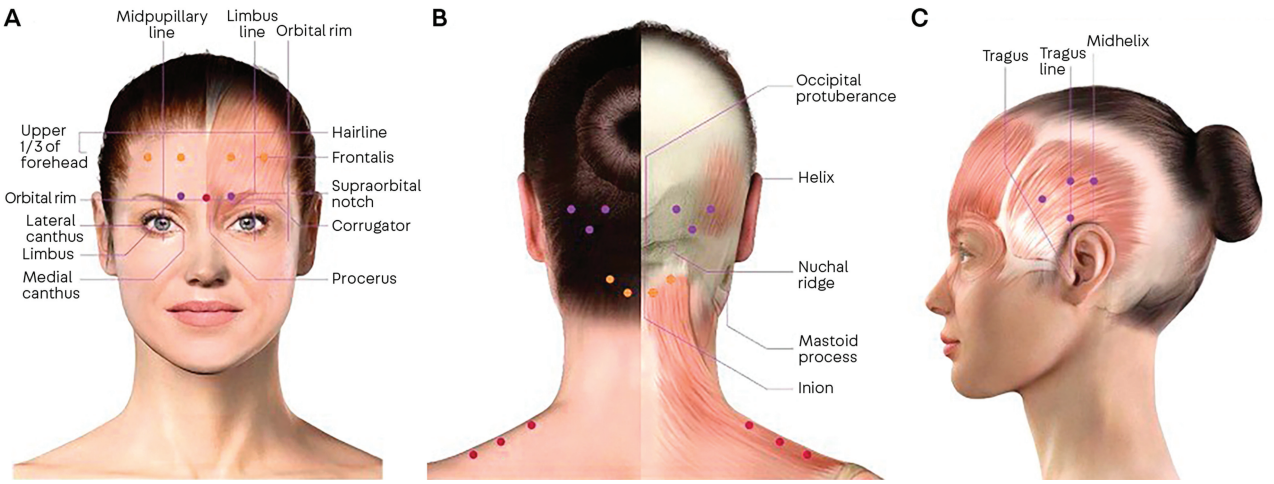

FIGURE 10-1

Injection paradigm for onabotulinumtoxinA in the treatment of chronic migraine. Injection site locations for onabotulinumtoxinA in the treatment of migraine include the following muscles: corrugator (*A*, *purple dots*), procerus (*A*, *red dot*), frontalis (*A*, *orange dots*), occipitalis (*B*, *purple dots*), cervical paraspinal muscles (*B*, *orange dots*), trapezius (*B*, *red dots*), and temporalis (*C*, *purple dots*).

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comparative studies versus oral preventive agents (CASE 10-1).[34] Although neck pain was the most common side effect in clinical trials, a protocol revision recommends more superior injection of cervical paraspinal injections to reduce its incidence by minimizing any neck extensor weakness.[33] Medial brow ptosis is also a potential cosmetic side effect, and the revised protocol may reduce its incidence by placing the lateral frontalis injection more lateral to the vertical plane of the midpupillary line. OnabotulinumtoxinA should be avoided in patients with any neuromuscular junction disorder, and caution should be exercised if the patient has a skull defect or an implanted neurostimulator in the head or neck. Reconstitution of onabotulinumtoxinA should only be with preservative-free normal saline; reconstitution with local anesthetics has been reported to cause fatal anaphylaxis.[35]

Although many clinicians avoid using onabotulinumtoxinA in pregnant women[36] and its safety for the treatment of chronic migraine in pregnant women is not well explored, no clear evidence to date has shown significant harm.[37] OnabotulinumtoxinA has a high molecular weight and should not cross the placenta. Cases of botulism by ingestion have not been associated with fetal toxicity. A database of pregnant women exposed to onabotulinumtoxinA in clinical trials and postmarketing surveillance did not show any increase in fetal loss or malformations relative to the general population.[38] OnabotulinumtoxinA is generally considered safe in breastfeeding women given its peripheral administration and large molecular weight.

One issue that has emerged with the use of onabotulinumtoxinA is the phenomenon of drug wear-off, defined broadly by the establishment of initial efficacy followed by diminishing therapeutic effect before the next scheduled dose. This phenomenon has recently been examined specifically in chronic

CASE 10-1

A 48-year-old man had a history of episodic migraine without aura that had evolved over the previous year to 25 days per month, of which 15 monthly days featured severe headache. Previous trials of topiramate, nortriptyline, and propranolol were not effective, so onabotulinumtoxinA injections were administered. After the first 12 weeks, his headache frequency reduced to 20 days per month with 13 severe headache days; however, 12 weeks after the second round of injections, his headache frequency had diminished to 12 days per month, with 5 severe headache days. He experienced no side effects.

COMMENT

This patient had episodic migraine that evolved to chronic migraine. OnabotulinumtoxinA or a calcitonin gene-related peptide ligand- or receptor-targeting monoclonal antibody are appropriate treatment options. The patient had only modest improvement after the first injection series but more robust improvement thereafter, which is often what is observed. This has led to the recommendation of a trial of at least two or three injection cycles before considering another preventive therapy. This patient experienced no side effects, which is typical for onabotulinumtoxinA, a treatment that is generally very well tolerated.

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migraine,[39,40] demonstrating a prevalence as high as two-thirds of patients. Although the mechanisms for wear-off may be biological or related to the nocebo response, it has been suggested that increasing the units administered within the range of 155 units to 195 units may mitigate against its occurrence.[39]

Although not specifically approved for these disorders, onabotulinumtoxinA has rationally been used in the same protocol for other chronic headache disorders that are otherwise treated like chronic migraine if they feature the same headache phenotype, including chronic posttraumatic headache[14] and new daily persistent headache.[13,14] Specialized protocols have been employed to use onabotulinumtoxinA for other headache and facial pain disorders featuring more unique pain distributions, such as sleep-related bruxism,[12] trigeminal neuralgia,[16] and nummular headache.[15]

PERIPHERAL NERVE BLOCKS

Peripheral nerve blocks for headache consist of injections of local anesthetic and, at times, steroids in accessible nerve branches on the head, including the greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supratrochlear nerve, and supraorbital nerve (FIGURE 10-2[41]).[33] Peripheral nerve blocks have generally been conceptualized and studied as acute or short-term preventive therapies (CASE 10-2), although they may be used on a scheduled basis as a preventive therapy.

The preponderance of higher-quality evidence for peripheral nerve blocks relates to the use of greater occipital nerve blocks or injections for migraine and cluster headache, although they are used widely for occipital neuralgia despite a lack of randomized controlled trials for this specific indication. Observational data suggest that the typical duration of benefit of greater occipital nerve injections for headache is approximately 1 to 4 weeks.[42,43] Therefore, the majority of clinical trials have focused on their use as short-term preventive therapies. Of the five sham/placebo-controlled randomized controlled trials for migraine, four studies demonstrated statistically significant benefits of the

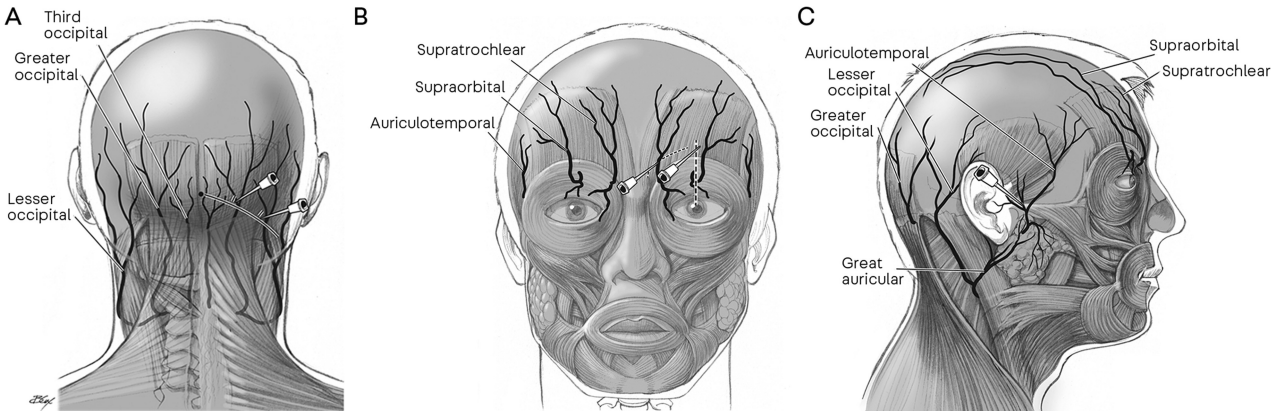

FIGURE 10-2

Cranial and upper cervical nerve branch injection sites for peripheral nerve blocks for headache disorders. Common peripheral nerve block injection site locations include the greater and lesser occipital nerves (*A*), the supraorbital and supratrochlear nerves (*B*, *C*), and the auriculotemporal nerves (*B*, *C*).

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primary end point over placebo for short-term prophylaxis.[6-9] The fifth study showed both active and placebo to be equally beneficial, although the primary end point for a single greater occipital nerve block was measured later at 4 weeks rather than at 2 weeks for the other trials,[17] possibly contributing to the result.[44] Two emergency department randomized trials also studied greater occipital nerve blocks in acute headache and demonstrated benefit over placebo[18] or parenteral therapies[19] in patients for whom first-line IV treatment had failed or in comparison to such therapies. However, a 2020 study showed that greater occipital nerve blocks were not as efficacious as IV metoclopramide as first-line therapy for migraine attacks in the emergency department.[45] Peripheral nerve blocks may be used in addition to repetitive IV medications for patients electively admitted for intractable migraine.[46]

For cluster headache, two randomized clinical trials demonstrated greater occipital nerve injections of steroid (either betamethasone or cortivazol [not available in the United States]) ipsilateral to the side of the pain as superior to placebo for short-term prevention, either as a single injection or in repeated injections over a few days.[4,5] This intervention provides an additional option to oral steroids for short-term cluster headache prevention. Although potentially safer given local rather than systemic steroid administration, a retrospective comparative study suggested outcomes may be better for oral steroids, although most patients improved with either treatment.[47] The two randomized trials led to greater occipital nerve steroid injections receiving a Level A recommendation in the latest American Headache Society guideline for cluster headache treatment.[48]

CASE 10-2

A 34-year-old woman with a history of frequent migraine without aura since the age of 12 developed a bout of gradual-onset, intractable throbbing, generalized headache with nausea and photophobia for 7 days that led her to miss work for 2 days. Repeated home doses of eletriptan and naproxen sodium were ineffective. She had previously had bouts of status migrainosus that had not responded well to courses of oral dexamethasone and oral methylprednisolone.

She did not wish to go to the emergency department or an urgent care facility, so she came to the clinic and was treated with bilateral occipital, auriculotemporal, supraorbital, and supratrochlear nerve blocks using 0.5% bupivacaine. She tolerated the injections well; within 24 hours her pain intensity reduced, and within 48 hours the attack ceased.

COMMENT

This patient with long-standing migraine developed another bout of status migrainosus. Although the evidence is quite limited for treatment in this particular setting after first-line therapies fail, peripheral nerve blocks provide a reasonable and safe option that may lead to the avoidance of an emergency department visit. Peripheral nerve blocks are often performed as just one component of treatment; other recommendations, such as augmentation of preventive therapy or counseling about acute medication overuse and lifestyle management, may be important in many individuals.

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No randomized controlled studies have yet examined whether the addition of other peripheral nerve blocks to greater occipital nerve blocks or injections would be superior to greater occipital nerve blocks alone for any headache disorder, but observational data suggest that it may be helpful for many patients,[43] even patients who have not responded to greater occipital nerve blocks.[49] Methodologically, finding the appropriate placebo for peripheral nerve block studies has been challenging,[50] as even saline injections or dry needling may have a neuromodulatory effect; an intradermal injection at the greater occipital nerve puncture site seemed more likely to be identified as a sham in a randomized controlled trial.[18]

Peripheral nerve blocks may work to treat headache disorders by targeting extracranial sensory trigeminal and upper cervical projections. All sites blocked peripherally have first-order neuronal projections that converge on the trigeminocervical complex in the brainstem. Clinical data suggest that the improvement that patients receive is not directly correlated to a simple local anesthetic effect, as the duration of analgesia generally far exceeds the duration of anesthesia. Other clinical observations strongly suggest a central mechanism of action for peripheral nerve blocks by demonstrating improvement of allodynia distant to the site injected as well as improvement in aura.[41] In addition, cluster headache is considered a trigeminal autonomic cephalalgia, but an upper cervical injection of steroid (greater occipital nerve) even without anesthetic use is effective.

Peripheral nerve blocks can be performed in an office-based setting effectively and safely, presuming understanding of peripheral nerve anatomy and

TABLE 10-2 **Safety Considerations for the Performance of Peripheral Nerve Blocks and Trigger Point Injections for Headache Disorders**[a]

Safety consideration	Concern	Action
Local anesthesia allergy	Allergic reaction, anaphylaxis	Use corticosteroids only
Pregnancy	Maternal and fetal toxicity	Use lidocaine or ropivacaine instead of bupivacaine; avoid steroids, particularly betamethasone and dexamethasone
Vasovagal attacks	Near syncope or syncope	Perform and allow for extra time in supine position; use bupivacaine instead of lidocaine; use lower anesthetic concentration; reduce total number of injections
Open skull defect or craniotomy	Intracranial anesthetic diffusion	Avoid injections in such locations
Antithrombotic or anticoagulant use	Hematoma	Compress at injection site for several minutes after injection
Cosmetic concerns	Alopecia	Avoid or use lower dose of steroids
Unclear anatomic landmarks because of body habitus	Pneumothorax	Avoid trapezius injections; use small gauge needle; use technology guidance (ultrasound, EMG)

EMG = electromyography.
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landmarks. All sites described (greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supraorbital nerve, supratrochlear nerve) can be injected bilaterally in the same appointment, as the cumulative anesthetic dose still lies far under the threshold of volumes associated with local anesthetic systemic toxicity.[41] In general, greater occipital nerve injections use the largest volumes (2 mL to 4 mL), followed by auriculotemporal nerve injections (0.5 mL to 1 mL) and supratrochlear nerve and supraorbital nerve injections (0.2 mL to 0.5 mL). No consensus exists for the most effective anesthetic; clinicians most commonly use lidocaine 1% to 2%, bupivacaine 0.5%, or ropivacaine 0.5% or a combination of any of these agents. A steroid should be administered in addition to an anesthetic for greater occipital nerve injections for cluster headache (typically methylprednisolone, dexamethasone, or triamcinolone) based on the available evidence and guidelines. However, for migraine, the few studies performing direct comparisons of anesthetics alone versus anesthetics with steroids do not show added benefit.[51,52] Ultrasound guidance has been proposed to provide anatomic insights and improve the efficacy and safety of greater occipital nerve injections in particular, but randomized trials comparing techniques are lacking.[7,53]

Peripheral nerve blocks generally cause numbness in the dermatomal distribution injected but otherwise have an excellent safety profile in properly selected patients. Peripheral nerve tenderness may help to predict respondents.[42] Procedural safety considerations are summarized in TABLE 10-2.[41] The most important precaution is to be aware of any skull bone defect or history of craniotomy or craniectomy, as two cases of reversible coma from intracranial diffusion of anesthetic have been reported. Although peripheral nerve blocks may be an excellent treatment option in pregnant patients with migraine,[21] ideally lidocaine or ropivacaine should be used as bupivacaine has more unpredictable pharmacokinetics and has been associated with maternal cardiac conduction abnormalities.[54,55] Peripheral nerve blocks may be an excellent and safe treatment option for older adults who frequently have more polypharmacy and intolerability to medications affecting the central nervous system.[22]

TRIGGER POINT INJECTIONS

Trigger point injections involve the administration of anesthetics into myofascial structures that may serve as mechanical sites that evoke or perpetuate an underlying headache disorder, most commonly tension-type headache or migraine. Trigger points are identified on physical examination (most commonly as a taut band of muscle) and are defined as sites of pain in muscle or fascia that when irritated or compressed evoke referred head, face, or neck pain, reproducing symptoms of the index disorder. Trigger points are found more often in patients with frequent tension-type headache or migraine. The hypothesis is that persistent activation of a myofascial structure leads to excessive local muscle contraction, ischemia, release of inflammatory substances, and peripheral sensitization.[56,57]

The evidence for trigger point injections includes randomized controlled trials for tension-type headache and migraine, with the strongest evidence for frequent tension-type headache.[10,11] In clinical practice, trigger point injections are rarely performed in isolation as they are most commonly indicated in patients otherwise requiring headache prophylaxis. In addition, trigger point injections may be performed in concert with peripheral nerve blocks.

KEY POINTS

- In the periphery, the inhibitory effect of onabotulinumtoxinA may prevent the release of inflammatory substances important in migraine and pain, such as calcitonin gene-related peptide.
- One of the major benefits of onabotulinumtoxinA relative to other preventive therapies, particularly oral drugs, is its tolerability, which has been verified in comparative studies versus oral preventive agents.
- Although not specifically approved for these disorders, onabotulinumtoxinA has rationally been used in the same protocol for chronic headache disorders that are otherwise treated like chronic migraine if they feature the same headache phenotype, including chronic posttraumatic headache and new daily persistent headache.
- Peripheral nerve blocks for headache consist of injections of local anesthetic and, at times, steroids in accessible nerve branches on the head, including the greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supratrochlear nerve, and supraorbital nerve.
- Clinical data suggest that the improvement that patients receive from peripheral nerve blocks is not directly correlated to a simple local anesthetic effect, as the duration of analgesia generally far exceeds the duration of anesthesia.

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Trigger point injections are performed based on physical examination. The most common sites of injection are the trapezius, sternocleidomastoid, and temporalis muscles, but other muscles of the head and neck are commonly injected (FIGURE 10-3). Anesthetics are generally used alone, given the local and systemic myotoxicity of steroids.[56] No clear evidence exists that onabotulinumtoxinA specifically injected into trigger points provides benefit; although the PREEMPT protocol allows for 40 additional units to be injected in areas of increased pain, these may not actually be active trigger points. Trigger point injections feature variable volumes (0.1 mL to 0.3 mL) but can be repeated frequently (at least monthly). Safety concerns are similar to peripheral nerve blocks (TABLE 10-2).

SPHENOPALATINE GANGLION BLOCKS

The sphenopalatine ganglion is a large parasympathetic ganglion lying in the pterygopalatine fossa that also contains trigeminal (V2) and sympathetic projections. The sphenopalatine ganglion is a reasonable target for blocks and neuromodulation as it is the key peripheral structure involved in the expression of cranial autonomic symptoms and plays an important role in the trigeminoautonomic reflex in trigeminal autonomic cephalalgias and migraine and in regulation of cerebral blood flow.[58] A number of therapies developed may

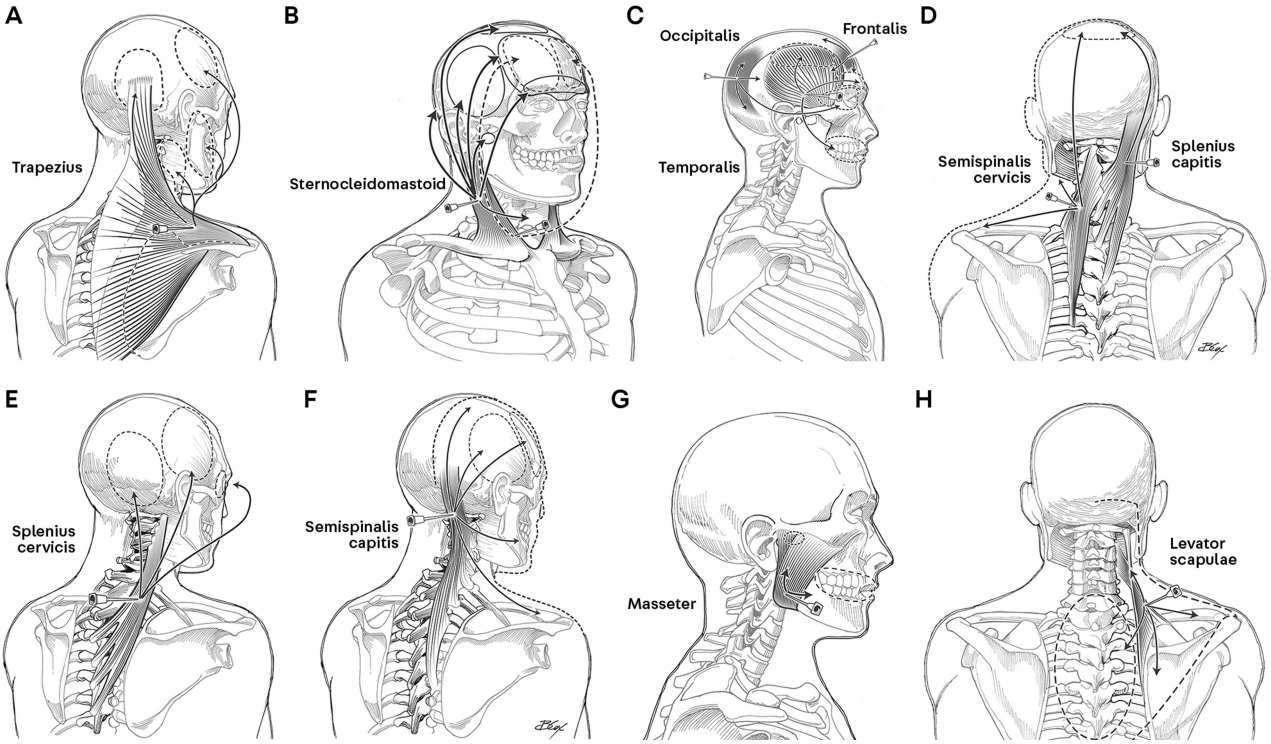

FIGURE 10-3

Common sites for trigger point injections for headache disorders. Muscle sites that may feature trigger points amenable to injections for headache disorders with their pain referral patterns (*arrows*) include the trapezius (*A*), sternocleidomastoid (*B*), temporalis (*C*), occipitalis (*C*), frontalis (*C*), semispinalis cervicis (*D*), splenius capitis (*D*), splenius cervicis (*E*), semispinalis capitis (*F*), masseter (*G*), levator scapulae (*H*).

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target the sphenopalatine ganglion, including intranasal medication delivery, percutaneous and intranasal blocks including new catheters, neurostimulation, chemical neurolysis, and ablation procedures.

For sphenopalatine ganglion blocks in the clinic, the evidence is somewhat limited and largely confined to one specific catheter. One randomized controlled trial in an emergency department setting that studied bilateral sphenopalatine ganglion blocks with bupivacaine for acute headache did not show benefit over placebo for the primary end point of pain and nausea reduction at 15 minutes but at 24 hours later demonstrated a higher proportion of pain freedom in the active treatment arm.[25] A randomized controlled trial assessed repetitive sphenopalatine ganglion blocks (twice weekly for 6 weeks) as an acute treatment for chronic migraine.[23,24] Acute pain reductions relative to placebo were achieved at multiple time points, but no statistically significant preventive effect was observed over 1 and 6 months after treatment.

Sphenopalatine ganglion blocks in the clinic are generally accomplished by two techniques. The older technique is to dip a cotton swab in liquid or viscous anesthetic such as lidocaine or bupivacaine and insert it into the nasal passage with the tip resting at or near the posterior wall while the patient lies supine. The second technique is to use a more recently developed nasal catheter attached to a syringe that administers the liquid anesthetic closer to the pterygopalatine foramen. No evidence suggests which technique may be more effective. Headache specialists surveyed do not seem to have a consensus for the most effective and feasible technique.[59]

Intranasal sphenopalatine ganglion blocks do not specifically require any imaging guidance and are generally safe to perform. However, they should be avoided in any patient with a history of any local bone or sinus defect, including a history of sinus surgery. Common side effects include a poor taste (from the anesthetic), numbness or paresthesia in the nose or throat (which indicates a patient should not swallow until resolved), low blood pressure, epistaxis, and nausea.

A much-needed future area of investigation is to elucidate the optimal sphenopalatine ganglion blocking approach. Imaging-guided percutaneous sphenopalatine ganglion blocks can be effective and safe but are more costly.[58] Recent anatomic studies have called into question the validity of the intranasal approach as the pterygopalatine foramen may be a closed passage with a longer distance than previously appreciated.[60] A related area of future study is the use of onabotulinumtoxinA administered to the sphenopalatine ganglion percutaneously, as demonstrated in pilot studies.[61]

TRAINING

Mechanisms for teaching headache procedures for neurologists in training and in practice are lacking. Although continuing medical education programs are available for neurologists to gain experience with indications, safety, and practice on models through the American Academy of Neurology and the American Headache Society, they do not provide real-world experience, and clinicians in practice may need to seek out training from colleagues in practice. In the long run, educating neurology residents in training may be most effective to help remedy this deficiency.

Although 12% of the US population has migraine[62] and 1% has chronic migraine,[63] headache education among neurology trainees is disproportionately

KEY POINTS

- A steroid should be administered in addition to local anesthetics when greater occipital nerve injections are used for cluster headache (typically methylprednisolone, dexamethasone, or triamcinolone) based on the available evidence and guidelines. However, for migraine, the few studies performing direct comparisons of anesthetics alone versus anesthetics with steroids do not show added benefit.
- Although peripheral nerve blocks may be an excellent treatment option in pregnant women with migraine, ideally lidocaine or ropivacaine should be used as bupivacaine has more unpredictable pharmacokinetics and has been associated with maternal cardiac conduction abnormalities.
- Trigger point injections involve the administration of anesthetics into myofascial structures that may serve as mechanical sites that evoke or perpetuate an underlying headache disorder, most commonly tension-type headache or migraine.
- The evidence for trigger point injections includes randomized controlled trials for tension-type headache and migraine, with the strongest evidence for frequent tension-type headache.

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KEY POINT

- **The sphenopalatine ganglion is a reasonable target for blocks and neuromodulation as it is the key peripheral structure involved in the expression of cranial autonomic symptoms and plays an important role in the trigeminoautonomic reflex in trigeminal autonomic cephalalgias and migraine and in regulation of cerebral blood flow.**

underrepresented in the graduate medical curriculum.[64] In a 2016 survey of neurology residency program directors,[65] formal training in these procedures by programs was uncommon. However, most residency program directors felt that exposure was important, and over half felt that headache procedural competence for their trainees was desired.

Proposed headache fellowship milestones dictate competence in performing these procedures for headache.[66] However, it is unreasonable to expect that only headache specialists should have such expertise given their relative scarcity and poor geographic distribution[67] and the high overall prevalence of headache disorders.

CONCLUSION

Procedures are important aspects of clinical practice for neurologists who manage patients with headache disorders. OnabotulinumtoxinA is an effective and safe preventive treatment for chronic migraine, and peripheral nerve blocks and trigger point injections are effective and safe for the acute and short-term preventive treatment of a variety of headache disorders. Intranasal sphenopalatine ganglion blocks are also feasible to perform in a clinic-based setting. More widespread training mechanisms are needed for neurologists to develop procedural expertise to better serve patients with these highly prevalent and disabling disorders.

USEFUL WEBSITES/RESOURCES

PERIPHERAL NERVE BLOCKS (*HEADACHE* VIRTUAL ISSUE)
This collection of articles published in *Headache* provides a useful evidence summary for peripheral nerve blocks.

headachejournal.onlinelibrary.wiley.com/doi/toc/10.1111/(ISSN)1526-4610.peripheral_nerve_blocks_in_headache_treatment

OCCIPITAL NERVE BLOCK: DR ANDREW BLUMENFELD
This video shows the procedure for administering an occipital nerve block.

youtube.com/watch?v=JGLOaZpZwqU

BOTOX FOR MIGRAINE BY DR ANDREW BLUMENFELD
This video shows the procedure for administering onabotulinumtoxinA injections for chronic migraine.

youtube.com/watch?v=hocClpTS7KU

THE SPHENOPALATINE GANGLION (SPG) AND HEADACHE
This page on the American Migraine Foundation website explains what the sphenopalatine ganglion is and its role in headache disorders; it also explains the role and procedure of sphenopalatine ganglion block.

americanmigrainefoundation.org/resource-library/understanding-migrainethe-sphenopalatine-ganglion-spg-and-headache/

INTERVENTIONAL HEADACHE PROCEDURES
This page on the American Migraine Foundation website explains the three most common interventional procedures to treat patients with migraine and other headache disorders: onabotulinumtoxinA injections, peripheral nerve blocks, and trigger point injections.

americanmigrainefoundation.org/resource-library/interventional-headache-procedures/

SPOTLIGHT ON: INTERVENTIONAL HEADACHE MANAGEMENT
This page on the American Migraine Foundation website describes approaches used for interventional headache management.

americanmigrainefoundation.org/resource-library/understanding-migrainespotlight-on-interventional-headache-management/

CERVICOGENIC HEADACHE
This page on the American Migraine Foundation website explains what cervicogenic headache is and how it is treated.

americanmigrainefoundation.org/resource-library/cervicogenic-headache/

SPHENOPALATINE GANGLION BLOCKS IN HEADACHE DISORDERS
This page on the American Migraine Foundation website describes the roles of the sphenopalatine ganglion and sphenopalatine ganglion block in headache disorders.

americanmigrainefoundation.org/resource-library/sphenopalatine-ganglion-blocks-in-headache-disorders/

OCCIPITAL NEURALGIA
This page on the American Migraine Foundation website provides a guide to occipital neuralgia.

americanmigrainefoundation.org/resource-library/occipital-neuralgia/

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THE BASICS OF TRIGGER POINT INJECTIONS FOR HEADACHE AND MIGRAINE
This page on the American Migraine Foundation website describes trigger points, what trigger point injections are, and who should receive them.

americanmigrainefoundation.org/resource-library/understanding-migrainethe-basics-of-trigger-point-injections-for-headache-and-migraine/

INTERVENTIONAL THERAPY FOR MIGRAINE
This video provides an explanation of and discussion on the use of interventional therapy for migraine.

youtube.com/watch?v=qnAYks-F-gQ

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Spontaneous Intracranial Hypotension

By Shuu-Jiun Wang, MD

ABSTRACT

PURPOSE OF REVIEW: **Spontaneous intracranial hypotension is a disorder caused by spinal CSF leakage. This article reviews the clinical presentation, diagnosis, and treatment of spontaneous intracranial hypotension.**

RECENT FINDINGS: **The hallmark symptom of spontaneous intracranial hypotension is acute orthostatic headache; however, clinical presentations can be heterogeneous. New evidence shows that lumbar puncture is not always necessary or sufficient to establish the diagnosis. Some patients may have normal opening pressure, which suggests that insufficiency of CSF volume (hypovolemia) rather than CSF pressure might be the underlying mechanism. Several neuroimaging modalities can aid in diagnosis and localization of the CSF leakage, including brain MRI, spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Complications, such as subdural hematoma, can lead to a change in the headache pattern and potentially life-threatening consequences. Conservative treatments, such as fluid supplementation, can provide temporary relief; however, epidural blood patches, especially targeted ones, are more effective and definitive. For patients with refractory spontaneous intracranial hypotension, surgical repair of spinal CSF leakages should be considered.**

SUMMARY: **Brain and spinal MRIs are important for the diagnosis and treatment of patients with spontaneous intracranial hypotension. Early treatment with epidural blood patches may be considered to shorten the disease duration and minimize the potential risk of complications.**

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RELATIONSHIP DISCLOSURE:
Dr Wang serves as an associate editor for *Cephalalgia*, *Headache*, and the *Journal of Headache and Pain* and as a consultant to the advisory boards of Daiichi Sankyo Company, Limited; Lilly; and Novartis AG. Dr Wang has received research/grant support from Allergan/AbbVie Inc; the Brain Research Center, National Yang Ming Chiao Tung University from The Featured Areas Research Program within the framework of the Higher Education Sprout Project by the Ministry of Education in Taiwan; Lilly; Novartis AG; Taipei Veterans General Hospital; Taiwan Ministry of Technology and Science; and Taiwan Headache Society.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Wang discusses the unlabeled/investigational use of theophylline for the treatment of postdural puncture headache.

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INTRODUCTION

Spontaneous intracranial hypotension is a disorder related to spinal CSF leakage.[1–3] According to the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*), a diagnosis of spontaneous intracranial hypotension requires the presence of low CSF pressure (<60 mm CSF) and/or evidence of a CSF leak on imaging.[4] However, typical presentations could occur in the absence of decreased CSF pressure, suggesting that inadequate CSF volume (ie, CSF hypovolemia) could be more important than inadequate CSF pressure (ie, CSF hypotension) in the underlying pathophysiology.[5,6] In particular, a 2016 study reported that the CSF pressure was less than 60 mm CSF in only 34% of confirmed cases of spontaneous intracranial hypotension, and a positive correlation seemed to exist between CSF

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pressure and disease duration.[7] Therefore, a CSF pressure of greater than 60 mm CSF in a patient with a prolonged course does not necessarily exclude the possibility of spontaneous intracranial hypotension.

The classic presentation of spontaneous intracranial hypotension is acute orthostatic headache, but the diagnosis can sometimes be challenging as some patients may present with atypical initial presentations, such as cochleovestibular manifestations, cranial nerve palsies, personality changes, or even movement disorders.[1,8] Based on these symptoms, brain imaging (rather than spinal imaging) is usually part of the initial diagnostic workup, which could lead to diagnostic delays, especially when brain CT or noncontrast brain MRI is arranged. Although the diagnostic entity includes the term *spontaneous*, a significant proportion of patients report a history of trivial trauma or strenuous physical activities before the onset. Patients may also develop orthostatic headaches or other symptoms resembling spontaneous intracranial hypotension after spinal anesthesia or diagnostic lumbar punctures. In the presence of such iatrogenic causes, a diagnosis of postdural puncture headache is made according to the *ICHD-3* diagnostic criteria. When the headache associated with CSF leakage occurs after a procedure or trauma, it is termed CSF fistula headache. In such cases, the headache syndrome typically remits after successful management of the CSF fistula.[4]

KEY POINTS

- **Spontaneous intracranial hypotension is a disorder related to spinal CSF leakage. Acute orthostatic headache is the most common clinical presentation, but some patients may present with nonheadache symptoms.**
- **The female to male ratio of spontaneous intracranial hypotension is about 2:1, and it typically occurs in patients in their midthirties to midfifties.**

CLINICAL PRESENTATION AND DEMOGRAPHICS

The most common and important presentation of spontaneous intracranial hypotension is acute orthostatic headaches.[1] Spontaneous intracranial hypotension has a female preponderance, with a female to male ratio of about 2:1, and it typically occurs in patients in their midthirties to midfifties.[9] Patients may have some accompanying nonheadache symptoms. However, some patients may present with a wide variety of predominantly nonheadache symptoms; therefore, a delay in diagnosis may occur, which can range from days to even more than a decade.[10] Misdiagnosis is not uncommon in spontaneous intracranial hypotension but may lead to potentially life-threatening consequences because of complications, such as subdural hematoma, uncal herniation, sinus thrombosis, brainstem ischemia, and Duret hemorrhage.

Headache Symptoms

According to the *International Classification of Headache Disorders, Second Edition* (*ICHD-2*) criteria (2004), the so-called orthostatic headache in patients with spontaneous intracranial hypotension should develop after they assume an upright posture and improve after they lie down.[4,11] However, the temporal relationship between headache and postural changes is somewhat variable. According to an early report, up to 24% of patients lacked a typical orthostatic headache.[12] In addition, in patients who have developed complications such as subdural hematoma or cerebral venous thrombosis, a change in the headache pattern may be seen.[13-15] The postural component of headache can be lost. In some cases, a paradoxical postural headache, in which the headache gets worse in the supine position, may develop.

The headache is usually bilateral, and the location of headaches can be variable. Some patients may have migrainelike features, such as nausea or phonophobia.[16,17] Cochleovestibular manifestations, including hypoacusis, Ménière-like syndrome, tinnitus, and dizziness, are not uncommon.[17-19] In an

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Italian study, nausea (42%), neck stiffness (33%), and hypoacusis (25%) were commonly reported by patients, followed by tinnitus (18%) and photophobia (16%).[12] In comparison, nausea (73%) and vomiting (48%) seem more common in patients in Taiwan.[20] The headache of spontaneous intracranial hypotension can sometimes be triggered or aggravated by Valsalvalike maneuvers and resembles exertional or exercise headache.[21,22]

Of note, although orthostatic headache is the hallmark of spontaneous intracranial hypotension, not all orthostatic headaches are caused by spinal CSF leaks. Occasionally, patients with postural tachycardia syndrome or cervical spine lesions could present with a clinical picture indistinguishable from that of spontaneous intracranial hypotension.[23,24]

Most of the orthostatic headache or other symptoms associated with postural changes may be relieved after adequate treatment. However, some patients may have residual headache only in the afternoon (ie, second-half-of-the-day headache), which could be attributed to slow-flow leaks or residual symptoms in a patient who has been partially treated.[25] Therefore, care should be exercised when obtaining a history from a patient who has been partially treated (CSF leakage sites not completely sealed or the CSF pressure not yet normalized), as the clinical presentation could become atypical.

Nonheadache Symptoms

Nonheadache symptoms have also been reported in patients with spontaneous intracranial hypotension (**TABLE 11-1**[26-37]), and these symptoms may or may not be accompanied by headache.[3] Downward displacement of the brain is common in patients with spontaneous intracranial hypotension and is commonly attributed to decreased CSF volume and buoyancy. This change could lead to traction or compression of cranial nerves or brainstem structures, posterior fossa crowdedness, or traction of cerebral structures. Therefore, abducens nerve palsies,[30] oculomotor nerve or trochlear nerve palsies,[28] parkinsonism,[35] and other movement disorders have been reported. Cochleovestibular manifestations, such as dizziness, tinnitus, and hypoacusis, are frequently reported symptoms and may be caused by changes in perilymph pressure.[18] Also, some patients may present with personality changes or frontotemporal dementia–like symptoms.[33] Some patients may develop altered consciousness or even coma[31]; thus, spontaneous intracranial hypotension should be considered among the differential diagnosis of altered consciousness, particularly in the presence of posterior fossa crowdedness or uncal herniation.

ETIOLOGY AND SUSCEPTIBILITY

Studies have identified some predisposing factors for spontaneous intracranial hypotension, including hypermobility disorders such as dolichostenomelia (disproportionately long limbs), Ehlers-Danlos syndrome, and Marfan syndrome.[38,39] However, most patients do not have obvious stigmata of connective tissue laxity,[39] and genetic studies looking for mutations of connective tissue disorders in spontaneous intracranial hypotension were negative.[40,41] Spinal meningeal diverticulum, presumably associated with focal weakness in the dura, has been believed to be a predisposing factor for CSF leakage.[5,42] However, controversies arise based on recent findings. Spinal meningeal diverticula are uncommon in Taiwanese patients[43]; moreover, the prevalence of spinal meningeal diverticula did not differ between patients with

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spontaneous intracranial hypotension and controls in a North American series.[44] Trivial trauma, which could lead to rupture of the preexisting dural weakness, is reported in a substantial minority of patients before the onset of spontaneous intracranial hypotension. In addition, osteophytes, diskogenic spurs, and other factors have been reported to be associated with spinal CSF leakage and should be considered in patients with spontaneous intracranial hypotension.[45-47] In such cases, surgical intervention to correct the underlying structural abnormality might be necessary in addition to the standard treatment of spontaneous intracranial hypotension. More evidence is needed for genetic factors and local structural variations to prove their roles in predisposition to the development of spontaneous intracranial hypotension.

DIAGNOSTIC INVESTIGATIONS

According to the *ICHD-3* criteria, spontaneous intracranial hypotension falls under the classification of headaches attributed to low CSF pressure (TABLE 11-2). In the *ICHD-2* criteria, spontaneous intracranial hypotension was defined as a

Clinical Manifestations of Spontaneous Intracranial Hypotension

TABLE 11-1

Headache and symptoms associated with headaches

- **Orthostatic headache**
- **Headache usually accompanied by**
  - Nausea
  - Vomiting
  - Hypoacusis
  - Neck stiffness or pain
  - Photophobia
  - Tinnitus
- **Migrainelike headache**[16]
- **Thunderclap headache**[26]
- **Headache mimicking benign exertional headache**[21]
- **Headache mimicking new daily persistent headache**[27]

Nonheadache symptoms

- **Diplopia due to oculomotor nerve palsy**[28] **and/or trochlear nerve palsy**[29]
- **Bilateral abducens nerve palsy**[30]
- **Ménière disease–like manifestations**[18]
- **Changes in consciousness or coma**[31]
- **Unsteady gait**[32]
- **Personality change, apathy, or frontotemporal dementia–like presentations**[33,34]
- **Movement disorders**
  - Parkinsonism[35]
  - Chorea[36]
- **Bibrachial amyotrophy, motor neuron disease–like presentations**[37]

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diffuse and/or dull headache that worsens within 15 minutes after sitting or standing, accompanied by at least one of the following associated symptoms: neck stiffness, tinnitus, hypoacusis, photophobia, or nausea. In addition, objective evidence should be derived from one of the following: typical brain MRI findings, radiologic evidence of CSF leakage, or CSF pressure less than 60 mm CSF.[11] In the *ICHD-3* criteria (TABLE 11-3), the diagnosis of spontaneous intracranial hypotension requires the presence of a headache that has developed in temporal relation to the low CSF pressure (<60 mm CSF) and/or evidence of CSF leakage on imaging. Also, a diagnosis of spontaneous intracranial hypotension requires the absence of a procedure or trauma known to cause CSF leakage. As mentioned above, the clinical presentation of spontaneous intracranial hypotension can be atypical.[21,22,25] Therefore, headache features and associated symptoms are no longer included in the *ICHD-3* criteria.[4] However, the *ICHD-2* criteria are, in fact, more informative, as the criteria give some clinical clues to remind clinicians how typical cases present. In both the *ICHD-2* and *ICHD-3* criteria, lumbar puncture is not mandatory, particularly in the presence of radiologic evidence of spinal CSF leakage.

Based on neuroimaging and intraoperative findings, Schievink and colleagues[9] proposed a classification system for spinal CSF leaks (FIGURE 11-1). Aside from dural tear (type 1) and meningeal diverticulum (type 2), CSF-venous fistula (type 3) is a newly proposed type of CSF leak. CSF-venous fistula is a direct communication between the spinal subarachnoid space and epidural venous plexus; hence, the extravasated CSF will be directly shunted into the venous circulation. Currently, the identification of CSF-venous fistulas requires dynamic CT myelography or digital subtraction myelography; spinal MRI is not capable of identifying them. Patients with more than one etiology or those who do not fit into types 1 through 3 are classified as having an indeterminate/unknown (type 4) CSF leak.[9,48]

TABLE 11-2 ***ICHD-3* Diagnostic Criteria for Headache Attributed to Low CSF Pressure**[a]

Headache attributed to low CSF pressure

A Any headache[b] fulfilling criterion C

B Either or both of the following:

- **1** Low CSF pressure (<60 mm CSF)
- **2** Evidence of CSF leakage on imaging[c]

C Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or led to its discovery[d]

D Not better accounted for by another *ICHD-3* diagnosis

CSF = cerebrospinal fluid; *ICHD-3 = International Classification of Headache Disorders, Third Edition.*

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[b] Headache attributed to low CSF is usually but not invariably orthostatic. Headache that significantly worsens soon after sitting upright or standing and/or improves after lying horizontally is likely to be caused by low CSF pressure, but this cannot be relied upon as a diagnostic criterion.

[c] Brain imaging showing brain sagging or pachymeningeal enhancement, or spine imaging (spine MRI, or MRI, CT or digital subtraction myelography) showing extradural CSF.

[d] Evidence of causation may depend upon onset in temporal relation to the presumed cause, together with exclusion of other diagnoses.

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Lumbar Puncture

Demonstration of low CSF pressure (<60 mm CSF) through lumbar puncture is part of the diagnostic criteria. However, lumbar puncture may not be necessary for all patients with suspected spontaneous intracranial hypotension, as CSF hypotension (ie, <60 mm CSF by the criteria) may not necessarily be present. An earlier study showed that 83% of patients with spontaneous intracranial hypotension had low or unmeasurable CSF pressures (n = 40).[49] However, in a 2013 study (n = 106), only 34% of confirmed spontaneous intracranial hypotension cases had CSF pressure less than or equal to 60 mm CSF, and 21% of patients even had CSF pressure greater than 120 mm CSF.[44] The discrepancies may be because of increasing recognition of this disease entity and growing understanding of neuroimaging findings, which lead to increasing diagnostic rates; hence, patients with atypical symptoms or minimal spinal CSF leaks can be diagnosed and incorporated into the analysis. Because the demonstration of nondecreased CSF pressure does not rule out the diagnosis of spontaneous intracranial hypotension and because lumbar puncture can be technically challenging in the presence of shrunken dura (which is common in spontaneous intracranial hypotension) and introduces additional dural defects that could potentially exacerbate CSF leakage, the diagnostic value of lumbar puncture becomes questionable, especially when evidence of spinal CSF leakage is demonstrated by brain or spinal neuroimaging studies.

Brain MRI Findings

As orthostatic headache is the most characteristic symptom of spontaneous intracranial hypotension, brain imaging is commonly part of the initial diagnostic workup. Brain CT is often nondiagnostic, as is noncontrast brain MRI; therefore, precontrast and postcontrast brain MRI should be arranged when spontaneous intracranial hypotension is clinically suspected. A variety of brain MRI findings have been described, with different diagnostic utilities and corresponding underlying mechanisms (**CASE 11-1**). Generally, they can be grouped into cerebral venous-related and brain descent–related signs (**TABLE 11-4**).[50]

TABLE 11-3

ICHD-3 Diagnostic Criteria for Headache Attributed to Spontaneous Intracranial Hypotension[a]

Headache attributed to spontaneous intracranial hypotension

A Headache fulfilling criteria for headache attributed to low CSF pressure, and criterion C below

B Absence of a procedure or trauma known to be able to cause CSF leakage[b]

C Headache has developed in temporal relation to occurrence of low CSF pressure or CSF leakage, or has led to its discovery[c]

D Not better accounted for by another *ICHD-3* diagnosis

CSF = cerebrospinal fluid; *ICHD-3 = International Classification of Headache Disorders, Third Edition*.

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[b] Headache attributed to spontaneous intracranial hypotension cannot be diagnosed in a patient who has had a dural puncture within the prior month.

[c] Dural puncture to measure CSF pressure directly is not necessary in patients with positive MRI signs of leakage such as dural enhancement with contrast.

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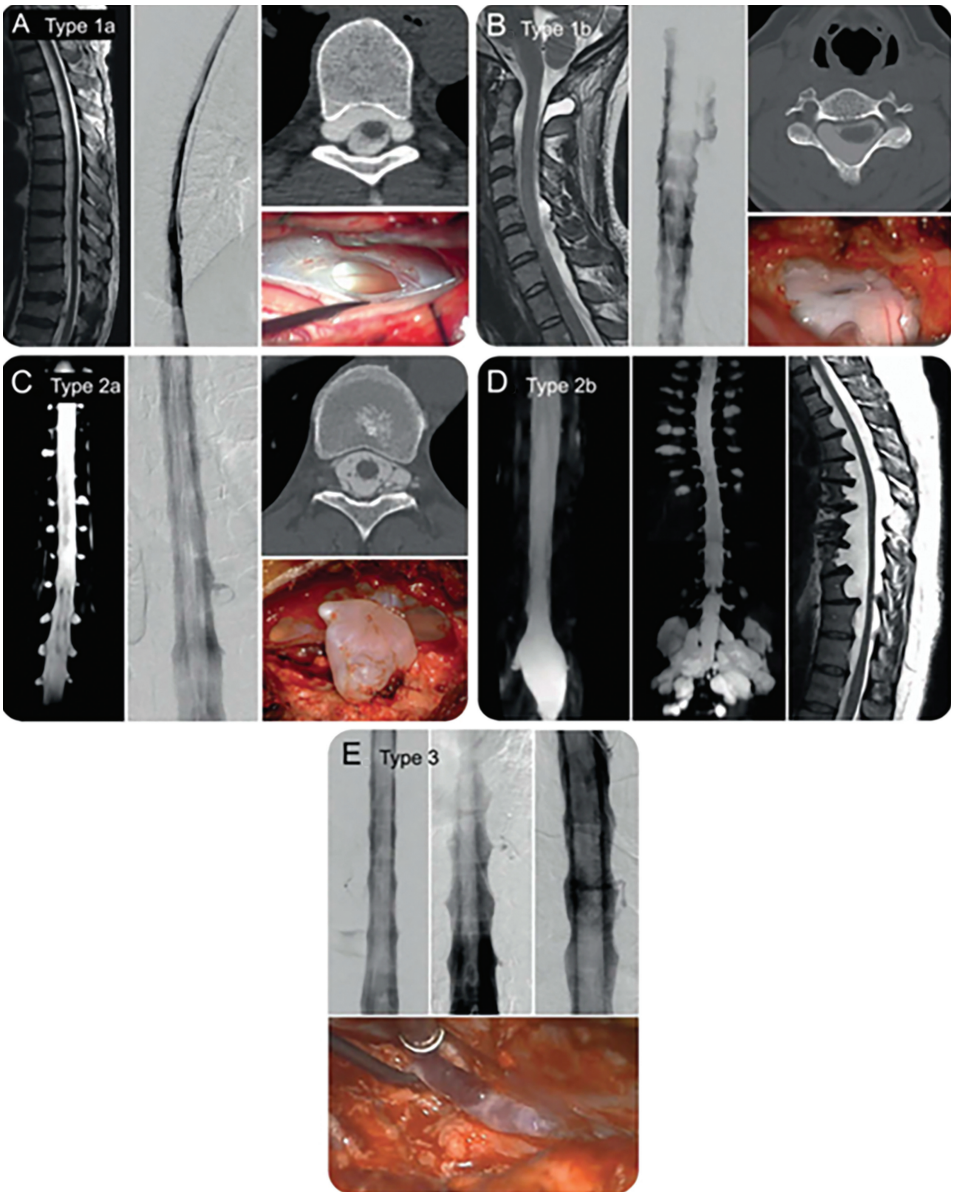

FIGURE 11-1

Classification of spontaneous spinal CSF leaks. *A*, Type 1a CSF leak: Sagittal T2-weighted MRI shows an extensive ventral fluid collection throughout the thoracic spine (*left panel*). Digital subtraction myelography (DSM) shows a ventral CSF leak at the T10-T11 level (*middle panel*). Post-DSM CT shows a ventral CSF collection (*right upper panel*). Intraoperative photograph shows a ventral dural tear measuring 6 mm (*right lower panel*). *B*, Type 1b CSF leak: Sagittal T2-weighted MRI shows an extensive dorsal fluid collection from C1-C2 to T1-T2 (*left panel*). DSM shows a posterolateral CSF leak at the C5-C6 level (*middle panel*). Post-DSM CT shows a posterolateral CSF collection (*right upper panel*). Intraoperative photograph shows a posterolateral dural tear measuring 2 mm (*right lower panel*). *C*, Type 2a CSF leak: Three-dimensional magnetic resonance (MR) myelogram shows several simple thoracic meningeal diverticula (*left panel*). DSM shows a CSF leak at the T11-T12 level outlining the meningeal diverticulum (*middle panel*). Post-DSM CT shows the meningeal diverticulum associated with extradural contrast (*right upper panel*). Intraoperative photograph shows the thin-walled meningeal diverticulum (*right lower panel*). *D*, Type 2b CSF leak: Three-dimensional MR myelograms show lumbosacral dural ectasia (*left panel*) and complex sacral cysts and multiple proximal and distal thoracic meningeal diverticula (*middle panel*). Sagittal T2-weighted MRI shows extensive thoracic dural ectasia (*right panel*). *E*, Type 3 CSF leak: DSMs show thoracic CSF-venous fistulas (*upper panels*). Intraoperative photograph shows a single venous channel draining CSF from the lateral common thecal sac (*lower panel*).

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CEREBRAL VENOUS-RELATED SIGNS. According to the Monro-Kellie doctrine, the sum of the volumes of brain tissue, vessels, and CSF is constant. The decrement of CSF volume during CSF leakage is compensated by the vascular structures because the brain tissue is presumably constant. Since the venous walls are more elastic than the walls of the arteries, intracranial venous structures can be dilated to a greater extent than the arteries.[51] Contrary to prior belief, a study by this author's group showed that brain tissue volume did not remain constant during CSF leakage but, indeed, slightly decreased (0.85%).[52]

The cerebral venous-related signs of spontaneous intracranial hypotension include diffuse pachymeningeal enhancement, the venous distension sign, and pituitary hyperemia (or pituitary enlargement). Diffuse pachymeningeal enhancement is the most well-recognized finding on postcontrast brain MRI and results from pachymeningeal venous dilation and increased contrast transit time (**FIGURE 11-2**). However, a number of other conditions can also present with pachymeningeal enhancement, such as pachymeningitis in granulomatous diseases, breast cancer metastasis, prostate cancer metastasis, secondary central nervous system lymphoma, and meningiomas.[53] Diffuse pachymeningeal enhancement in spontaneous intracranial hypotension is typically a homogeneous thickening of the dura, whereas pachymeningeal enhancement in the other conditions can be localized or heterogeneous. It is worth noting that diffuse pachymeningeal enhancement can be absent in a proportion of patients, especially when the timing of brain MRI is suboptimal.[54] In a study comparing patients with spontaneous intracranial hypotension with and without diffuse pachymeningeal enhancement, it was found that patients without diffuse pachymeningeal enhancement had shorter symptom duration (6.5 ± 4.4 days compared to 20.4 ± 16.3 days, $P<.001$).[55] However, another study concluded that patients without diffuse pachymeningeal enhancement had longer symptom duration (45.3 ± 59.0 weeks compared to 15.1 ± 33.0 weeks, $P=.002$).[56] The results of these two studies are not contradictory because the time scales are different. Taken together, diffuse pachymeningeal enhancement is present within a particular time window, and the absence of diffuse pachymeningeal enhancement does not exclude spontaneous intracranial hypotension from the differential diagnosis, especially when the postcontrast brain MRI is obtained too early (ie, <1 week) or too late (ie, >45 weeks).

The venous distension sign of the dominant transverse sinus (a convex rather than concave shape) has both high sensitivity and high specificity for spontaneous intracranial hypotension.[57] Pituitary gland hyperemia or enlargement is also commonly noted and could be misinterpreted as pituitary adenoma or tumor (**FIGURE 11-2**).[2] The diagnostic value of pituitary gland enlargement or hyperemia was challenged in a 2019 report.[58] In addition to alterations in the intracranial venous system, the size of superior ophthalmic veins may also serve as a useful guide in patients with spontaneous intracranial hypotension. A positive correlation is seen between the size of superior ophthalmic veins and intracranial pressure, and patients with spontaneous intracranial hypotension typically showed collapsed superior ophthalmic veins, the size of which recovered after treatment.[59,60]

BRAIN DESCENT–RELATED SIGNS. Downward displacement of brain structures is common in patients with spontaneous intracranial hypotension because of CSF leakage. Signs include closure of the midbrain-pons angle,[20] narrowing of the angle between the vein of Galen and the straight sinus,[61] flattening of the pons,[62]

KEY POINTS

- Diagnostic investigations for spontaneous intracranial hypotension include postcontrast brain MRI and spinal neuroimaging, such as spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Lumbar puncture is not always necessary or sufficient for diagnosis.
- Spinal CSF leaks can be classified as dural tear, meningeal diverticulum, or CSF-venous fistula. CSF-venous fistula is a direct communication between the spinal subarachnoid space and epidural venous plexus. The identification of CSF-venous fistulas requires dynamic CT myelography or digital subtraction myelography; spinal MRI is not capable of identifying them.
- Normal CSF pressure (>60 mm CSF) does not exclude the diagnosis of spontaneous intracranial hypotension. Insufficiency of intracranial CSF volume (ie, hypovolemia) may be more important in the pathophysiology of spontaneous intracranial hypotension.
- Brain neuroimaging findings in patients with spontaneous intracranial hypotension include cerebral venous-related signs and brain descent–related signs.

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tonsillar descent, and posterior fossa crowdedness.[1] These brain MRI signs reflect the downward displacement of brain structures at different levels or brain structural deformities. The measurements of brain descent–related signs, including the midbrain-pons angle,[20] mamillopontine distance, height of the suprasellar cistern, diameter of the prepontine cistern, angle between the vein of Galen and the straight sinus, and venous hinge, could reflect the severity of brain sagging or deformity (CASE 11-2).[58] Among these signs, closure of the midbrain-pons angle is associated with poorer response rates to the first epidural blood patch.[20] These neuroimaging findings are helpful not only for diagnosis but also for prediction of treatment response.

Spinal Imaging Findings

Decreased intracranial CSF pressure or volume, or both, is the consequence of spinal CSF leakage; therefore, localization of spinal CSF leaks provides diagnostic clues and a therapeutic guide.

CASE 11-1

A 30-year-old man presented to a headache clinic with a severe headache that developed after playing basketball and had persisted for about 1 month. The pain was located at the bilateral temple and occipital regions; was throbbing in quality; and was accompanied by phonophobia, photophobia, and vomiting. The patient rated it 10 out of 10 on the numeric rating scale. His headache worsened immediately after standing up and improved within 5 minutes after lying down. He was a surgeon and could not perform surgery because the headache was unbearable after standing for a while. He had no past history of primary headache disorders, such as migraine.

Neurologic examination did not show any abnormal findings. Postcontrast brain MRI showed diffuse pachymeningeal enhancement, pituitary hyperemia, and flattening of the pons (FIGURE 11-2). Spinal MRI disclosed spinal CSF leaks at the T2-T3 level. The patient received analgesics and hydration with normal saline 3000 mL/d for 3 days, but the headache persisted. A targeted epidural blood patch with 21 mL autologous blood was performed at the T2-T3 level, and the orthostatic headache partially improved. Another targeted epidural blood patch with 21 mL autologous blood was done 3 days later. However, the patient's orthostatic headache changed paradoxically to worsening while lying down and improving with sitting up after the second epidural blood patch. He received acetazolamide 250 mg 2 times a day, and his headache totally subsided 3 days later.

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SPINAL CT FINDINGS. CT myelography has been considered the gold standard in the localization of spinal CSF leaks. This imaging procedure involves the injection of iodinated contrast material into the thecal sac, followed by whole-spine axial CT. The distribution of CSF is visualized, and CSF extravasation can be localized.[2,63] In addition, CSF pressure can be directly measured. However, localization of high-flow (or fast-flow) CSF leaks may be challenging, as the contrast medium may spread throughout the epidural space quickly before acquisition of the CT myelogram.[63] One solution is the use of ultrafast dynamic CT myelography, which involves serial acquisition of the images immediately after the intrathecal injection of the contrast medium.[64,65] However, it is not clear whether spinal CSF leaks visualized on CT myelography colocalize with dural defects. According to a study comparing intraoperative findings with CT myelography, only a minority of patients had active CSF leakage at the locations of CSF leaks identified on CT myelography.[66] Whether these "spinal CSF leaks" could

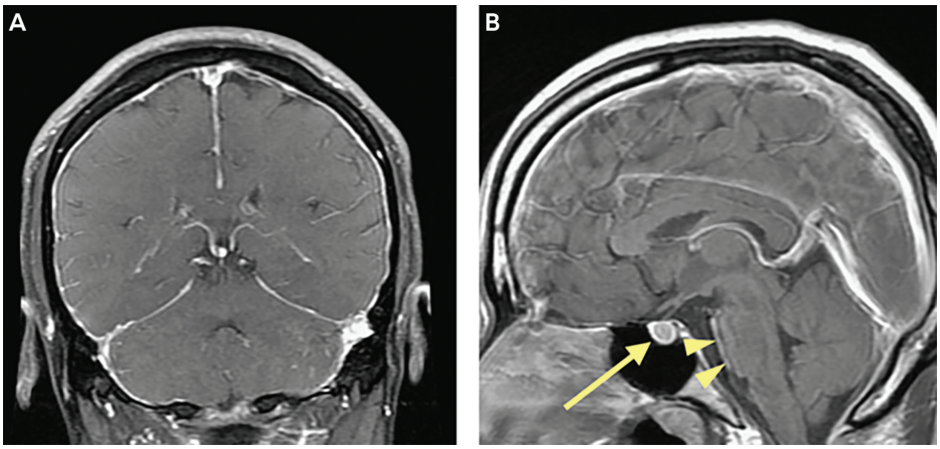

FIGURE 11-2
Imaging of the patient in CASE 11-1. *A*, Coronal postcontrast T1-weighted image shows diffuse pachymeningeal enhancement. *B*, Sagittal postcontrast T1-weighted image shows pituitary hyperemia (*arrow*) and flattening of the pons (*arrowheads*). These brain MRI signs are typical for spontaneous intracranial hypotension.

COMMENT

This patient's headache had features of migraine, including throbbing, photophobia, phonophobia, and vomiting. However, the acute orthostatic feature of his headache was a red flag for spontaneous intracranial hypotension. His brain MRI showed several typical features of spontaneous intracranial hypotension, including diffuse pachymeningeal enhancement, pituitary hyperemia, and flattening of the pons. This patient received two epidural blood patches and developed features of transient intracranial hypertension after the second. This phenomenon is called *rebound intracranial hypertension* and is one of the complications of epidural blood patch. Rebound intracranial hypertension is reversible; acetazolamide is helpful in patients with severe or intractable symptoms.

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represent the final common pathways of CSF drainage rather than the active process of CSF leakage awaits further clarification. Weaknesses of CT myelography include its invasiveness and radiation exposure. The lumbar puncture required for intrathecal contrast administration could potentially exacerbate CSF leakage. More important, the amount of radiation exposure is considerable, especially for ultrafast dynamic CT myelography.[64]

SPINAL MRI FINDINGS. Spinal MRI can also be used for the diagnosis of spontaneous intracranial hypotension.[63] Conventional T2-weighted spinal MRI can reveal only indirect signs of spinal CSF leaks, such as epidural CSF collection, distention of epidural veins, and collapsed dura.[67,68] As spinal CSF leaks cannot be visualized directly, its clinical utility is limited.

Heavily T2-weighted magnetic resonance myelography is an imaging technique that can be used to visualize spinal CSF leaks; it was demonstrated to be comparable to the gold standard CT myelography.[43,69,70] It is a noninvasive imaging technique and does not require IV or intrathecal contrast administration. Spinal CSF leakages seen on heavily T2-weighted magnetic resonance myelography can be divided into three types: high-cervical retrospinal CSF collections, epidural CSF collections, and periradicular leaks (**FIGURE 11-4**).[43,70] High-cervical retrospinal CSF collection is a well-known false localizing sign, and its presence does not indicate the location of dural tears.[71] After leakage from the dural tears, the extravasated CSF is distributed in the epidural space (ie, epidural collection) in the direction of gravity and is subsequently drained out of the spinal canal via the neuroforamina (ie, periradicular leaks). As demonstrated

TABLE 11-4 Brain MRI Signs of Spontaneous Intracranial Hypotension

Cerebral venous-related signs

- Diffuse pachymeningeal enhancement
- Venous distension sign
- Pituitary hyperemia (or pituitary enlargement)

Brain descent–related signs

- Closure of the midbrain-pons angle
- Narrowing of the angle between the vein of Galen and straight sinus
- Flattening of the pons
- Tonsillar descent
- Posterior fossa crowdedness

Measurements for brain descent

- Midbrain-pons angle
- Mamillopontine distance
- Height of suprasellar cistern
- Diameter of the prepontine cistern
- The angle between the vein of Galen and straight sinus
- Venous hinge

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CASE 11-2

A 52-year-old man presented with pulsatile headache and drowsiness after 2 weeks of a weight-lifting program. The pulsatile headache was located at the bilateral temples and accompanied by photophobia, and the intensity was 8 to 9 out of 10. He also reported that he had been sleepy and lacked motivation over the previous 2 weeks. An initial brain MRI showed closure of the midbrain-pons angle (0 degrees), narrowing of the angle between the vein of Galen and the straight sinus, flattening of the pons, and posterior fossa crowdedness (FIGURE 11-3A). Magnetic resonance myelography showed periradicular leaks at C7-T1 and T1-T2, suggestive of the CSF leakage sites. After three targeted epidural blood patches, the patient finally recovered, and follow-up brain MRI showed widening of the midbrain-pons angle compared to the initial brain MRI (FIGURE 11-3B).

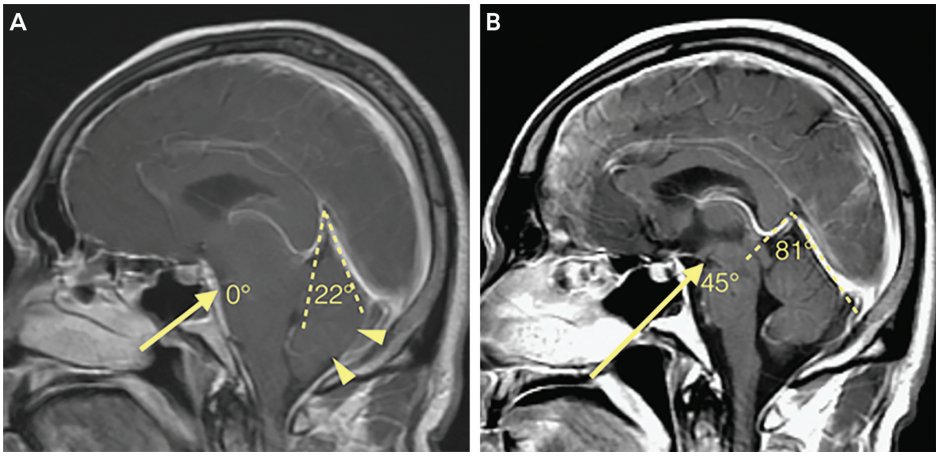

FIGURE 11-3
Imaging of the patient in CASE 11-2. *A*, Initial sagittal postcontrast T1-weighted image shows closure of the midbrain-pons angle (0 degrees, *arrow*), narrowing of the angle between the vein of Galen and the straight sinus (22 degrees), flattening of the pons, and posterior fossa crowdedness (*arrowheads*). *B*, Sagittal postcontrast T1-weighted image after recovery shows widening of the midbrain-pons angle (45 degrees, *arrow*) and the angle between the vein of Galen and the straight sinus (81 degrees) compared to the initial MRI. Also, the flattening of the pons and posterior fossa crowdedness have subsided.

COMMENT

Patients with spontaneous intracranial hypotension can present with nonheadache symptoms, including cognitive changes. Closure of the midbrain-pons angle, narrowing of the angle between the vein of Galen and the straight sinus, flattening of the pons, and posterior fossa crowdedness are brain descent-related signs of spontaneous intracranial hypotension. The symptoms of patients with closure of the midbrain-pons angle are more refractory to treatment, and these patients usually need more than one epidural blood patch.

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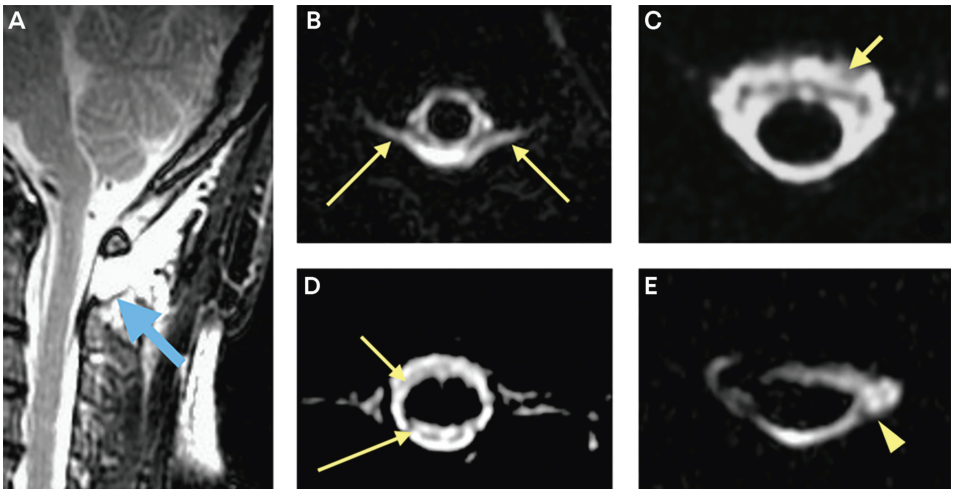

FIGURE 11-4

Spinal imaging signs of spontaneous intracranial hypotension. Spinal CSF leakage on heavily T2-weighted magnetic resonance myelography includes three different presentations: high cervical retrospinal CSF collection (*A, arrow*), periradicular leak (*B, arrows*), and epidural CSF collection (*C, D, arrows*). The length of the epidural collection could have prognostic value, and patients with extensive anterior (or ventral) epidural CSF collections (*C*) may require more than one epidural blood patching.[20] Some patients may have a spinal meningeal diverticulum (*E, arrowhead*).

in patients receiving lumbar puncture, about two-thirds of periradicular leaks are within three vertebral segments of the dural defect, presumably at the puncture sites (ie, L2-L3 level),[69] which makes them reasonable targets for an epidural blood patch since the injected blood can spread to the nearby segments.[72] The distribution of epidural CSF collection is much wider, based on which the exact location of dural tears cannot be ascertained.[69] However, the length of the epidural collection has prognostic value, and patients with extensive anterior (or ventral) epidural CSF collection may require more than one epidural blood patch.[20]

Intrathecal gadolinium-enhanced magnetic resonance cisternography (myelography) is gaining interest for the detection of spinal CSF leaks. It involves intrathecal administration of gadolinium followed by T1-weighted spinal MRI. The method was demonstrated to have superior detection rates for spinal CSF leaks as compared to CT myelography and is therefore increasingly being used in the diagnosis of spontaneous intracranial hypotension.[73] However, a number of issues remain. The gadolinium contrast medium has not been approved for intrathecal use. More important, as with other invasive neuroimaging techniques, lumbar puncture is necessary for intrathecal contrast administration and may introduce additional dural defects. It may not be easy to tell whether the detected gadolinium leakage results from the spontaneous intracranial hypotension itself or from the lumbar puncture meant for contrast administration, especially when the localized CSF leaks are in the vicinity of the upper lumbar regions. In fact, a study by this author's group showed post–lumbar puncture CSF leakages were not restricted to puncture levels and may spread to nearby, or even remote, levels.[69]

DIGITAL SUBTRACTION MYELOGRAPHY. Digital subtraction myelography is a powerful tool to detect the location of spinal CSF leaks. This procedure requires a

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fluoroscopic-guided lumbar puncture and intrathecal injection of a contrast medium.[74] After the intrathecal injection, the procedure table is tilted head down so that extravasation of the contrast medium through the dural defects can be visualized in real time. The major advantage of digital subtraction myelography is the detection of high-flow (or fast-flow) CSF leaks. However, digital subtraction myelography requires the patient's cooperation and is relatively invasive.

RADIONUCLIDE CISTERNOGRAPHY. Radionuclide cisternography has been commonly used in the detection of spinal CSF leakages, although it is no longer suggested by the *ICHD-3*.[4] It requires intrathecal injection of an iodinated tracer (indium 111 diethylenetriamine pentaacetic acid [^{111}InDTPA]), followed by sequential scanning immediately and at 1, 2, 4, and 24 hours and sometimes 48 hours.[75] The findings of radionuclide cisternography can be divided into direct and indirect evidence of spinal CSF leaks. Direct evidence is increasing radioactivity at parathecal regions near the leakage sites. Indirect evidence includes paucity of activity over the cerebral convexities and the radioactivity usually not extending beyond the basal cisterns.[75] Early radioactivity at the kidney and bladder is also indirect evidence, but this finding may be confounded by systemic reuptakes of leaked iodinated tracer from the lumbar puncture site.[75] The major disadvantage of radionuclide cisternography is the suboptimal spatial and temporal resolution; an advantage is the longer duration of sequential scanning, which may be helpful in individuals with extremely slow-flow CSF leaks.[63]

COMPLICATIONS

The most common complication of spontaneous intracranial hypotension is subdural hematoma. According to recent studies, subdural hematoma can be demonstrated in about 20% to 25% of patients with spontaneous intracranial hypotension who underwent their first brain imaging study after symptom onset.[13,20] Patients with subdural hematoma may have neurologic deficits or worsening headaches, and a large subdural hematoma may cause herniation and even mortality.[13] In patients with spontaneous intracranial hypotension with subdural hematoma, surgical intervention (ie, a burr hole) should be considered when the thickness of the subdural hematoma is greater than or equal to 10 mm or they show cognitive deterioration, and the CSF leakage should be adequately treated simultaneously with either epidural blood patches or surgical repair.[15]

Other complications include cerebral venous thrombosis, bibrachial amyotrophy, and superficial siderosis.[1] Cerebral venous thrombosis has been reported and is an uncommon complication of spontaneous intracranial hypotension.[76,77] The underlying mechanism behind cerebral venous thrombosis in spontaneous intracranial hypotension can be explained by the Virchow triad.[76] Following the Monro-Kellie doctrine, cerebral venous dilation occurs during spinal CSF leaks, resulting in slowing cerebral venous flow velocity, which causes a hypercoagulable state and venous thrombosis.[14] Bibrachial amyotrophy is a rare complication, and the underlying mechanism is compression from the ventral extradural CSF collection.[37,78] Superficial siderosis is a remote but rare complication of spontaneous intracranial hypotension, but the underlying mechanism linking spinal CSF leaks and repetitive subarachnoid hemorrhage remains unknown.[1,79] In some situations, the spinal dural defects caused by the spinal cord herniation may be the bleeding points, and this bleeding from dural lacerations may be the reason for the superficial siderosis.[80] In addition, brain

KEY POINTS

- The Monro-Kellie doctrine states that the sum of the volumes of brain tissue, vessels, and CSF within the skull is constant. The decrement of CSF volume during CSF leakage is compensated by the dilation of intracranial venous structures. Cerebral venous-related signs of spontaneous intracranial hypotension include diffuse pachymeningeal enhancement, the venous distension sign, and pituitary hyperemia (or pituitary enlargement).
- Brain descent–related signs reflect the downward displacement of brain structures or brain structural deformities in patients with spontaneous intracranial hypotension. Among these signs, closure of the midbrain-pons angle is associated with a poorer response to the first epidural blood patch. These neuroimaging findings are helpful not only for diagnosis but also for prediction of treatment response.
- Localization of spinal CSF leaks by spinal neuroimaging can provide clues for diagnosis and guide therapeutic interventions.
- Heavily T2-weighted magnetic resonance myelography can be used to visualize spinal CSF leaks; it was demonstrated to be comparable to the gold standard CT myelography. It is a noninvasive imaging technique and does not require IV or intrathecal contrast administration.

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sagging following spinal CSF leaks may cause traction of the cerebellar veins and then subarachnoid hemorrhage, which may, in part, explain the reason for the superficial siderosis.[81]

TREATMENT

The treatment of spontaneous intracranial hypotension includes conservative observation, medications, epidural blood patch, or surgical repair.[1] Because of limited clinical studies, no consensus currently exists on how to treat these patients. FIGURE 11-5 provides an algorithm of treatment strategies.

Conservative Treatments

Conservative treatment strategies include strict bed rest, adequate hydration, analgesics, and abdominal binders. One study analyzed eight patients with spontaneous intracranial hypotension who received conservative treatment, including absolute bed rest and IV hydration.[82] The study showed that only three out of eight patients totally recovered immediately after conservative treatments; two patients completely recovered after 6 to 8 months, and the three remaining patients had persistent mild headaches. Currently, no controlled studies have investigated the efficacy of conservative treatments. Considering the devastating complications (eg, subdural hematoma) and disabling symptoms of spontaneous intracranial hypotension, epidural blood patch or even surgical repair should be considered when patients do not improve after conservative strategies. In the author's practice, targeted epidural blood patch is usually performed as early as possible even without conservative treatments.

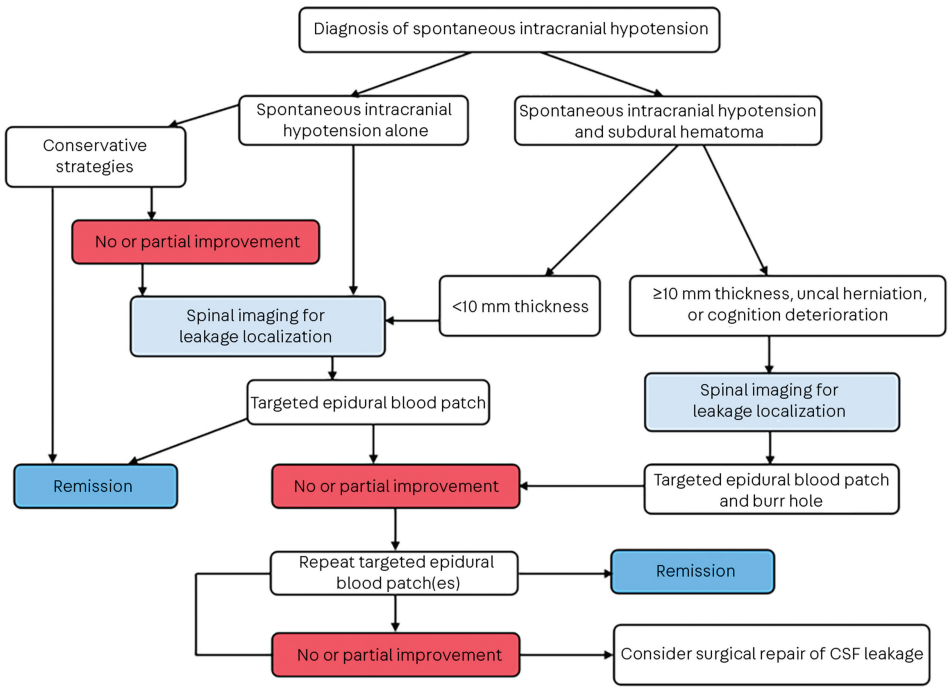

FIGURE 11-5
Algorithm of treatment strategies of patients with spontaneous intracranial hypotension.

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Medications

The options for pharmacologic treatment include analgesics, caffeine, theophylline, and corticosteroids.[1] In animal models, caffeine can increase CSF production; thus, it may be helpful in CSF hypovolemia.[83] A double-blind placebo-controlled trial showed that caffeine could reduce headache severity in postdural puncture headache, but the effect was transient, and patients still needed epidural blood patch.[84,85] Theophylline may be another option. A randomized controlled trial in postdural puncture headache showed patients receiving 250 mg IV aminophylline had lower headache intensity 8 hours after the treatment compared with the placebo group.[86] In addition, some studies reported that greater occipital nerve block could improve postdural puncture headache.[87-89] To date, only case reports have shown the effectiveness of corticosteroids; however, one controlled study did not show any therapeutic benefit of corticosteroids in postdural puncture headache.[90,91]

Epidural Blood Patch

Currently, epidural blood patch is the treatment of choice for spontaneous intracranial hypotension. The underlying mechanism of epidural blood patch includes the early effect of direct compression of the dural sac and occupying of the epidural space by injected blood and the late effect of fibrosis and healing of the dural tears.[1] Patients usually improve immediately or within 1 day after the procedure whether or not the epidural blood patch is delivered in the vicinity of the dural tear. However, further observation is needed to ensure that the CSF leaks are adequately treated; repeat epidural blood patch is sometimes necessary for those with incomplete response. The epidural blood patch can be performed by an experienced anesthesiologist with or without the guidance of fluoroscopy or CT scan. Protocols are variable, with different injection techniques, blood amounts, and duration of bed rest after the treatment; therefore, the success rate after epidural blood patches is also variable.[1]

Epidural blood patches can be divided into blinded (lumbar) epidural blood patches and targeted epidural blood patches. The injection site of a blinded epidural blood patch is always at the lumbar level. After the injection, the Trendelenburg position is suggested by some experts to facilitate the spread of the injected blood to the thoracic and higher levels.[92] Targeted epidural blood patch involves delivery of blood to the leakage sites; hence, localization of spinal CSF leaks through adequate spinal neuroimaging is mandatory, which may require an experienced neuroradiologist.[93] Cho and colleagues[94] showed that the success rate of targeted epidural blood patch is higher than that of blinded lumbar epidural blood patch. Wu and colleagues[20] found that a larger amount of injected blood (≥22.5 mL) predicted a better response to the first epidural blood patch. Moreover, some neuroimaging findings, such as the length of ventral epidural CSF collections and a narrower midbrain-pons angle (<40 degrees), could also predict responsiveness. The possible side effects of epidural blood patch include rebound intracranial hypertension and radicular pain at the dermatome of injection; these conditions are usually transient and reversible.[1] Other rare side effects of epidural blood patch include arachnoiditis, transient bilateral paraplegia, and cauda equina syndrome.[95]

Considering the inefficacy of conservative treatment and the high rate of complications in patients with spontaneous intracranial hypotension, epidural blood patch (especially targeted epidural blood patch) is suggested to be used as early as possible.

KEY POINTS

- **Subdural hematoma is the most common complication of spontaneous intracranial hypotension, especially in patients who develop a change in their headache pattern.**
- **Purely conservative treatments for spontaneous intracranial hypotension (eg, fluid supplementation) are usually temporizing measures, and definitive treatment (eg, targeted epidural blood patches) is more effective. For patients with refractory spontaneous intracranial hypotension, surgical repair of the spinal leaks should be considered.**

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Surgical Repair

Surgical approaches usually include partial or bilateral laminectomy, and the extent of bone removal depends on the presurgical spinal neuroimaging findings.[96] If the spinal CSF leak is extensive, laminectomy should be performed at more than one spinal level. Since the surgical approach is more invasive, surgery should be reserved for spontaneous intracranial hypotension refractory to at least three epidural blood patches or other less invasive treatment options. The dural tear or hole can be directly repaired by suture with or without fibrin glue coverage[2]; however, anaphylaxis to fibrin glue may occur. Leaking meningeal diverticula are usually ligated by suture or buttressed with muscle or absorbable gelatin compressed sponge. In some situations, a metal aneurysm clamp can be used for ligation.[66]

CONCLUSION

Spontaneous intracranial hypotension can be easily diagnosed based on acute orthostatic headache; however, it can also present atypically. Typical brain MRI studies are diagnostic for patients even without a lumbar puncture. Recent advances include spinal neuroimaging studies to localize leakage sites. Early use of targeted epidural blood patch may be warranted since conservative treatment in patients with spontaneous intracranial hypotension usually results in a prolonged disabling state. For patients with refractory spontaneous intracranial hypotension, surgical repair of the CSF leakage may be considered.

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False Claims Act Overview and Implications for Neurologists

By Rachel V. Rose, JD, MBA; Joseph S. Kass, MD, JD, FAAN

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

The US Department of Health and Human Services Office of the Inspector General identifies the five most important federal fraud and abuse laws that are most applicable to physicians: the False Claims Act, the Anti-Kickback Statute, the Physician Self-Referral Law (Stark Law), the Exclusion Authorities, and the Civil Monetary Penalties Law

The False Claims Act is the US government's primary tool for combating fraud perpetrated through the filing of false claims for federal government reimbursement. Neurologists and companies serving the needs of neurologic patients have not been immune from False Claims Act–related legal action. This article provides an overview of the False Claims Act, uses real-life neurologic cases to illustrate the range of False Claims Act violations and recoveries, and offers some practical compliance suggestions.

INTRODUCTION

Also known as the Lincoln Law, the False Claims Act dates back to the US Civil War.[1] Then, as now, the primary purpose of the law was to root out fraud perpetrated against the federal government. The False Claims Act allows the federal government to recover improperly paid claims and simultaneously protect patient safety. In 2019, the US Department of Justice recovered more than $3 billion in False Claims Act settlements and judgments,[2] and $2.6 billion of the recovered funds came from the health care industry, including drug and medical device manufacturers, managed care providers, hospitals, pharmacies, hospice organizations, laboratories, and physicians.[2] Increasingly, physicians who recognize fraud bring False Claims Act suits as *qui tam* relators (private party whistleblowers) and, with the aid of their own attorneys, file lawsuits "for violations of the [False Claims Act] on behalf of the government."[3] To promote compliance with federal antifraud statutes, including the False Claims Act, the Centers for Medicare & Medicaid Services (CMS) mandates annual fraud, waste, and abuse training for providers. Therefore, all providers and health care organization employees should be aware of these complex laws and the regulations responsible for implementing them.

False Claims Act cases are unique in a variety of ways: (1) either the government or a *qui tam* relator (ie, a private party whistleblower represented by

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an attorney) may initiate a case; (2) the case is filed under seal (a case does not become a matter of public record while under seal) for a minimum of 60 days, but the seal is often extended to enable the government to conduct its investigation; and (3) in the event of a settlement by the government, a relator is entitled to a certain portion of the recovery.[4]

Participating in Medicare, Medicaid, and other federal government programs such as TRICARE qualifies health care providers, including physicians, as government contractors who are subject to the False Claims Act. Physicians typically run afoul of the False Claims Act by violating Medicare or Medicaid reimbursement rules. However, health care providers are on notice about the consequences of violating federal antifraud statutes. They are required to sign an agreement as a condition of participation in government health care programs and must attest to their having read and understood the terms of these agreements and related laws.[5] Subsequently, each claim form submitted to a government program for payment requires that a provider attest to the following:

> In submitting this claim for payment from federal funds, I certify that: 1) the information on this form is true, accurate and complete; 2) I have familiarized myself with all applicable laws, regulations, and program instructions, which are available from the Medicare contractor; 3) I have provided or will provide sufficient information required to allow the government to make an informed eligibility and payment decision; 4) this claim, whether submitted by me or on my behalf by my designated billing company, complies with all applicable Medicare and/or Medicaid laws, regulations, and program instructions for payment including but not limited to the Federal anti-kickback statute and Physician Self-Referral law (commonly known as Stark law); 5) the services on this form were medically necessary and personally furnished by me or were furnished incident to my professional service by my employee under my direct supervision, except as otherwise expressly permitted by Medicare and TRICARE; 6) for each service rendered incident to my professional service, the identity (legal name and NPI, license #, or SSN) of the primary individual rendering each service is reported in the designated section. For services to be considered "incident to" a physician's professional services, 1) they must be rendered under the physician's direct supervision by his/her employee, 2) they must be an integral, although incidental part of a covered physician service, 3) they must be of kinds commonly furnished in physician's offices, and 4) the services of non-physicians must be included on the physician's bills.
>
> For TRICARE claims, I further certify that I (or any employee) who rendered services am not an active duty member of the Uniformed Services or a civilian employee of the United States Government or a contract employee of the United States Government, either civilian or military (refer to 5 USC 5536). For Black-Lung claims, I further certify that the services performed were for a Black Lung-related disorder.
>
> No Part B Medicare benefits may be paid unless this form is received as required by existing law and regulations (42 CFR 424.32).

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NOTICE: Any one who misrepresents or falsifies essential information to receive payment from Federal funds requested by this form may upon conviction be subject to fine and imprisonment under applicable Federal laws (emphasis added).[6]

By submitting a claim, a provider assures that the information is truthful, accurate, and substantiated by medical necessity and is warned about the consequences of false or fraudulent claims, including violations of federal laws such as the Stark Law and the Anti-Kickback Statute (eg, taking kickbacks in exchange for referrals based on volume or value), since violations of these laws can form the basis of a false and fraudulent claim for payment.

RELEVANT CASES

False Claims Act settlements may range from hundreds of thousands to billions of dollars, depending on the size and scope of the fraud. The Department of Justice is currently on the lookout for COVID-19–related fraud while maintaining its vigilance for traditional non–COVID-19 fraud.[7]

Here are four neurology-related False Claims Act settlements highlighting the types of fraudulent behaviors that fall under the False Claims Act and the range of penalty amounts paid out. The facts in these cases are a matter of public record.

- **June 5, 2020: Alaska Neurology Center LLC and its owner settled False Claims Act allegations related to the knowing submission of false billing claims to the government for $2 billion.[8] Over a nearly 5-year period from 2013 through 2018, Alaska Neurology Center engaged in the following fraudulent schemes: (1) submitting claims with false dates of service to obtain reimbursement beyond program caps, (2) submitting claims for infusion services provided by an unqualified medical assistant, (3) submitting claims for physical therapy when the service provided was nonreimbursable massage therapy, (4) submitting claims using multiple unbundled billing codes, rather than a single required billing code, to obtain overpayment for the service, (5) submitting claims with false names of performing and/or referring medical providers, and (6) resubmitting claims with false service or diagnosis information, and without consulting a medical provider, after an original claim was rejected.[9]**
- **September 26, 2019: Avanir Pharmaceuticals was charged for paying kickbacks to induce physicians to prescribe Nuedexta (dextromethorphan HBr and quinidine sulfate),[10] a drug used to treat pseudobulbar affect.[11] Between 2010 and 2016, Avanir Pharmaceuticals paid kickbacks in a variety of forms (eg, cash, honoraria, travel, and food) to induce physicians to write Nuedexta prescriptions. The $108 million settlement is significant because of the criminal and civil cases.[10] Of the $108 million, $95 million resolved the civil False Claims Act allegations related to the payment of kickbacks and illicit marketing. The criminal indictments were more narrowly curtailed to a relationship between Avanir Pharmaceuticals and various individuals, including an unnamed physician. The Northern District of Georgia handled the case, and, in addition to the deferred prosecution, which spans 3 years, Avanir paid a monetary penalty of $7,800,000 and a forfeiture amount of $5,074,895.**
- **May 20, 2015: A neurologist in Jacksonville, Florida, settled False Claims Act allegations for $150,000 for providing medically unnecessary services and drugs to government program beneficiaries.[12] Over an approximately 2.5-year period from 2009 to 2012, the neurologist "knowingly misdiagnosed certain patients with various neurological disorders, such as multiple sclerosis (MS), which caused federal health care programs to be billed for medically unnecessary services and drugs."[12] Notably, a separate and related settlement was reached with the physician's former employer, Baptist Health System, Inc (Jacksonville, Florida) in the amount of $2.5 million.[13]**
- **December 17, 2020: Biogen Inc agreed to pay $22 million to resolve claims that it violated the False Claims Act by illegally using foundations to pay the copays of Medicare patients**

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taking the company's multiple sclerosis drugs Avonex and Tysabri. Biogen illegally manipulated its charitable patient assistance programs to subsidize copays for their own products. First Assistant United States Attorney Nathaniel R. Mendell explained that "[b]y treating the foundations simply as conduits to pay the co-pays of its own patients, Biogen violated the anti-kickback statute and undermined Medicare's co-pay structure, which Congress intended as a safeguard against inflated drug prices."[14] In addition, the charitable patient assistance program agreed to pay $1.4 million in damages, and the whistleblower who filed the case is expected to receive a settlement of $3.96 million.

These four cases illustrate that the government will settle with individual physicians, providers, and pharmaceutical companies in proportion to each party's role in the fraud. The government may pursue not only civil penalties but also criminal action against fraudsters, and the penalty range for civil penalties is vast.

COMPLIANCE SUGGESTIONS

Understanding the type of conduct leading to False Claims Act violations is the first step to preventing fraud. Often, as with the two neurologists in the cases above, physicians who find themselves culpable of the False Claims Act violations commit deliberate fraud that has the potential to harm patients. Anyone with knowledge of these neurologists' practices would be well positioned, well incentivized, and, in the authors' opinions, morally obligated to serve as a *qui tam* relator. Employed physicians who violate the False Claims Act will likely entangle their employers in a False Claims Act cause of action, because a health system's compliance department should be monitoring for signs of fraud in physician billing. The Avanir Pharmaceuticals case, however, demonstrates how physicians who lack education about federal fraud statues may find themselves entangled in a web of fraudulent corporate inducements to influence their prescribing behavior. Neurologists offered such inducements may become whistleblowers, bringing suit against the pharmaceutical company on behalf of the government and recovering a portion of a potentially substantial financial settlement. As the Biogen whistleblower's settlement illustrates, the financial rewards of a False Claims Act *qui tam* relator have the potential to be very substantial.

In addition to the very fundamental imperative of practicing medicine ethically and billing payors honestly, how else can neurologists prevent fraud in their workplace? Here are some suggestions from one large academic health system to assist physicians in avoiding False Claims Act liability:

- Adopt a compliance program. Large organizations usually have a separate compliance office, but even neurologists in solo private practice must comply with CMS-mandated fraud, waste, and abuse training and have a program to ensure appropriate compliance.
- Understand the billing and coding rules for the goods ordered and the services performed and apply the rules appropriately.
- Ensure the medical necessity of all goods or services billed to payors is substantiated in the medical record.
- Implement proper office policies and procedures to ensure that staff and medical colleagues comply with federal antifraud laws and regulations.[15]

In addition, when receiving payments from pharmaceutical companies, medical device manufacturers, or medical services providers, assess whether payment is received in good faith for a service rendered or if the purpose of the payment is to induce either referrals or prescriptions. Furthermore, engage a

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third-party audit company to assess a statistically significant sample of charts on at least an annual basis to ensure claims have been coded in alignment with documentation.

CONCLUSION

In its ruling against Alaska Neurology Center LLC, the US Department of Justice stated, "Healthcare providers who submit false bills hurt honest providers and the nation's taxpayers."[8] They may also hurt patients through improper diagnosis, harmful therapeutics, and unnecessary interventions. Complying with the False Claims Act requires behaving honestly and understanding applicable government regulations. The False Claims Act also incentivizes private citizens with knowledge of fraudulent behavior to bring suit against alleged fraudsters on behalf of the government by allowing them to share in the recovery of a portion of the government's settlement.

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HEADACHE
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By Adam G. Kelly, MD, FAAN; Allison L. Weathers, MD, FAAN

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ARTICLE 1: DIAGNOSING SECONDARY AND PRIMARY HEADACHE DISORDERS

1 A 25-year-old woman presents to the emergency department with a severe headache. This is her fifth attack in the past 6 weeks. Her headaches are bilateral and squeezing in character and last 8 to 12 hours. They are associated with neck pain and nausea. The headache is not made worse by nor does it preclude routine physical activity. She denies sensitivity to light or noise. Neurologic examination is normal. Her headaches meet *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for which of the following diagnoses?

A migraine
B paroxysmal hemicrania
C probable migraine
D secondary headache
E tension-type headache

2 Which of the following premonitory headache symptoms makes a diagnosis of migraine much less likely?

A impaired concentration
B increased urination
C neck stiffness
D sinus pain/pressure
E transient hearing loss

3 A 28-year-old woman diagnosed with migraine 5 years ago presents with increasing frequency of her headaches. Over the past month, she has had one of her typical migraine headaches on 15 days, but when specifically asked about any headache, she reports that she has had probably 18 or 19 total headache days. She takes ibuprofen 12 days a month and always follows it with rizatriptan as the ibuprofen on its own does not fully resolve her headache. She has been following this regimen for 6 months. On days when she is able to go right to sleep, she tries not to take any analgesics. She reports no other change in her migraine characteristics and has no new neurologic symptoms, and her neurologic examination remains normal. Which of the aspects of her history does not support a diagnosis of medication-overuse headache based on the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) diagnostic criteria for medication-overuse headache?

A number of days per month using a nonsteroidal anti-inflammatory drug (NSAID)
B number of days per month using a triptan
C number of migraine headache days per month
D number of total headache days per month
E total amount of time in which an acute or symptomatic headache medication has been overused

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4 Symptoms including polyuria, food cravings, irritability, and mood changes are reported by approximately 80% of patients with migraine in which phase of the disorder?

A aura
B headache
C interictal phase
D postdromal phase
E prodromal phase

5 Using positron emission tomography (PET) scanning, activation of which of the following brain areas is seen more commonly in patients with nausea as a prominent part of their migraine, suggesting its role in the pathophysiology of this symptom?

A anterior thalamus
B dorsal medulla
C locus coeruleus
D prefrontal cortex
E substantia nigra

6 During the 24 to 48 hours after resolution of typical migraine symptoms (eg, headache, nausea), the postdromal phase, which of the following symptoms are most commonly seen?

A blurry vision
B difficulty concentrating
C feeling tired or weary
D phonophobia
E stiff neck

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ARTICLE 3: ACUTE MIGRAINE TREATMENT

7 Which of the following best explains the concept of stratified care in the treatment of acute migraine attacks?

A initial management is always pharmacologic, with progression to neuromodulation devices only after an adequate trial of at least three different classes of migraine-specific medications
B initial management is tailored to the characteristics of the specific attack, with more than one treatment option available to the patient
C initial management is with the lowest possible dose of a migraine-specific medication, with dosing escalation only after an adequate trial of at least 1 month
D initial management is with a non–migraine-specific therapy; if response is unsatisfactory after an adequate trial of at least 1 month, a migraine-specific medication is then prescribed
E initial management is with a non–migraine-specific therapy; if response is unsatisfactory after 2 hours, patients escalate to a migraine-specific medication

8 A 28-year-old woman presents with a 10-year history of migraine attacks that occur once every several months. She has always used over-the-counter medications, including acetaminophen, naproxen, or ibuprofen, which for many years provided adequate relief. However, over the past year, her headaches have slightly worsened in severity and now typically come on slowly and last many hours despite treatment, limiting her ability to work on her migraine days. She does not have significant nausea associated with her migraine attacks. Which of the following triptans would likely be most beneficial in this patient?

A eletriptan
B naratriptan
C rizatriptan
D sumatriptan
E zolmitriptan

9 Dihydroergotamine is effective in the treatment of moderate to severe migraine attacks with which of the following associated symptoms?

A allodynia
B aphasia
C hemiplegia
D scintillating scotomas
E vertigo

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10 A 48-year-old man with a 25-year history of migraine attacks that were well managed with sumatriptan is being switched to lasmiditan after having a recent myocardial infarction. Specific counseling should be given to avoid which activity for 8 hours after taking this medication?

A driving
B eating
C exercising
D fasting
E taking anticoagulants or aspirin

11 Which of the following characteristics differentiates between rimegepant and ubrogepant?

A efficacy
B IV versus oral route of administration
C option for repeat dosing
D side effect profile
E tolerability

ARTICLE 4: PREVENTIVE MIGRAINE TREATMENT

12 Which of the following medications used for the prevention of migraine has received the highest level of recommendation from European and Canadian neurologic societies and the American Academy of Neurology/American Headache Society?

A amitriptyline
B candesartan
C gabapentin
D topiramate
E verapamil

13 A 31-year-old man is seen in clinic for follow-up for migraine. Despite adequate lifestyle modifications such as caffeine restriction and improved sleep, he is experiencing multiple migraine headaches per week that result in missed days at work. Use of amitriptyline and topiramate at recommended doses resulted in minimal change in migraine frequency, and both options were associated with side effects of cognitive slowing. Therapy with erenumab is considered. Which of the following side effects should this patient be counseled about before starting therapy?

A constipation and obstipation
B diarrhea
C hair loss
D paradoxical worsening of headaches
E risk of developing diabetes

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14 A 19-year-old woman is seen in clinic for recurrent headaches. She reports one to two attacks per week that result in some interference with her usual activities. Various prevention options are reviewed, and the patient has a strong preference for a nonmedication strategy. Which of the following supplements has been deemed to have Level B evidence for migraine prevention by the 2012 American Academy of Neurology/American Headache Society guidelines?

A coenzyme Q10
B glucosamine-chondroitin
C riboflavin (vitamin B_2)
D vitamin B_{12}
E vitamin E

ARTICLE 5: CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

15 Central activation through which of the following brainstem nuclei is believed to be a key generator of cluster headache attacks?

A main trigeminal nucleus
B solitary nucleus
C spinal trigeminal nucleus
D superior salivatory nucleus
E trigeminal motor nucleus

16 Galcanezumab is a monoclonal antibody against which of the following targets?

A calcitonin gene-related peptide
B galanin-like peptide
C glucagon-like peptide 1
D pituitary adenylate cyclase-activating polypeptide
E vasoactive intestinal polypeptide

17 Which of the following strategies is the recommended approach to the use of preventive treatment for cluster headaches between attack periods?

A continue for 2 weeks past the complete cessation of cluster symptoms, then discontinue until needed again
B discontinue immediately on symptom cessation and restart a month before the usual seasonal onset of an attack period
C maintain at dose required to achieve maximum cluster symptom control until patient has had at least 3 months symptom free
D maintain at lowest possible dosing between bouts, with dosing titrations as needed for subsequent attack periods
E slowly taper over at least 1 month once cluster symptoms start to improve; restart when needed

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18 Which of the following surgical procedures may be beneficial in the management of short-lasting unilateral neuralgiform headache attacks (SUNHA)?

A deep brain stimulation
B peripheral sphenopalatine ganglion blockade
C posterior fossa decompression
D vagus nerve stimulator implantation
E vascular decompression surgery

ARTICLE 6: OTHER PRIMARY HEADACHE DISORDERS

19 A 64-year-old man is seen in clinic for evaluation of headache. He describes recurrent episodes of holocephalic pain that are not associated with any other symptoms, generally last 20 to 30 seconds, and are always provoked by cough or, less commonly, other Valsalva maneuvers. He has no neurologic symptoms between episodes. Examination and brain imaging are both normal. Which of the following is the best course of treatment in this patient?

A acetazolamide
B cough suppressants
C high-volume lumbar puncture
D noninvasive vagus nerve stimulation
E referral for suboccipital decompression

20 A 26-year-old woman is seen in clinic for evaluation of recurrent episodes of headache. She states that her events only occur after consuming cold beverages or ice cream, generally resolve within 1 to 20 minutes, and are bitemporal in location without other symptoms. She is concerned since a friend of hers with a similar pattern of headaches was recently diagnosed with a brain aneurysm. Examination is normal. Which of the following is best next step in management of this patient?

A gabapentin
B ibuprofen as needed 30 minutes before consuming cold foods or beverages
C indomethacin
D reassurance and education on trigger avoidance
E referral for magnetic resonance angiogram (MRA) of the brain

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21 A 54-year-old man is seen in clinic for recurrent episodes of transient head pain. He describes stereotyped episodes of fairly intense pain over his right forehead that occur roughly 20 to 30 times per day and last for only several seconds. He does not report any autonomic symptoms, conjunctival tearing or injection, or sensory changes in his face. Examination is normal when seen in the office; cutaneous stimulation over the forehead and at the supraorbital notch did not elicit his usual pain. Which of the following is the most likely diagnosis?

A carotid-cavernous fistula
B cluster headache
C primary stabbing headache
D short-lasting unilateral neuralgiform headache with conjunctival tearing and injection (SUNCT)
E trigeminal neuralgia

22 Which of the following primary headache disorders is most likely to improve with daily caffeine dosing?

A hypnic headache
B new daily persistent headache
C nummular headache
D primary exercise headache
E primary stabbing headache

ARTICLE 7: CRANIAL NEURALGIAS

23 A 40-year-old man presents with facial pain of his right cheek of 2 months' duration. The pain is severe in intensity and episodic, lasting 1 minute to 90 seconds at a time, and the patient describes as stabbing in characteristic. Occasionally, some of his episodes spread to the right side of his chin. The attacks are spontaneous, with no known triggers or stimuli such as chewing, talking, shaving, or brushing his teeth. Which aspect of the patient's presentation prevents a diagnosis of trigeminal neuralgia from being made based on the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria?

A duration of individual attacks
B lack of precipitating stimuli
C occasional spread of his pain beyond his cheek
D stabbing nature of his pain
E 2-month duration of his episodes

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24 The refractory period that can occur following severe trigeminal neuralgia paroxysmal pain attacks is a result of which of the following pathophysiologic mechanisms?

A alterations in ligand-gated ion channels
B ectopic pacemakers with self-sustained firing
C ephaptic transmission between fibers
D membrane depolarization
E membrane hyperpolarization

25 Neuropathy isolated to which of the following nerves should raise concern for a systemic malignancy?

A auriculotemporal
B infraorbital
C lingual
D mental
E supraorbital

26 A 45-year-old man presents with 2 months of paroxysmal shooting pain that begins at the base of the skull and radiates over the back of his head to the vertex. Neurologic examination is normal, with the exception of allodynia with palpation of the scalp. He has no loss of sensation in the distribution of the region of pain. MRI of the brain and cervical spine is obtained and are normal. Which of the following should be considered early in the management of this patient?

A microvascular decompression
B occipital nerve stimulation
C onabotulinumtoxinA
D physical therapy
E pulsed radiofrequency treatment

ARTICLE 8: HEADACHE IN WOMEN

27 During which of the following time points is a reduction in migraine frequency most likely to be experienced by women with migraine?

A first trimester of pregnancy
B 1 month postpartum
C perimenopausal period
D surgical menopause following oophorectomy
E third trimester of pregnancy

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28 A 29-year-old woman is seen in follow-up for menstrual migraine without aura. Over the past 8 months, seven of her menstrual cycles have been associated with severe headaches and nausea that have not responded to her usual strategy of an over-the-counter pain medication. She does not experience migraine headaches outside the context of menses, and she reports her menstrual cycles are on a very predictable schedule of every 28 to 29 days. Which of the following is the best approach to management in this patient?

A add chlorpromazine when the over-the-counter medication is taken for abortive effect
B begin onabotulinumtoxinA injections
C begin topiramate 2 times a day for migraine prevention
D prescribe frovatriptan 2 times a day for 5 days each month, starting 2 days before menses is expected to begin
E refer for acupuncture treatments to be done immediately before the expected start of menses

29 Compared to women who have migraine without aura, women with a diagnosis of migraine with aura are more likely to experience which of the following pregnancy-associated outcomes?

A coexistent tension-type headaches
B gestational hypertension
C hyperemesis gravidarum
D preeclampsia
E preterm labor

ARTICLE 9: HEADACHE IN CHILDREN AND ADOLESCENTS

30 Which of the following patient characteristics at onset may predict the need for preventive therapy in children with migraine?

A early menarche
B fracture of a long bone before age 10
C history of late measles-mumps-rubella vaccination
D nausea as a predominant symptom
E onset before age 6

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31 A 10-year-old boy is referred to neurology by his general pediatrician for 4 months of headaches. He has had approximately eight attacks during this time. He describes the pain as a 7 to 8 in intensity using the Faces Pain Scale, throbbing/pulsating in quality, and bilateral in location. His attacks last 2 to 3 hours, and during them, he wants to just lie on his bed in the dark and try to sleep. He has associated nausea. Neurologic examination is normal. He has not tried any medication to treat these attacks. Which of the following is the most appropriate next step in his management?

A acetaminophen
B butalbital, aspirin, caffeine
C ibuprofen
D indomethacin
E an opioid medication

32 Parents of children started on topiramate as a preventive migraine treatment should be specifically counseled about the increased risk of which of the following?

A decreased effectiveness of hormonal contraception
B liver toxicity
C seizures
D suicidality
E worsened asthma

ARTICLE 10: CLINIC-BASED PROCEDURES FOR HEADACHE

33 Which of the following best describes the current understanding of the safety of onabotulinumtoxinA therapy during pregnancy and while breastfeeding?

A first-trimester use of onabotulinumtoxinA is associated with major fetal malformations, although it can be used safely at later stages of pregnancy
B the long half-life of onabotulinumtoxinA dictates that treatments should be stopped 3 months before conception
C no clear evidence of harm exists for onabotulinumtoxinA during pregnancy or breastfeeding
D onabotulinumtoxinA is concentrated within breast milk, and its use is contraindicated in women who plan to breastfeed
E passive transfer of onabotulinumtoxinA via the placenta is associated with neonatal botulism in a small number of cases

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34 Evidence for the use of trigger point injection approaches is strongest for which of the following headache disorders?

A acute migraine
B chronic migraine
C cluster headache
D temporal-mandibular joint dysfunction
E tension-type headache

35 Which of the following best describes the safe and effective use of peripheral nerve blocks for management of different headache disorders?

A bilateral peripheral nerve blocks should be avoided because of an excessive cumulative anesthetic dose
B greater occipital nerve blocks for cluster headache should include both anesthetic and steroid
C peripheral nerve blocks for migraine are more effective when a combination of anesthetic and steroid is injected
D trigger point injections and peripheral nerve blocks should not be used as combination therapy in patients with headache disorders
E ultrasound guidance should be used for peripheral nerve blocks, even for experienced practitioners

36 A 45-year-old man is seen in clinic for chronic migraine. He currently reports a steady headache frequency of roughly 24 headache days per month, and in the past he did not respond well to lifestyle modifications and could not tolerate the side effects of multiple preventive medications. OnabotulinumtoxinA injections are offered as an option, although the patient has concerns about short-term and long-term side effects of treatment. Which of the following best describes the durability and safety profile of onabotulinumtoxinA in this setting?

A drug wear-off is common with repeated injections, and safety concerns prevent injection of more than 155 units per session
B neck extensor weakness and concomitant neck pain are seen in one-fourth of patients
C onabotulinumtoxinA injections lose effectiveness over time, and the patient will likely need to consider an alternative approach after 2 years
D pain relief is unlikely to be seen until approximately 3 months after his first series of injections
E the tolerability of onabotulinumtoxinA is a significant advantage over oral preventive therapies, given its local administration

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37 A 45-year-old woman presents with severe headache associated with photophobia, phonophobia, tinnitus, mild dizziness, and slight hearing loss. All her symptoms began a week and a half ago following a fall when she slipped on ice, landing on her back. Initially her headache pain worsened within minutes of standing and improved with lying down; however, over the past few days, she has noted that her pain is unchanged with standing and at times is even improved compared to lying down. Which of the following is the most likely explanation for the change in her symptoms?

A development of cerebral venous sinus thrombosis
B development of epidural hematoma
C evolution of migraine headache
D natural history of spontaneous intracranial hypotension
E resolution of cervical muscle spasm

38 Which of the following radiologic findings has a high sensitivity and specificity for the diagnosis of spontaneous intracranial hypotension?

A diffuse pachymeningeal enhancement
B inferior ophthalmic vein collapse
C pituitary gland enlargement
D pituitary gland hyperemia
E venous distension sign

39 A 34-year-old man is seen in the hospital for orthostatic headache after starting a new weightlifting regimen. His symptoms are much improved when he lies supine, and brain MRI shows diffuse pachymeningeal enhancement suggestive of intracranial hypotension. The presence of which of the following additional imaging findings may predict a failure to respond to epidural blood patch in this patient?

A closure of the midbrain-pons angle
B flattening of the pons
C narrowing of the angle between the vein of Galen and the straight sinus
D posterior fossa crowding
E tonsillar descent

40 Which of the following imaging modalities is more likely to demonstrate slow CSF leaks at the expense of poor spatial resolution?

A CT myelography
B digital subtraction myelography
C magnetic resonance cisternography
D radionuclide cisternography
E spinal MRI

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Postreading Self-Assessment and CME Test—Preferred Responses

By Adam G. Kelly, MD, FAAN; Allison L. Weathers, MD, FAAN

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HEADACHE

Following are the preferred responses to the questions in the Postreading Self-Assessment and CME Test in this *Continuum* issue. The preferred response is followed by an explanation and a reference with which you may seek more specific information. You are encouraged to review the responses and explanations carefully to evaluate your general understanding of the article topic. The comments and references included with each question are intended to encourage independent study.

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ARTICLE 1: DIAGNOSING SECONDARY AND PRIMARY HEADACHE DISORDERS

1 The preferred response is **C (probable migraine)**. The patient meets all but one of the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for migraine. Her headache attacks last between 4 and 72 hours, but she has only had one of the four pain characteristics in the pain category (severe headache pain). However, her headaches are associated with one of the two cardinal associated symptoms (nausea). Her headaches are not better accounted for by another *ICHD-3* diagnosis and do not fulfill *ICHD-3* criteria for any other headache disorder. Probable migraine is defined by meeting either the pain criteria or associated symptom criteria. This patient meets the associated symptom criteria, but not the pain criteria. Although the patient's headaches could be mistaken for tension-type headaches given the bilateral squeezing nature of her attacks with associated neck pain, the more accurate diagnosis based on *ICHD-3* criteria is probable migraine. For more information, refer to **page 580** of the *Continuum* article "Diagnosing Secondary and Primary Headache Disorders."

2 The preferred response is **E (transient hearing loss)**. Phonophobia and photophobia are part of the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) diagnostic criteria for migraine. However, transient hearing loss has not been well described and should raise concern for an alternative diagnosis. The other symptoms listed are all relatively common. The presence of sinus pain/pressure and nasal congestion often leads to an incorrect diagnosis of sinus headache, and the presence of neck stiffness can lead to an incorrect diagnosis of tension-type headache. For more information, refer to **pages 581-582** of the *Continuum* article "Diagnosing Secondary and Primary Headache Disorders."

3 The preferred response is **A (number of days per month using a nonsteroidal anti-inflammatory drug [NSAID])**. This patient meets the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) diagnostic criteria for medication-overuse headache; however, the criteria specify that overuse is defined as taking all acute medications 10 or more days per month, with the exception of simple analgesics, such as acetaminophen or an NSAID, for which overuse is defined as taking the medication 15 or more days per month. Regular overuse has to occur for more than 3 months. Therefore, although the patient meets the criteria based on her triptan usage, she does not meet it based on her NSAID usage. To meet the criteria, patients have to have headache occurring on 15 or more days per month; however, it is not specified that these have to be typical for their migraine headaches. The diagnosis of medication-overuse headache may be missed if the total

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number of headache days is not inquired about. For more information, refer to **page 583** of the *Continuum* article "Diagnosing Secondary and Primary Headache Disorders."

ARTICLE 2: PATHOPHYSIOLOGY OF MIGRAINE

4 The preferred response is **E (prodromal phase)**. The current pathophysiologic conceptualization of migraine classifies the disorder as having five phases, including (in order) prodromal, aura, headache, postdromal, and interictal phases. The symptoms listed here, while potentially overlapping with other phases, are most commonly observed in the prodromal phase consisting of the hours to days before aura and headache. For more information, refer to **page 587** of the *Continuum* article "Pathophysiology of Migraine."

5 The preferred response is **B (dorsal medulla)**. Nausea is a common and debilitating symptom in many patients with migraine. Positron emission tomography (PET) scanning in patients with prominent nausea as part of the headache phase of migraine has shown increased activation in various brain regions, including the periaqueductal gray and rostral dorsal medulla, compared to in patients without nausea. For more information, refer to **page 590** of the *Continuum* article "Pathophysiology of Migraine."

6 The preferred response is **C (feeling tired or weary)**. Even after resolution of the cardinal symptoms of a migraine attack (eg, headache, nausea, phonophobia), many patients with migraine will continue to experience some symptoms over the next 24 to 48 hours, representing the postdromal phase. The most common symptom reported in this phase is a feeling of tiredness or weariness, described by more than 80% of patients. For more information, refer to **page 591** of the *Continuum* article "Pathophysiology of Migraine."

ARTICLE 3: ACUTE MIGRAINE TREATMENT

7 The preferred response is **B (initial management is tailored to the characteristics of the specific attack, with more than one treatment option available to the patient)**. An individual patient's migraine attacks may vary extensively in characteristics, including timing of onset, associated symptoms, and severity. In stratified care, patients have multiple treatment options available to them and are educated and empowered to choose the right option based on a particular attack. The other options are consistent with step care approaches, in which

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treatment must fail for a patient before authorization is obtained from insurers/payers for more expensive therapies. Initial management with a non–migraine-specific therapy is a reasonable approach in patients with infrequent mild to moderate migraine. For more information, refer to **page 599** of the *Continuum* article "Acute Migraine Treatment."

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8 The preferred response is **B (naratriptan)**. The patient in this case has a many-year history of migraine headaches that are debilitating and have become less responsive to over-the-counter agents, with attacks that come on slowly and last for many hours. A longer-lasting oral agent is a reasonable first choice given the patient's longer attacks that are slow in onset and the absence of associated nausea. Naratriptan and frovatriptan have a longer half-life than the other triptans (6 to 26 hours as opposed to 2 to 4 hours). For more information, refer to **page 601** of the *Continuum* article "Acute Migraine Treatment."

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9 The preferred response is **A (allodynia)**. Dihydroergotamine is available in nonoral formulations and has been shown to be effective in patients with moderate to severe migraine attacks that do not respond to triptans and that have associated allodynia. The nasal route of administration has Level A evidence from the American Headache Society. For more information, refer to **page 603** of the *Continuum* article "Acute Migraine Treatment."

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10 The preferred response is **A (driving)**. Lasmiditan belongs to the novel ditan category of acute migraine treatments. Ditans are 5-hydroxytryptamine, serotonin $(5\text{-HT})_{1F}$ receptor agonists and do not cause vasoconstriction as do triptans, which are 5-HT_{1B} agonists. Therefore, they are a good alternative in patients who have responded well to triptans but then develop a vascular contraindication to their use. Driving studies showed that participants had driving impairment after a single dose that persisted for up to 8 hours. Patients being started on this class of medication should be counseled to avoid driving after use. For more information, refer to **page 604** of the *Continuum* article "Acute Migraine Treatment."

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11 The preferred response is **D (option for repeat dosing)**. Calcitonin gene-related peptide antagonists, known as gepants, are a novel treatment class for acute migraine. Thus far, two gepants (ubrogepant and rimegepant) have received US Food and Drug Administration (FDA) approval for the acute treatment of migraine in adults. As they are part of the same drug class, these medications are very similar, especially in efficacy and tolerability, but they differ in availability of formulation (rimegepant comes in an orally disintegrating tablet) and in the option

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for repeat dosing (ubrogepant). For more information, refer to **pages 605-606** of the *Continuum* article "Acute Migraine Treatment."

ARTICLE 4: PREVENTIVE MIGRAINE TREATMENT

12 The preferred response is **D (topiramate)**. Valproate, topiramate, propranolol, and metoprolol are options for migraine prevention that have received the highest level of recommendation from European and Canadian neurologic societies and the American Academy of Neurology/American Headache Society. Amitriptyline previously had a Level A rating from the American Academy of Neurology/American Headache Society but received a Level B rating in the 2012 recommendations. For more information, refer to **pages 616-617** of the *Continuum* article "Preventive Migraine Treatment."

13 The preferred response is **A (constipation and obstipation)**. This patient's migraine history, including ongoing headaches despite appropriate lifestyle modifications and a trial of two well-supported medications, justifies a trial of calcitonin gene-related peptide monoclonal antibody therapy. Although a detailed side effect profile of calcitonin gene-related peptide antibody therapy is still being developed as these medications are used with more frequency, treatment with erenumab has been associated with severe constipation and obstipation, resulting in an addition to the package insert. For more information, refer to **page 622** of the *Continuum* article "Preventive Migraine Treatment."

14 The preferred response is **C (riboflavin [vitamin B_2])**. Various vitamins, supplements, and herbal preparations have been studied as approaches to migraine prevention. Given that some patients may specifically request a nonmedication option in this setting, neurologists should be well versed in the evidence supporting some of these approaches. In the 2012 American Academy of Neurology/American Headache Society migraine prevention guidelines, riboflavin, magnesium, and feverfew were all assigned a Level B evidence rating for their preventive effects. For more information, refer to **pages 625-626** of the *Continuum* article "Preventive Migraine Treatment."

ARTICLE 5: CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

15 The preferred response is **D (superior salivatory nucleus)**. The superior salivatory nucleus is the origin of the cranial parasympathetic autonomic

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vasodilator fibers. Central activation through this nucleus with influence by the sphenopalatine ganglion and trigeminal ganglion is believed to result in cluster headache attacks through activation of the posterior hypothalamus, which, in turn, connects to the trigeminal system. For more information, refer to **page 636** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

16 The preferred response is **A (calcitonin gene-related peptide)**. Calcitonin gene-related peptide, along with pituitary adenylate cyclase-activating polypeptide, vasoactive intestinal polypeptide, and nitrous oxide, mediates the effects of the sphenopalatine ganglion and the trigeminal ganglion on central activation. Galcanezumab is a monoclonal antibody that targets calcitonin gene-related peptide. It is US Food and Drug Administration (FDA) approved for the treatment of episodic cluster headache in adults and has been found to be effective when administered shortly after the start of a period of attacks. For more information, refer to **page 641** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

17 The preferred response is **A (continue for 2 weeks past the complete cessation of cluster symptoms, then discontinue until needed again)**. It is not recommended that preventive treatment for cluster headache be continued between attack periods. No evidence has shown that preventive treatment will prevent subsequent bouts, and continuing treatment increases the risk of tachyphylaxis. A slow taper is not necessary, but it is recommended that symptoms be fully resolved for 2 weeks before discontinuing preventive treatment. For more information, refer to **page 642** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

18 The preferred response is **E (vascular decompression surgery)**. Short-lasting unilateral neuralgiform headache attacks (SUNHA) comprise a disorder similar to V1 trigeminal neuralgia but with associated autonomic symptoms. It is felt to be caused by trigeminal nerve irritation that occurs in combination with hypothalamic dysfunction. As with trigeminal neuralgia, vascular loop compression of the ipsilateral trigeminal nerve is found in some cases, and vascular decompression surgery may be beneficial for these patients. Therefore, all patients with SUNHA should have neuroimaging performed to assess for vascular loop compression and for pituitary abnormalities. Peripheral sphenopalatine ganglion blockade may be efficacious in the treatment of cluster headache, although evidence is not yet sufficient for this treatment. Deep brain stimulation has been tried experimentally for the treatment of cluster headache, but sufficient evidence is lacking, especially given the risks of this treatment. Posterior fossa decompression and vagus nerve stimulator implantation do not have

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a role in the management of cluster headache or other trigeminal autonomic cephalalgias. For more information, refer to **page 646** of the *Continuum* article "Cluster Headache and Other Trigeminal Autonomic Cephalalgias."

ARTICLE 6: OTHER PRIMARY HEADACHE DISORDERS

19 The preferred response is **B (cough suppressants)**. This patient's presentation is consistent with the diagnosis of primary cough headache. Given that his symptoms are largely provoked by cough, it is reasonable to begin with a conservative approach, including cough-suppressant therapy. If this is ineffective, other options, including indomethacin, acetazolamide, and high-volume lumbar puncture can be considered. For more information, refer to **page 654** of the *Continuum* article "Other Primary Headache Disorders."

20 The preferred response is **D (reassurance and education on trigger avoidance)**. This patient's history of headaches that are relatively brief in nature, not associated with any other symptoms, and always provoked by exposure to cold beverages and foods is consistent with a diagnosis of cold-stimulus headache. This is a benign condition that does not require specific pharmacotherapy, although it can be managed with trigger avoidance and patient education. Brain and cerebrovascular imaging are not needed. For more information, refer to **page 656** of the *Continuum* article "Other Primary Headache Disorders."

21 The preferred response is **C (primary stabbing headache)**. This patient is presenting with frequent brief paroxysms of intense pain over his forehead region. Although this headache pattern can be seen with several different disorders, the lack of any autonomic features and the lack of any elicitation of symptoms with cutaneous stimulation make a diagnosis of primary stabbing headache most likely. For more information, refer to **page 657** of the *Continuum* article "Other Primary Headache Disorders."

22 The preferred response is **A (hypnic headache)**. Hypnic headache is unique among chronic headache disorders in that daily caffeine consumption can result in improvement in headache, as opposed to exacerbation or no benefit seen in other headache syndromes. For more information, refer to **page 659** of the *Continuum* article "Other Primary Headache Disorders."

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23 The preferred response is **B (lack of precipitating stimuli)**. According to the *International Classification of Headache Disorders, Third Edition* (*ICHD-3*) criteria for trigeminal neuralgia, although some attacks may appear spontaneous, patients must have a history or examination finding of pain precipitated by innocuous stimuli within the trigeminal distribution. Although this patient's attacks are on the longer side, according to the *ICHD-3* criteria, attacks must last a fraction of a second up to 2 minutes. Duration in months of the overall attacks of pain is not included as part of the criteria. The pain of the attacks must be described as electric shock–like, sharp, shooting, or stabbing and must be unilateral, without radiation beyond the trigeminal distribution. The pain may involve more than one division of the trigeminal nerve. For more information, refer to **page 666** of the *Continuum* article "Cranial Neuralgias."

24 The preferred response is **E (membrane hyperpolarization)**. It is theorized that during a trigeminal neuralgia pain attack, calcium-activated potassium channels open, allowing potassium ions to exit the neuron. Once this efflux results in membrane hyperpolarization, the burst of firing will stop. If the hyperpolarization is significant enough that additional firing is unable to occur, it results in a refractory period. For more information, refer to **page 669** of the *Continuum* article "Cranial Neuralgias."

25 The preferred response is **D (mental)**. Unexplained neuropathy in one or more branches of the trigeminal nerve should increase suspicion for a possible focal malignancy with direct invasion of the nerve. However, neuropathy isolated to the mental (or inferior alveolar) nerve may also occur with systemic malignancy, related to mandibular or leptomeningeal metastases with breast cancer being the most commonly associated malignancy. Mental neuropathy presents as numbness isolated to the unilateral chin and lower lip. Neuropathic pain may also occur in the same distribution. For more information, refer to **page 676** of the *Continuum* article "Cranial Neuralgias."

26 The preferred response is **D (physical therapy)**. The patient's presentation is consistent with occipital neuralgia. Physical therapy can be an effective first-line treatment in the management of patients with occipital neuralgia and should be tried before more invasive treatments, such as occipital nerve stimulation, onabotulinumtoxinA, or pulsed radiofrequency treatment. Antiseizure drugs, occipital nerve blocks, and tricyclic antidepressants may also be effective and should

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be considered before more invasive management. For more information, refer to **page 682** of the *Continuum* article "Cranial Neuralgias."

ARTICLE 8: HEADACHE IN WOMEN

27 The preferred response is **E (third trimester of pregnancy)**. The relationship between migraine frequency and ovarian hormones in women is complex, although in general, periods of time in which estrogen levels are relatively stable are often when migraine becomes less frequent. Of the options listed, the third trimester of pregnancy is a time of relatively stable and high estrogen and progesterone levels and is a time when migraine attacks are less common. Because of this, an increase in headache frequency at that time should prompt investigation for a possible secondary cause of headache, such as preeclampsia. For more information, refer to **page 687** of the *Continuum* article "Headache in Women."

28 The preferred response is **D (prescribe frovatriptan 2 times a day for 5 days each month, starting 2 days before menses is expected to begin)**. This patient is presenting with a headache history that suggests pure menstrual migraine, with events that occur only in the context of the perimenstrual period. Because her events are not responding to conservative approaches and occur on a consistent basis within a predictable menstrual cycle, she is a good candidate for a mini-prevention strategy. Of the options listed, a triptan medication (such as frovatriptan used 2 times a day starting 1 to 2 days before her expected menses and continuing for 5 days) is the preferred option. For more information, refer to **pages 690-691** of the *Continuum* article "Headache in Women."

29 The preferred response is **D (preeclampsia)**. Migraine is associated with vascular disorders of pregnancy, including preeclampsia and gestational hypertension. Of these, the presence of migraine with aura is associated with a higher risk of preeclampsia than migraine without aura; no clear risk difference based on the presence or absence of aura is seen with respect to gestational hypertension. For more information, refer to **pages 695-696** of the *Continuum* article "Headache in Women."

ARTICLE 9: HEADACHE IN CHILDREN AND ADOLESCENTS

30 The preferred response is **E (onset before age 6)**. Children whose headaches begin before the age of 6 have been shown to be more likely to need preventive therapy. Early menarche (younger than 12 years old) is

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associated with increased odds of migraine and headaches of other types in adolescent girls but not with a worse prognosis. The presence of nausea does not predict whether preventive therapy will eventually be needed. Although a number of comorbidities, including anxiety related to academics, acute family financial distress, history of abuse, depression, and poor sleep, have been associated with increased risk of chronic daily headache, vaccination history and history of childhood long bone fractures have not. For more information, refer to **pages 709-710** of the *Continuum* article "Headache in Children and Adolescents."

31 The preferred response is **C (ibuprofen)**. Based on the 2019 American Academy of Neurology/American Headache Society guidelines, ibuprofen 7.5 mg/kg to 10 mg/kg is the recommended first-line agent for the acute treatment of migraine in children and should be used at the onset of an attack before the pain becomes severe. Triptans are recommended as second-line agents, with rizatriptan being the only US Food and Drug Administration (FDA)–approved triptan for children as young as 6 years of age. Antiemetic medications may also be added. Opioid medications should not be used for the treatment of headaches in children. For more information, refer to **page 712** of the *Continuum* article "Headache in Children and Adolescents."

32 The preferred response is **A (decreased effectiveness of hormonal contraception)**. The 2019 American Academy of Neurology and American Headache Society practice guideline update on the pharmacologic treatment for pediatric migraine prevention recommends that clinicians discuss with patients and their families the evidence for amitriptyline combined with cognitive-behavioral therapy for migraine prevention and that they be informed of the potential side effects including the risks of suicide. Propranolol, another guideline-recommended therapy, can cause worsened asthma and exercise intolerance. For more information, refer to **page 717** of the *Continuum* article "Headache in Children and Adolescents."

ARTICLE 10: CLINIC-BASED PROCEDURES FOR HEADACHE

33 The preferred response is **C (no clear evidence of harm exists for onabotulinumtoxinA during pregnancy or breastfeeding)**. Currently, no clear evidence has shown that onabotulinumtoxinA use for chronic migraine during pregnancy or breastfeeding is associated with harm to the mother or child. In particular, no evidence has shown that its use is associated with major fetal malformations, and its large molecular weight prevents it from crossing the placenta or becoming concentrated in breast milk. For more information, refer to **page 735** of the *Continuum* article "Clinic-based Procedures for Headache."

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34 The preferred response is **E (tension-type headache)**. Trigger point injections are an interventional approach that can be considered for a variety of different headache disorders, particularly those that are associated with tightness or activation of a myofascial structure. Support for their use is strongest in tension-type headache, in which this pathophysiology plays a central role. For more information, refer to **page 739** of the *Continuum* article "Clinic-based Procedures for Headache."

35 The preferred response is **B (greater occipital nerve blocks for cluster headache should include both anesthetic and steroid)**. Peripheral nerve blocks are an effective procedure for the acute management and short-term prevention of various headache disorders. Different nerves can be targeted depending on the clinical features of the headache syndrome, and peripheral nerve blocks can be combined with trigger point injections or other pharmacologic options when indicated. In general, anesthetic should be combined with steroid therapy when greater occipital nerve injections are performed for cluster headache management; for migraine, no evidence supports combination therapy over anesthetic alone. For more information, refer to **page 739** of the *Continuum* article "Clinic-based Procedures for Headache."

36 The preferred response is **E (the tolerability of onabotulinumtoxinA is a significant advantage over oral preventive therapies, given its local administration)**. OnabotulinumtoxinA injections are a well-supported and well-established treatment option for patients with chronic migraine and less so for other chronic headache disorders. Although patients may have concerns about onabotulinumtoxinA use, in general the tolerability of this approach compares very favorably to oral preventive alternatives since its local administration is associated with fewer systemic side effects. For more information, refer to **pages 734-735** of the *Continuum* article "Clinic-based Procedures for Headache."

ARTICLE 11:SPONTANEOUS INTRACRANIAL HYPOTENSION

37 The preferred response is **A (development of cerebral venous sinus thrombosis)**. Acute orthostatic headaches are the hallmark presenting feature of spontaneous intracranial hypotension, although a minority of patients may not present with the classic headache or their presentation may be composed of mainly nonheadache symptoms. Patients who develop secondary complications of spontaneous intracranial hypotension, such as cerebral venous sinus thrombosis or subdural hematoma, can have a change in their headache pattern with disappearance of the postural component or even development of a paradoxical postural aspect in which the headache worsens with lying

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down. For more information, refer to **page 747** of the *Continuum* article "Spontaneous Intracranial Hypotension."

38 The preferred response is **E (venous distension sign)**. The venous distension sign of the dominant transverse sinus has a high sensitivity and specificity for spontaneous intracranial hypotension. Diffuse pachymeningeal enhancement on postcontrast brain MRI is a classic sign of spontaneous intracranial hypotension, occurring because of pachymeningeal venous dilation and increased contrast transit time. However, the differential of this finding is broad, with a number of other disease states also causing pachymeningeal enhancement, although this is usually more nodular or localized than what is seen in spontaneous intracranial hypotension. Also, pachymeningeal enhancement may not be found in patients with spontaneous intracranial hypotension depending on the timing of the imaging study. The degree of superior ophthalmic vein collapse, as opposed to inferior ophthalmic vein collapse, has been shown to have a correlation with intracranial pressures, with resolution of collapse noted after treatment of spontaneous intracranial hypotension. Pituitary gland enlargement and pituitary hyperemia can be seen patients with spontaneous intracranial hypotension but are not highly specific or sensitive findings. For more information, refer to **page 753** of the *Continuum* article "Spontaneous Intracranial Hypotension."

39 The preferred response is **A (closure of the midbrain-pons angle)**. This patient's clinical presentation of orthostatic headache is strongly suggestive of intracranial hypotension, as is the finding of diffuse pachymeningeal enhancement. A number of imaging findings related to brain descent can also be seen in patients with spontaneous intracranial hypotension; of these, closure of the midbrain-pons angle is associated with a suboptimal response to at least a first attempt at epidural blood patch. For more information, refer to **pages 753-754** of the *Continuum* article "Spontaneous Intracranial Hypotension."

40 The preferred response is **D (radionuclide cisternography)**. Radionuclide cisternography was commonly used for the detection of CSF leaks in the past, although poor spatial resolution relative to other techniques has led to it being replaced by other modalities in many patients. However, one major advantage to this approach is the ability to obtain sequential imaging at later time points, even 24 to 48 hours after radionuclide administration, which is not feasible with most other imaging options to detect CSF leaks; this is especially advantageous in looking for slow leaks. For more information, refer to **page 759** of the *Continuum* article "Spontaneous Intracranial Hypotension."

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ERRATUM

In the February 2021 issue of *Continuum* (Spinal Cord Disorders, Vol. 27, No. 1), the following errors occurred:

In "Spinal Cord Anatomy and Localization" by Todd A. Hardy, MD, PhD, MBBS, FRACP (Continuum: Lifelong Learning in Neurology 2021:27:24), the mechanism and clinical features of autonomic dysreflexia above the level of the lesion are incorrectly stated as "Above the lesion, the parasympathetic activity results in pupil constriction, flushing, and sweating." The corrected text is shown below:

Above the lesion, flushing and sweating are common clinical features.

Hardy TA. Spinal cord anatomy and localization. Continuum (Minneap Minn) 2021;27(1, Spinal Cord Disorders):12-29. doi:10.1212/CON.0000000000000899

The error in the text noted above led to an erroneous correct answer (D pupillary constriction) to question 2 in the Postreading Self-Assessment and CME Test (Continuum: Lifelong Learning in Neurology 2021:27:268,280). An updated question with corrected preferred response is shown below and has been replaced online:

2 A 40-year-old woman who sustained a spinal cord injury at the T2 level in a car accident 2 years ago has been experiencing episodes of hypertension, bradycardia, and facial sweating when she forgets to catheterize herself and her bladder gets too full. Which of the following is most likely to develop during one of these episodes?

A biceps, brachioradialis, and triceps hyperreflexia
B biceps, brachioradialis, and triceps hyporeflexia
C facial pallor
D facial flushing
E warm lower extremities

The preferred response is **D (facial flushing)**. Spinal cord lesions above the T6 level can block descending control of preganglionic autonomic neurons, but those neurons can still be activated reflexively by segmental sensory stimuli because the spinal circuitry below the lesion remains intact. Because many of these neurons are vasoconstrictor, this results in hypertension and the lower extremities become cool and pale. This reflex is most often triggered by distention of a hollow viscus such as the bladder or rectum. The hypertension triggers a reflex vagal response via an intact brainstem baroreflex arc that succeeds in lowering the heart rate, but the hypertension persists because the vasoconstrictive drive to the vascular beds below the level of the lesion is no longer subject to descending inhibition. In contrast, vasoconstrictor drive to blood vessels above the level of the lesion is withdrawn, so these blood vessels relax, resulting in facial flushing. Sweating above the level of the lesion reflects sympathoexcitatory responses initiated by preganglionic sudomotor neurons located above the level of the lesion. These episodes are referred to as autonomic dysreflexia. For more information, refer to **page 24** of the *Continuum* article "Spinal Cord Anatomy and Localization.

Gelb DJ, Zazulia AR. Postreading self-assessment and CME test. Continuum (Minneap Minn) 2021;27(1, Spinal Cord Disorders):267-278.

Gelb DJ, Zazulia AR. Postreading self-assessment and CME test. Continuum (Minneap Minn) 2021;27(1, Spinal Cord Disorders):279-288.

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ERRATUM

In the December 2020 issue of *Continuum* (Neuro-oncology, Vol. 26, No. 6), the following error occurred:

In "Familial Nervous System Tumor Syndromes" by Roy E. Strowd, III, MD, MEd, MS, and Scott R. Plotkin, MD, PhD (Continuum: Lifelong Learning in Neurology 2020:26(6, Neuro-oncology): 1547), the criteria for the clinical diagnosis of von Hippel-Lindau disease are stated incorrectly as "In patients with a family history of von Hippel-Lindau disease, a diagnosis can be established in the setting of (1) two or more CNS hemangioblastomas or (2) one CNS hemangioblastoma and a visceral tumor (excluding epididymal or renal cysts). In patients lacking a family history, genetic testing is supported by the presence of at least (1) one CNS hemangioblastoma, (2) pheochromocytoma, or (3) clear cell renal carcinoma (TABLE 4-7)." The corrected criteria are shown below:

A diagnosis of von Hippel-Lindau disease can be made by clinical diagnosis or genetic testing. In patients with a family history of von Hippel-Lindau disease, a diagnosis can be established in the setting of (1) one CNS hemangioblastoma, (2) pheochromocytoma, or (3) clear cell renal carcinoma. In patients lacking a family history, clinical diagnosis is supported by the presence of at least (1) two or more CNS hemangioblastomas or (2) one CNS hemangioblastoma and a visceral tumor (excluding epididymal or renal cysts). In these cases genetic testing should be pursued (TABLE 4-7).

The criteria shown in Table 4-7 are correct.

Strowd RE III, Plotkin SR. Familial nervous system tumor syndromes. Continuum (Minneap Minn) 2020;26(6, Neuro-oncology):1523-1552. doi:10.1212/CON.0000000000000950

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LEARNING OBJECTIVES AND CORE COMPETENCIES

Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Headache issue, participants will be able to:

- Develop a systematic diagnostic approach to the patient with headache, differentiate secondary from primary headache disorders, and diagnose some of the most common secondary and primary headache disorders
- Discuss the current understanding of the pathophysiologic basis of each phase of the migraine cycle
- Identify migraine-specific and nonspecific acute treatment options and when to consider novel agents and neuromodulation
- Describe pharmacologic and nonpharmacologic preventive treatments for migraine, outline their advantages and disadvantages, and identify when they should be considered
- Distinguish between and among primary and secondary presentations of trigeminal autonomic cephalalgias and apply evidence-based management strategies to practice
- Diagnose and manage uncommon primary headache disorders
- Discuss the differential diagnosis, evaluation, and management of neuralgic pain in the head and neck
- Describe the presentation and treatment of headache in women in relation to hormonal changes and throughout the phases of life
- Describe the differential diagnosis and treatment of headache disorders, especially migraine, in children and adolescents
- Describe the evidence, safety, risks, adverse effects, indications, and mechanisms for clinic-based procedures for headache
- Discuss the clinical presentations, diagnostic investigations, neuroimaging findings, and treatment strategies of spontaneous intracranial hypotension
- Discuss the potential criminal and civil ramifications for not complying with the Stark Law and Anti-Kickback Statute

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Headache issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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LIST OF ABBREVIATIONS

Headache

5-HT	5-Hydroxytryptamine, serotonin
AAN	American Academy of Neurology
AHS	American Headache Society
CGRP	Calcitonin gene-related peptide
CMS	Centers for Medicare & Medicaid Services
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
DHE	Dihydroergotamine
ECG	Electrocardiogram
ED	Emergency department
EEG	Electroencephalogram; electroencephalography
FDA	US Food and Drug Administration
FDG-PET	Fludeoxyglucose positron emission tomography
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GABA-ergic	γ-Aminobutyric acid–mediated
ICER	Institute for Clinical and Economic Review
ICHD	*International Classification of Headache Disorders*
ICHD-2	*International Classification of Headache Disorders, Second Edition*
ICHD-3	*International Classification of Headache Disorders, Third Edition*
IM	Intramuscular
IV	Intravenous
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NMDA	*N*-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drugs
PACAP	Pituitary adenylate cyclase-activating polypeptide
PCR	Polymerase chain reaction
PET	Positron emission tomography
PRES	Posterior reversible encephalopathy syndrome
RCVS	Reversible cerebral vasoconstriction syndrome
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SUNA	Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
SUNHA	Short-lasting unilateral neuralgiform headache attacks
TAC	Trigeminal autonomic cephalalgia

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HEADACHE

ARTICLE 1: DIAGNOSING SECONDARY AND PRIMARY HEADACHE DISORDERS

David W. Dodick, MD, FAAN, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):572–585.

ABSTRACT

PURPOSE OF REVIEW:

This article provides a systematic diagnostic approach to the patient with headache.

RECENT FINDINGS:

The vast majority of patients presenting with headache in clinical practice have a primary headache disorder. The most common primary headache disorder in clinical practice is overwhelmingly migraine. Unfortunately, a substantial proportion of patients with migraine do not receive an accurate diagnosis. In addition, the clinical features of migraine overlap with secondary causes of headache, making a careful history and deliberative evaluation for warning symptoms or signs of a secondary headache disorder of paramount importance.

SUMMARY:

The approach to the patient with headache requires knowledge of the diagnostic criteria for primary headache disorders, recognition of the importance of a systematic evaluation for red flags associated with secondary headache disorders, and awareness of the pearls and pitfalls encountered in the diagnostic evaluation of a patient with headache.

KEY POINTS

- **The $SNOOP_4$ acronym is a useful guide to assist clinicians in systematically evaluating for warning symptoms and signs of a secondary cause of headache.**
- **Since secondary causes of headache often have features that resemble migraine, tension-type headache, or a trigeminal autonomic cephalalgia, caution must be exercised and warning signs and symptoms of secondary headache must be evaluated.**
- **A headache history is the most important aspect of the evaluation of a patient presenting with headache, and eliciting worrisome features with directed questioning is necessary. The history must be taken without assuming that key features will be volunteered by the patient.**
- **Brain MRI is the imaging procedure of choice when evaluating for intracranial or neurovascular causes of headache. Other than the detection of skull fracture or acute intracranial blood, the use of CT in the evaluation of secondary headaches should be restricted, especially in children.**

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- PITS (parenchymal, intraventricular, truncal, sulci) is a useful acronym that highlights the anatomic areas where subarachnoid blood can be overlooked.
- In the setting of a thunderclap headache, MRI of the brain and intracranial and extracranial vasculature should always be obtained after subarachnoid hemorrhage is excluded.
- Knowledge of the qualitative and quantitative findings on MRI in patients suspected of having intracranial hypertension or hypotension is important and can help support a diagnosis.
- The overwhelming majority (94%) of patients presenting with recurrent nonsecondary headaches as a chief complaint in clinical practice have migraine.
- If clinicians remember any part of the *International Classification of Headache Disorders, Third Edition*, it should be the diagnostic criteria for migraine, chronic migraine, and medication-overuse headache as these are the most common primary headaches seen in clinical practice.

ARTICLE 2: PATHOPHYSIOLOGY OF MIGRAINE

Ana Recober, MD. Continuum (Minneap Minn). June 2021; 27 (3 Headache):586–596.

ABSTRACT

PURPOSE OF REVIEW:

This article summarizes the current understanding of the pathophysiology of migraine, including some controversial aspects of the underlying mechanisms of the disorder.

RECENT FINDINGS:

Recent functional neuroimaging studies focusing on the nonpainful symptoms of migraine have identified key areas of the central nervous system implicated in the early phases of a migraine attack. Clinical studies of spontaneous and provoked migraine attacks, together with preclinical studies using translational animal models, have led to a better understanding of the disease and the development of disease-specific and targeted therapies.

SUMMARY:

Our knowledge of the pathophysiology of migraine has advanced significantly in the past decades. Current evidence supports our understanding of migraine as a complex cyclical brain disorder that likely results from dysfunctional sensory processing and dysregulation of homeostatic mechanisms. This article reviews the underlying mechanisms of the clinical manifestations of each phase of the migraine cycle.

KEY POINTS

- It is widely accepted that migraine is an inherited disorder of sensory processing, but many aspects of the underlying basis of this disorder still remain unknown.
- Migraine attacks are often preceded by alterations in homeostasis, supporting the role of the hypothalamus in the prodromal phase.
- Neuroimaging studies have found hypothalamic activation and altered connectivity with other brain and brainstem regions that could explain the polyuria, yawning, food cravings, and changes in appetite reported in the prodromal phase.
- During the prodromal phase, photophobia is associated with activation of the visual cortex, and nausea is associated with activation of the rostral dorsal medulla and periaqueductal gray. Neck stiffness or discomfort is attributed to early activation of the trigeminocervical complex, the region of the brainstem and upper cervical spinal cord where pain signals from the trigeminal and cervical nerves converge.

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- Taken together, the nature of the symptoms and neuroimaging findings support the current understanding of migraine as a disorder of the central nervous system and not as a vascular disorder.
- Traditionally, aura has been described as preceding the headache phase; however, the aura can overlap with headache, and it is not rare for the aura to occur in the absence of headache.
- Cortical spreading depolarization is widely accepted to be the pathophysiologic mechanism of aura.
- Cortical spreading depolarization is a bioelectrical phenomenon consisting of a wave of intense cortical neuronal activity associated with hyperemia, followed by a more prolonged period of neuronal activity suppression associated with cortical oligemia.
- Cortical spreading depolarization has been demonstrated to occur in the human brain as a result of acute injury in the setting of stroke or traumatic brain injury; however, no direct evidence of the simultaneous occurrence of cortical spreading depolarization and aura has been seen in humans.
- The aura can start in multiple sites of the visual cortex in the same individual, although certain areas show higher propensity to be the initiating focus.
- The mechanisms underlying visual aura appear to propagate in a linear fashion along gyri or sulci, rather than spreading as a concentric wave as usually depicted based on studies of cortical spreading depolarization in animal models.
- The aura may propagate silently in the cortex, without clinical manifestations.
- Migraine pain is mediated by the trigeminovascular pathway.
- Some experts maintain that nociceptive activation of the peripheral trigeminal nociceptors is necessary for the perception of head pain and implicate cortical spreading depolarization and peripheral sensitization of perivascular sensory nerve terminals. Others argue that migraine pain is the result of abnormal central processing of otherwise normal sensory input from the peripheral trigeminal sensory system.
- Some studies have challenged the presumption that the pulsating quality of pain in migraine is determined by arterial pulsations and suggest a neuronal rather than vascular "pacemaker" of the throbbing pain in migraine.
- The postdrome can last for 24 to 48 hours after resolution of the headache. Some experts have suggested that global reductions in cerebral blood flow could occur in this phase and could be mediated by activation of brainstem nuclei, resulting in widespread vasoconstriction. Alternatively, this reduction in regional cerebral blood flow has been attributed to the persistent hypoperfusion that follows cortical spreading depolarization.
- People with migraine report cognitive, autonomic, and sensory symptoms between their migraine attacks. Resting-state functional connectivity MRI studies have demonstrated altered network connectivity in multiple cortical and subcortical brain regions during the interictal phase.
- Multiple neurotransmitters, neuropeptides, and neurochemical systems play a role in migraine. The most studied include calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), serotonin, and noradrenergic and dopaminergic mechanisms.

ARTICLE 3: ACUTE MIGRAINE TREATMENT

Jessica Ailani, MD, FAHS, FAAN. Continuum (Minneap Minn). June 2021; 27 (3 Headache):597–612.

ABSTRACT

PURPOSE OF REVIEW:

Migraine is a disabling disease of attacks of moderate to severe pain with associated symptoms. Every person with migraine requires treatment for acute attacks. Treatments can range from behavioral management and nonspecific medications to migraine-specific medications and

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neuromodulation. For many with migraine, having a combination of tools allows for effective treatment of all types of attacks.

RECENT FINDINGS:

Over the past several years, four neuromodulation devices have been cleared by the US Food and Drug Administration (FDA) for treatment of acute migraine, and three medications with novel mechanisms of action have been FDA approved. They add to the arsenal available to people with migraine and focus on migraine-specific pathways to allow for precise care with fewer side effects.

SUMMARY:

This article discusses acute migraine therapy, focusing on best-level evidence.

KEY POINTS

- Migraine attacks are disabling and require treatment. Ineffective treatment can increase emergency department visits and place the patient at increased risk for chronic migraine.
- Acute treatment can be nonspecific or migraine specific. Opioids and barbiturates should be limited in their use for migraine.
- Triptans, acetaminophen, aspirin, ibuprofen, naproxen, and diclofenac sodium have Level A evidence for the acute treatment of migraine.
- A nonoral route for migraine medication is preferred in patients with nausea or vomiting or rapid-onset attacks.
- Stratified care is best for patients with multiple types of migraine attacks.
- Triptans are considered first-line treatment for moderate to severe migraine attacks.
- Triptans are contraindicated in people with vascular disease.
- Dihydroergotamine has shown to be effective early or late in a migraine attack. Consider dihydroergotamine in a patient who has found triptans to be ineffective.
- Lasmiditan 50 mg, 100 mg, or 200 mg can be considered in patients with cardiovascular contraindications to triptans.
- Patients who are prescribed lasmiditan must be instructed not to drive for 8 hours after taking medication.
- Ubrogepant is dosed as needed for migraine, with an additional second dose as needed in 2 to 24 hours.
- Rimegepant is dosed once a day as needed for migraine.
- Consider adding neuromodulation in patients who have side effects to current therapy, prefer nondrug therapy, or are overusing acute medications.
- The goals of acute migraine treatment are to treat attacks quickly and consistently, prevent recurrence, and restore the patient to functionality.

ARTICLE 4: PREVENTIVE MIGRAINE TREATMENT

Rebecca Burch, MD, FAHS. Continuum (Minneap Minn). June 2021;
27 (3 Headache):613-632.

ABSTRACT

PURPOSE OF REVIEW:

This article provides an overview of preventive interventions for migraine, including when to start and how to choose a treatment, pharmacologic options (both older oral treatments and new monoclonal antibodies to calcitonin gene-related peptide [CGRP] or its receptor),

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nonpharmacologic treatment such as neuromodulation, and preventive treatment of refractory migraine.

RECENT FINDINGS:

The migraine preventive treatment landscape has been transformed by the development of monoclonal antibodies targeting CGRP or its receptor. These treatments, which are given subcutaneously or intravenously monthly or quarterly, have high efficacy and were well tolerated in clinical trials. Emerging real-world studies have found higher rates of adverse events than were seen in clinical trials. They are currently recommended for use if two traditional preventive therapies have proven inadequate. Since the commonly cited 2012 American Headache Society/American Academy of Neurology migraine prevention guidelines were released, clinical trials supporting the preventive use of lisinopril, candesartan, and memantine have been published. Neuromodulation devices, including external trigeminal nerve stimulation and single-pulse transcranial magnetic stimulation devices, have modest evidence to support preventive use. The American Headache Society/American Academy of Neurology guidelines for the preventive treatment of migraine are currently being updated. A new class of oral CGRP receptor antagonists (gepants) is being tested for migraine prevention.

SUMMARY:

Successful preventive treatment of migraine reduces disease burden and improves quality of life. Many pharmacologic and nonpharmacologic treatment options are available for the prevention of migraine, including newer therapies aimed at the CGRP pathway as well as older treatments with good evidence for efficacy. Multiple treatment trials may be required to find the best preventive for an individual patient.

KEY POINTS

- Preventive treatment reduces migraine-related disability over and above the associated reduction in attack frequency.
- A collaborative approach to choosing preventive treatment may improve adherence and patient satisfaction with treatment options.
- The goal of preventive treatment is reduction of disability and improvement in quality of life rather than complete relief from migraine attacks.
- Objective measures are helpful for tracking response to preventive treatment and may be more reliable than patient recall.
- Prevention is started when migraine attacks are frequent, disabling, or hard to treat, or if acute medications have been overused.
- Oral preventive treatments with good evidence include sodium valproate, topiramate, propranolol, metoprolol, and amitriptyline.
- Amitriptyline and venlafaxine are the antidepressant drugs with the best evidence for prevention of migraine.
- Propranolol and verapamil are the antihypertensive drugs most commonly used for migraine prevention and are generally well tolerated.
- Recent evidence suggests that lisinopril and candesartan are effective migraine preventives with a good side effect profile.
- Topiramate and sodium valproate are potent migraine preventives but have a higher side effect burden than other preventives.
- Antiepileptic drugs sometimes used for prevention include gabapentin, pregabalin, and zonisamide.
- Oral medication choice depends on effectiveness, side effect profile, contraindications, and patient preference.
- Four calcitonin gene-related peptide (CGRP) monoclonal antibodies are now US Food and Drug Administration approved for migraine prevention.
- CGRP monoclonal antibodies are given monthly or quarterly, either subcutaneously or intravenously.

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- CGRP monoclonal antibodies are effective for migraine prevention, with up to 60% of patients seeing a 50% or greater reduction in headache days.
- Studies showed that CGRP monoclonal antibodies are effective for refractory migraine and sustain efficacy over several years.
- Discontinuation because of adverse events was less than 5% in clinical trials of CGRP monoclonal antibodies, but these trials may not have accurately captured the side effects seen in clinical practice.
- The long-term safety of CGRP blockade, particularly the risk of rare but serious cardiovascular events, is not completely known.
- CGRP monoclonal antibodies may have a faster onset of action than oral preventives.
- Limitations of CGRP monoclonal antibody use include cost and access issues, long duration of any side effects that may occur, and the need to avoid use during pregnancy.
- American Headache Society guidelines suggest that CGRP monoclonal antibodies may be considered if two traditional (oral or neurotoxin) preventives are not effective or not tolerated.
- OnabotulinumtoxinA, topiramate, and the CGRP monoclonal antibodies have good evidence for prevention of chronic migraine.
- Medication-overuse headache is often treated with a combination of discontinuation of the overused medication and starting preventive medication. OnabotulinumtoxinA and topiramate have the best evidence for prevention in patients with medication overuse.
- Patients with chronic migraine have a higher burden of medical and psychiatric comorbidity and benefit significantly from a multidisciplinary approach.
- Important lifestyle factors to consider in people with migraine include getting adequate and good-quality sleep, maintaining good hydration, eating well-balanced frequent meals, avoiding alcohol, keeping caffeine to a modest level and at a regular time each morning, managing stress, and participating in regular physical activity.
- The herbal and nutritional supplements with the best evidence for migraine prevention are magnesium and riboflavin. Evidence for feverfew has been conflicting.
- *Petasites* (butterbur) is no longer recommended as a preventive because of possible contamination with hepatotoxic alkaloids.
- Behavioral therapies with good evidence for migraine prevention include cognitive-behavioral therapy, relaxation training, thermal or electromyographic biofeedback, and mindfulness meditation.
- Layering behavioral and pharmacologic treatment is more effective than either approach alone, particularly for people with both migraine and mood disorders.
- Acupuncture is a popular nonpharmacologic treatment that has good evidence for use in migraine prevention and is generally well tolerated.
- The decision on whether to use devices for migraine prevention in clinical practice is often driven by cost and access concerns.
- The external trigeminal nerve stimulation device and the single-pulse transcranial magnetic stimulation device have evidence for migraine prevention.

ARTICLE 5: CLUSTER HEADACHE AND OTHER TRIGEMINAL AUTONOMIC CEPHALALGIAS

Stephanie J. Nahas, MD, MSEd, FAHS, FAAN. Continuum (Minneap Minn). June 2021; 27 (3 Headache):633-651.

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ABSTRACT

PURPOSE OF REVIEW:

The trigeminal autonomic cephalalgias (TACs) are relatively rare, but they represent a distinct set of syndromes that are important to recognize. Despite their unique features, TACs often go undiagnosed or misdiagnosed for several years, leading to unnecessary pain and suffering. A significant proportion of TAC presentations may have secondary causes.

RECENT FINDINGS:

The underlying pathophysiology of TACs is likely rooted in hypothalamic dysfunction and derangements in the interplay of circuitry involving trigeminovascular, trigeminocervical, trigeminoautonomic, circadian, and nociceptive systems. Recent therapeutic advancements include a better understanding of how to use older therapies more effectively and the identification of new approaches.

SUMMARY:

TAC syndromes are rare but important to recognize because of their debilitating nature and greater likelihood for having potentially serious underlying causes. Although treatment options have remained somewhat limited, scientific inquiry is continually advancing our understanding of these syndromes and how best to manage them.

KEY POINTS

- The trigeminal autonomic cephalalgias share some similarity with migraine phenotype, pathophysiology, and therapy but represent a distinct set of syndromes requiring different management.
- The pain of trigeminal autonomic cephalalgias tends to be relatively short and intense, and, by definition, it is accompanied by symptoms reflective of autonomic dysfunction.
- The pathophysiology of trigeminal autonomic cephalalgias is likely linked to dysfunction of the hypothalamus, trigeminally mediated reflexes, and nociception.
- Trigeminal autonomic cephalalgias are distinguished clinically by temporal patterns and combinations of symptoms.
- Cluster headache attacks must be addressed with rapid-onset therapies (eg, inhaled or injected), and, since attacks can be frequent, toxicity from repeated treatments must be considered.
- Corticosteroids (administered orally, via suboccipital injection, or, less commonly, intravenously) are instrumental as transitional therapy in cluster headache.
- Episodic cluster headache should be managed with maintenance therapy only during bouts, not continuously without interruption.
- Paroxysmal hemicrania is clusterlike, with a female predominance, greater attack frequency, less periodicity, different triggers, and, above all else, exquisite response to indomethacin.
- Indomethacin is most useful for paroxysmal hemicrania and hemicrania continua, requires proper titration, and monitoring for prolonged use for its potential adverse effects.
- If indomethacin is contraindicated or intolerable for patients with paroxysmal hemicrania and hemicrania continua, alternative therapies are available.
- If a chronic primary headache diagnosis is unclear, consider an indomethacin trial, particularly if there are no contraindications, and if cranial autonomic symptoms are present.
- Short-lasting unilateral neuralgiform headache attacks are like V1 trigeminal neuralgia, with autonomic features and no refractory period to cutaneous triggering (when present); look for pituitary pathology and vascular loop compression in all cases, repeatedly in refractory cases.
- Hemicrania continua is increasingly recognized as a mimic of chronic migraine.
- In many cases, syndromic overlap exists in the presentation of trigeminal autonomic cephalalgias, and treatment should be tailored initially to the entity with the closest fit based on diagnostic criteria.

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ARTICLE 6: OTHER PRIMARY HEADACHE DISORDERS

Jonathan H. Smith, MD, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache): 652–664.

ABSTRACT

PURPOSE:

This article provides an overview of a diverse group of primary headache disorders that are categorized in the *International Classification of Headache Disorders, 3rd Edition* (*ICHD-3*), as "other primary headache disorders." This article provides clinicians with a distilled understanding of the diagnoses and their epidemiology, pathophysiology, and management.

RECENT FINDINGS:

Cough-induced headache requires neuroimaging to exclude posterior fossa pathology and recently has been reported as a common symptom in patients with CSF-venous fistula. Clinical overlap is observed between patients with primary exercise headache and primary headache associated with sexual activity. Patients with recurrent thunderclap headache associated with sexual activity should be presumed to have reversible cerebral vasoconstriction syndrome until proven otherwise. De novo external-pressure headache is a common sequela among health care workers using personal protective equipment during the COVID-19 pandemic. New daily persistent headache is an important mimicker of chronic migraine or chronic tension-type headache and is distinguished by a daily-from-onset progression of persistent headache; a treatment-refractory course is often observed, and early involvement of a multidisciplinary team, including a psychotherapist, is advised.

SUMMARY:

Patients with primary headache disorders that are classified as "other primary headache disorders" have presentations with unique diagnostic and management considerations. The disorders are highly recognizable, and an appreciation of the diagnoses will aid clinicians in providing safe and effective care for patients presenting with headache.

KEY POINTS

- Clinical distinction must be made between headache that is triggered by a Valsalva maneuver (a red flag) and headache that is aggravated by a Valsalva maneuver (typical of migraine).
- In nearly two-thirds of patients, a history of cough-induced headache may indicate a posterior fossa lesion, most often a Chiari malformation type I.
- Although not part of the diagnostic criteria for primary cough headache, the disorder classically responds to treatment with indomethacin.
- Unlike migraine, primary exercise headache often has a short duration and generally does not have typical migraine features apart from a throbbing pain character.
- Among older adults at risk for coronary artery disease, cardiac angina may present with an exertional headache (termed *cardiac cephalalgia*).
- Primary exercise headache exists as a self-limited disorder in the majority of patients.
- Recurrent thunderclap headaches associated with sexual activity should be presumed to be reversible cerebral vasoconstriction syndrome until proven otherwise. A patient with an initial presentation of headache associated with sexual activity should be evaluated for the possibility of subarachnoid hemorrhage.

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- External-pressure headache should be considered in occupational groups in which helmets or personal protective equipment are commonly worn.
- Routine neuroimaging for suspected primary stabbing headache is not recommended in the absence of additional red flags.
- Patients with recurrent thunderclap headache should be initially presumed to have a clinical diagnosis of reversible cerebral vasoconstriction syndrome. Patients with a new presentation of thunderclap headache should first be evaluated for subarachnoid hemorrhage.
- To help distinguish hypnic headache from cluster headache, the diagnostic criteria specify that hypnic headache is not associated with cranial autonomic symptoms or restlessness.
- Hypnic headache appears to occur more often in adults older than 50 years.
- Polysomnography has not shown a consistent association with sleep stage and hypnic headache onset.
- Hypnic headache is unique relative to other headache disorders because frequent caffeine use is advocated as therapy.
- The scalp area affected by the nummular headache should be examined for alopecia or a visible skin lesion, which may indicate a dermatologic condition.
- Migrainous features are not typical of nummular headache, although comorbid migraine is common.
- The temporal progression should be ascertained for all patients presenting for evaluation of a refractory chronic daily headache because the hallmark of new daily persistent headache is a daily-from-onset progression of chronic headache.
- In specialty headache practices, disorders of intracranial pressure, including idiopathic intracranial pressure with or without papilledema and spontaneous CSF leak, are relatively common; these disorders should be considered when evaluating patients for new daily persistent headache.
- New daily persistent headache is characteristically refractory to standard therapies, and empiric treatment guided by the underlying phenotype (eg, chronic migraine) is recommended.
- Early acknowledgment of a refractory course allows for early involvement of a multidisciplinary team to help bolster self-efficacy and self-management strategies in patients with new daily persistent headache.

ARTICLE 7: CRANIAL NEURALGIAS

Carrie Robertson, MD, FAHS. Continuum (Minneap Minn). June 2021;
27 (3 Headache):665-685.

ABSTRACT

PURPOSE OF REVIEW:

This article discusses the differential diagnosis, evaluation, and management of trigeminal neuralgia and reviews other neuralgias of the head and neck, including those that contribute to neuralgic ear pain.

RECENT FINDINGS:

Most cases of trigeminal neuralgia are related to vascular compression, a demyelinating plaque, or a compressive mass affecting the trigeminal nerve. However, recent studies have shown that up to 11% of patients have a family history of trigeminal neuralgia, suggesting that some patients may have a genetic predisposition to demyelination or nerve hyperexcitability. In these patients, trigeminal neuralgia may occur at a younger age, on both sides of the face, or in combination with other neuralgias.

SUMMARY:

When a patient presents with neuralgic pain, the diagnosis is made by careful history and neurologic examination, with attention to the dermatome involved, the triggers, and the

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presence of any associated sensory deficit. All patients with new neuralgia or neuropathic facial pain warrant a careful evaluation for a secondary cause. The presence of sensory deficit on bedside examination is particularly concerning for an underlying secondary etiology.

KEY POINTS

- *Neuralgia* describes sharp, stabbing, shocklike pain that is often triggered by touching within the sensory dermatome of the affected nerve, whereas *neuropathy* describes sensory deficit within the nerve distribution, sometimes with persistent neuropathic pain, such as burning, tingling, or prickling.
- Classical trigeminal neuralgia is trigeminal neuralgia related to neurovascular compression; nerve atrophy or displacement is required on imaging (not just vascular contact). Secondary trigeminal neuralgia is trigeminal neuralgia related to another cause, such as demyelinating plaque or local mass. Idiopathic trigeminal neuralgia is trigeminal neuralgia without a known cause.
- Most patients with trigeminal neuralgia are pain free between attacks, but a subset can develop near-continuous background pain.
- Mild sensory changes may be present in trigeminal neuralgia, but true loss of sensation should alert the clinician to look for secondary causes.
- Approximately 99% of patients with trigeminal neuralgia report triggers.
- Some patients with trigeminal neuralgia may describe a refractory period after severe attacks, during which additional attacks are diminished.
- Bilateral trigeminal neuralgia can occur but is uncommon and should raise suspicion for secondary trigeminal neuralgia, such as from multiple sclerosis.
- Trigeminal neuralgia associated with pronounced autonomic symptoms should raise clinical suspicion for a trigeminal autonomic cephalalgia.
- Unexplained numbness isolated to the chin is a red flag for potential malignancy.
- Neurovascular contact of the trigeminal nerve is common even in people without symptoms. Therefore, the severity of compression on imaging may be more relevant, including nerve displacement or atrophy.
- A family history of trigeminal neuralgia may be present in up to 11% of patients. Familial cases may have an earlier onset and may be associated with additional neuralgias, such as glossopharyngeal neuralgia or hemifacial spasm.
- Patients with multiple sclerosis may have both a demyelinating plaque and neurovascular compression near the trigeminal nerve root entry zone, causing neuralgia through a "double crush" mechanism.
- Postherpetic neuralgia should be considered in patients presenting with trigeminal neuralgia who have a history of erythema or rash in the affected area at the onset of pain.
- Because of overlap from cervical cutaneous branches over the jawline, the most reliable area to test the mandibular (V3) division is over the chin.
- If the patient's pain is predominantly in V2 and V3 and without cutaneous triggers, a dental evaluation should be considered.
- Carbamazepine is considered first-line treatment for trigeminal neuralgia.
- For urgent treatment of refractory trigeminal neuralgia, IV fosphenytoin, IV lidocaine, or peripheral blocks can be considered.
- A patient with trigeminal neuralgia that is refractory to medical therapy should be referred to a neurosurgeon. If neurovascular compression is present on imaging, microvascular decompression is typically considered first. If not, a neuroablative procedure (with injury to the nerve) is typically considered first.
- Recurrence of trigeminal neuralgia after microvascular decompression may be because of a new or previously missed vessel, compression with the synthetic material used in decompression, or arachnoid adhesions.
- Repeat microvascular decompression has a lower chance of pain relief and higher risk of complications.
- The best dosing and location of radiosurgery (where to aim along the trigeminal root) for trigeminal neuralgia is still being studied.

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- Pain relief from radiosurgery may start 2 weeks to 2 months after treatment, whereas decreased sensation may start an average of 6 to 36 months after treatment.
- Trigeminal neuropathy following a neuroablative procedure for trigeminal neuralgia is called *painful posttraumatic trigeminal neuropathy*.
- By convention, the term *postherpetic neuralgia* is used for either neuralgic or neuropathic facial pain starting in an area with active herpes zoster rash and persisting for more than 3 months.
- Brain MRI is not adequate for numb chin syndrome as it may not visualize the mandible and may miss a malignancy located there.
- Stabbing ear pain may be referred along six nerves with overlapping dermatomes: the auriculotemporal nerve, lesser occipital nerve, great auricular nerve, nervus intermedius, glossopharyngeal nerve, and vagus nerve.
- Brain MRI is not adequate for unexplained ear pain, as it cannot visualize many structures that radiate pain to the ear, such as the throat, cervical vessels, and thyroid.
- Glossopharyngeal neuralgia is provoked by swallowing, yawning, or coughing.
- Patients with lightheadedness, palpitations, or syncope with their glossopharyngeal neuralgia pain may require ambulatory ECG monitoring to look for an associated bradyarrhythmia.
- Similar to trigeminal neuralgia, glossopharyngeal neuralgia may be related to neurovascular compression or other lesions along the nerve path.
- Either microvascular decompression or sectioning of the glossopharyngeal nerve (and sometimes vagus nerve rootlets) is considered a reasonable first-line treatment for medically refractory glossopharyngeal neuralgia.
- Nervus intermedius neuralgia may present with stabbing pain deep in the ear triggered by cold wind or using a cotton swab in the ear canal.
- Nervus intermedius neuralgia may develop in the setting of classic Bell's palsy or Ramsay Hunt syndrome (herpes zoster affecting the ear and facial nerve).
- Occipital neuralgia is typically described as shooting or stabbing pain that starts at the posterior skull base and radiates either to the vertex (greater occipital nerve) or over the ear toward the temple (lesser occipital nerve).
- If loss of sensation is present with occipital neuralgia, a secondary cause of pain should be considered.

ARTICLE 8: HEADACHE IN WOMEN

Jelena M. Pavlović, MD, PhD. Continuum (Minneap Minn). June 2021; 27 (3 Headache):686–702.

ABSTRACT

PURPOSE OF REVIEW:

Women are greatly overrepresented among patients seeking treatment for symptoms of headache pain in general and migraine in particular. Understanding the presentation of headache in women in relation to hormonal changes both during the menstrual cycle and throughout the life span is essential for appropriate diagnosis and treatment.

RECENT FINDINGS:

Although perimenstrual migraine attacks are generally without aura, the diagnosis of migraine with aura has been added to the headache classification for menstrual migraine to account for women with the diagnosis of migraine with aura who experience menstrual migraine attacks. Emerging knowledge regarding the differences between menstrual and nonmenstrual attacks, the variability of attack triggering within and between women, and the response of women with

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menstrually related migraine to new migraine drug classes is contributing to better understanding and more effective treatment of these particularly burdensome and refractory attacks. Given the burden of migraine, almost one-fourth of women with migraine avoid or delay pregnancy. Women who experience migraine during pregnancy are more likely to have a hypertensive disorder and stroke during pregnancy and/or delivery and the postpartum period. Treatment of headache in general and migraine in particular in pregnancy is challenging because of fetal and maternal risks; however, a 2021 systematic review suggests that triptans and low-dose aspirin may not be associated with fetal/child adverse effects and could be more strongly considered for headache treatment in pregnancy.

SUMMARY:

Headache in general and migraine in particular are extraordinarily common in women of reproductive age and fluctuate with hormonal changes and phases of life. Improved knowledge of the epidemiology, pathophysiology, and response to treatment of perimenstrual attacks is essential for more effective response to this most burdensome headache type. Treatment of headache in pregnancy remains challenging.

KEY POINTS

- Migraine is predominantly a disorder of women that is affected by fluctuations in ovarian hormones, affecting women throughout their lifetime by varying in frequency and burden with hormonal changes.
- Perimenstrual migraine attacks are thought to be due to estrogen withdrawal before menstruation.
- Although generally neuroexcitatory, estrogen appears to have a protective role in migraine, with migraine occurrence being related to low estrogen levels.
- Perimenstrual migraine attacks are more intense, more burdensome, and more refractory to treatment than nonmenstrual attacks, requiring a proactive approach. The predictive nature of perimenstrual attacks provides an opportunity for treatment.
- Perimenstrual migraine attacks are commonly migraine without aura, even in women who otherwise have attacks with aura.
- Clinicians and patients must recognize that menstruation can affect migraine in women in many different ways. To get a better sense of how menstruation and migraine are related in a given woman, a diary should be kept for a longer period of time than the currently recommended 3 months.
- Perimenstrual migraine can be treated with routine acute migraine treatment agents or with mini-prevention approaches in which triptans or nonsteroidal anti-inflammatory drugs are taken 2 times a day for about 5 days starting at the onset of perimenstrual migraine, typically 2 days before onset of menstruation.
- Perimenopause and the menopausal transition are marked by hormonal fluctuations and present an often-eventful time for women with migraine, who may experience an increase in both attack frequency and symptoms of perimenopause.
- Migraine is the most common primary headache disorder for which women seek help during pregnancy.
- Migraine frequency and symptomatology typically improve as pregnancy progresses, yet many women delay pregnancy for fear of migraine worsening or potential complications to themselves or the fetus. Education of women on the natural course of migraine in pregnancy is essential.
- New migraine phenomena during pregnancy are more likely to be migraine with aura than migraine without aura. Isolated auras can also occur. This is likely due to a high estrogen to progesterone ratio, which decreases the threshold for cortical spreading depression.
- Sleep deprivation and other stressors of early motherhood and infant care should be addressed and patients educated on biobehavioral approaches to this challenging time of a woman's life.
- Migraine is associated with higher rates of both medical and obstetric events; pregnant women with a history of migraine, particularly those with frequent attacks, should be considered at higher risk of adverse outcomes and should be monitored with a heightened index of suspicion.

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- The prothrombotic state of pregnancy adds additional risk to pregnant women with migraine who may already be prone to often-undiagnosed hypercoagulabilities. Women with migraine with aura should be followed by their obstetricians with extra caution.
- Triptans, which are the mainstay of acute headache treatment in nonpregnant and nonlactating women, have recent reassuring safety data, and select medications in this category may be considered in these populations.
- The majority of drugs currently used as first-line acute migraine treatment have not been associated with deleterious effects to the fetus during pregnancy exposure. As most women with migraine experience improvement in their headache during pregnancy, preventive treatments are generally not needed.
- Secondary headaches likely to present in pregnancy are generally due to a prothrombotic state (stroke and thrombosis) and states of elevated blood pressure (preeclampsia).

ARTICLE 9: HEADACHE IN CHILDREN AND ADOLESCENTS

Christina Szperka, MD, MSCE, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):703-731.

ABSTRACT

PURPOSE OF REVIEW:

This article reviews the approach to a child or adolescent with headache, the criteria for common diagnoses, and the evidence base for treatments.

RECENT FINDINGS:

The guidelines for acute and preventive treatment of migraine were updated in 2019. These guidelines summarize the available evidence and outline the questions that should be addressed in future research. The US Food and Drug Administration (FDA) approval of several new classes of drugs and devices to treat adult migraine in the past few years has resulted in ongoing or planned pediatric trials.

SUMMARY:

Headache is a common symptom in children, and it is important to take a detailed history and perform a thorough physical examination to make the diagnosis. Nearly 1 in 10 children experience recurrent headaches due to migraine, which cause significant impairment in school performance and quality of life. The acute and preventive treatments that are currently available will help at least two-thirds of children with migraine, and several trials of new therapies offer hope for the future.

KEY POINTS

- Headaches are a very common and disabling problem for children and adolescents. Globally, nearly 60% of children and adolescents experience significant headache, and 7.7% to 9.1% have migraine.
- Children with migraine miss more school than their peers and have impaired school performance and impaired quality of life, similar to that of children with rheumatoid arthritis or cancer. This disability is complicated by the fact that migraine is a silent disease; no outward findings are visible, so the child's report of pain may be doubted, leading to shame and frustration.
- Migraine is the leading cause of disability worldwide for older adolescents and young adults.
- Children may not volunteer other symptoms that come with headache, so they should be explicitly and concretely asked.

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- Studies have demonstrated that adverse experiences in childhood (financial stress; physical, emotional, or sexual abuse; parental divorce; death; mental illness; or addiction) predispose to headache in childhood as well as later in life.
- It is important to know what the child does not have as well as what the child does have. Life-threatening causes such as brain tumors occur in approximately 2% to 3% of children who present to the emergency department for headache and in about 1% of children with headache seen in primary care.
- Several studies support that neuroimaging is unnecessary for children with stable frequency of headaches, the absence of concerning features, and a normal neurologic examination.
- Migraine is a primary headache disorder characterized by recurrent (at least five) episodes of moderate to severe pulsating head pain lasting hours and accompanied by nausea/vomiting and sensitivity to light and sound.
- Migraine prevalence and features vary from childhood to adolescence and from boys to girls. Migraine affects approximately 5% of boys and girls by the age of 10, 7% of girls and 5% of boys up to age 15, and 10% of girls and 6% of boys by the age of 20.
- Tension-type headache occurs in 10% to 24% of children and adolescents but does not usually bring the child to medical attention because the attacks are mild and cause little disability.
- In population-based self-report studies, at least 1.5% of children report headaches several times per week or daily.
- All children with migraine should receive an acute treatment plan to be used at the start of an episode that includes a school note permitting the child to be excused from class at symptom onset to hydrate, take an acute medication, and rest before returning to class.
- Menstrual migraine can be particularly disabling and difficult to treat, with the added difficulty of irregular menstrual cycles making prediction more difficult for adolescents.
- Consistent lifestyle habits may help to minimize migraine triggers and should be discussed with all patients.
- Factors outside the child's control may preclude the development of healthy lifestyle habits, including school start time, homework, and work schedules of parent(s)/guardian(s). Even when children intend to follow the advice, adherence is difficult. Furthermore, little evidence is available to guide which specific changes actually impact headache frequency.
- Preventive treatment should be considered in all children who have frequent headaches or significant headache-related disability, or both.
- High placebo response in trials limits the ability to demonstrate efficacy of a medication. However, in clinical practice, placebo response can be beneficial, as the goal is patient improvement without harm. The guidelines recommend consideration of topiramate, propranolol, and amitriptyline combined with cognitive-behavioral therapy, which was demonstrated to be superior to amitriptyline plus headache education.
- Nutraceuticals were not reviewed in the current guidelines for pediatric migraine prevention, but some have evidence of benefit and safety and are commonly used by patients even before they are recommended by clinicians.
- Children with recurrent headaches have approximately double the likelihood of recurrent headaches in adulthood and also have increased likelihood of having other physical symptoms and psychiatric comorbidities.
- Children with migraine who seek care, receive a diagnosis, and take appropriate treatments have at least a two-thirds chance of significant and sustained improvement.
- Recurrent headaches are common in children and adolescents. The most common cause, migraine, is underdiagnosed and undertreated. Many unanswered questions about the "correct" approach to migraine treatment for children and adolescents remain.

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ARTICLE 10: CLINIC-BASED PROCEDURES FOR HEADACHE

Matthew S. Robbins, MD, FAAN, FAHS. Continuum (Minneap Minn). June 2021; 27 (3 Headache):732-745.

ABSTRACT

PURPOSE OF REVIEW:

Headache disorders are common and disabling, and many therapies that are effective and safe are procedural.

RECENT FINDINGS:

After pivotal clinical trials, onabotulinumtoxinA has become an established preventive therapy for chronic migraine; it is better tolerated than many other treatments and may be useful for other headache disorders. Peripheral nerve blocks, especially greater occipital nerve blocks, have amassed evidence from randomized trials in the acute and short-term preventive treatment of migraine and cluster headache. Trigger point injections and sphenopalatine ganglion blocks have recent trials suggesting efficacy and safety in properly selected patients. Medical education initiatives are needed to train neurologists in these procedures to help manage the large population of patients with headache disorders who need them.

SUMMARY:

Evidence exists for the efficacy and safety of procedural therapies to be incorporated into neurology practice for the management of patients with migraine, cluster headache, and other headache disorders.

KEY POINTS

- In the periphery, the inhibitory effect of onabotulinumtoxinA may prevent the release of inflammatory substances important in migraine and pain, such as calcitonin gene-related peptide.
- One of the major benefits of onabotulinumtoxinA relative to other preventive therapies, particularly oral drugs, is its tolerability, which has been verified in comparative studies versus oral preventive agents.
- Although not specifically approved for these disorders, onabotulinumtoxinA has rationally been used in the same protocol for chronic headache disorders that are otherwise treated like chronic migraine if they feature the same headache phenotype, including chronic posttraumatic headache and new daily persistent headache.
- Peripheral nerve blocks for headache consist of injections of local anesthetic and, at times, steroids in accessible nerve branches on the head, including the greater occipital nerve, lesser occipital nerve, auriculotemporal nerve, supratrochlear nerve, and supraorbital nerve.
- Clinical data suggest that the improvement that patients receive from peripheral nerve blocks is not directly correlated to a simple local anesthetic effect, as the duration of analgesia generally far exceeds the duration of anesthesia.
- A steroid should be administered in addition to local anesthetics when greater occipital nerve injections are used for cluster headache (typically methylprednisolone, dexamethasone, or triamcinolone) based on the available evidence and guidelines. However, for migraine, the few studies performing direct comparisons of anesthetics alone versus anesthetics with steroids do not show added benefit.
- Although peripheral nerve blocks may be an excellent treatment option in pregnant women with migraine, ideally lidocaine or ropivacaine should be used as bupivacaine has more unpredictable pharmacokinetics and has been associated with maternal cardiac conduction abnormalities.

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- Trigger point injections involve the administration of anesthetics into myofascial structures that may serve as mechanical sites that evoke or perpetuate an underlying headache disorder, most commonly tension-type headache or migraine.
- The evidence for trigger point injections includes randomized controlled trials for tension-type headache and migraine, with the strongest evidence for frequent tension-type headache.
- The sphenopalatine ganglion is a reasonable target for blocks and neuromodulation as it is the key peripheral structure involved in the expression of cranial autonomic symptoms and plays an important role in the trigeminoautonomic reflex in trigeminal autonomic cephalalgias and migraine and in regulation of cerebral blood flow.

ARTICLE 11: SPONTANEOUS INTRACRANIAL HYPOTENSION

Shuu-Jiun Wang, MD. Continuum (Minneap Minn). June 2021; 27 (3 Headache):746–766.

ABSTRACT

PURPOSE OF REVIEW:

Spontaneous intracranial hypotension is a disorder caused by spinal CSF leakage. This article reviews the clinical presentation, diagnosis, and treatment of spontaneous intracranial hypotension.

RECENT FINDINGS:

The hallmark symptom of spontaneous intracranial hypotension is acute orthostatic headache; however, clinical presentations can be heterogeneous. New evidence shows that lumbar puncture is not always necessary or sufficient to establish the diagnosis. Some patients may have normal opening pressure, which suggests that insufficiency of CSF volume (hypovolemia) rather than CSF pressure might be the underlying mechanism. Several neuroimaging modalities can aid in diagnosis and localization of the CSF leakage, including brain MRI, spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Complications, such as subdural hematoma, can lead to a change in the headache pattern and potentially life-threatening consequences. Conservative treatments, such as fluid supplementation, can provide temporary relief; however, epidural blood patches, especially targeted ones, are more effective and definitive. For patients with refractory spontaneous intracranial hypotension, surgical repair of spinal CSF leakages should be considered.

SUMMARY:

Brain and spinal MRIs are important for the diagnosis and treatment of patients with spontaneous intracranial hypotension. Early treatment with epidural blood patches may be considered to shorten the disease duration and minimize the potential risk of complications.

KEY POINTS

- Spontaneous intracranial hypotension is a disorder related to spinal CSF leakage. Acute orthostatic headache is the most common clinical presentation, but some patients may present with nonheadache symptoms.
- The female to male ratio of spontaneous intracranial hypotension is about 2:1, and it typically occurs in patients in their midthirties to midfifties.
- Diagnostic investigations for spontaneous intracranial hypotension include postcontrast brain MRI and spinal neuroimaging, such as spinal MRI, CT myelography, digital subtraction myelography, and radionuclide cisternography. Lumbar puncture is not always necessary or sufficient for diagnosis.

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- Spinal CSF leaks can be classified as dural tear, meningeal diverticulum, or CSF-venous fistula. CSF-venous fistula is a direct communication between the spinal subarachnoid space and epidural venous plexus. The identification of CSF-venous fistulas requires dynamic CT myelography or digital subtraction myelography; spinal MRI is not capable of identifying them.
- Normal CSF pressure (>60 mm CSF) does not exclude the diagnosis of spontaneous intracranial hypotension. Insufficiency of intracranial CSF volume (ie, hypovolemia) may be more important in the pathophysiology of spontaneous intracranial hypotension.
- Brain neuroimaging findings in patients with spontaneous intracranial hypotension include cerebral venous-related signs and brain descent–related signs.
- The Monro-Kellie doctrine states that the sum of the volumes of brain tissue, vessels, and CSF within the skull is constant. The decrement of CSF volume during CSF leakage is compensated by the dilation of intracranial venous structures. Cerebral venous-related signs of spontaneous intracranial hypotension include diffuse pachymeningeal enhancement, the venous distension sign, and pituitary hyperemia (or pituitary enlargement).
- Brain descent–related signs reflect the downward displacement of brain structures or brain structural deformities in patients with spontaneous intracranial hypotension. Among these signs, closure of the midbrain-pons angle is associated with a poorer response to the first epidural blood patch. These neuroimaging findings are helpful not only for diagnosis but also for prediction of treatment response.
- Localization of spinal CSF leaks by spinal neuroimaging can provide clues for diagnosis and guide therapeutic interventions.
- Heavily T2-weighted magnetic resonance myelography can be used to visualize spinal CSF leaks; it was demonstrated to be comparable to the gold standard CT myelography. It is a noninvasive imaging technique and does not require IV or intrathecal contrast administration.
- Subdural hematoma is the most common complication of spontaneous intracranial hypotension, especially in patients who develop a change in their headache pattern.
- Purely conservative treatments for spontaneous intracranial hypotension (eg, fluid supplementation) are usually temporizing measures, and definitive treatment (eg, targeted epidural blood patches) is more effective. For patients with refractory spontaneous intracranial hypotension, surgical repair of the spinal leaks should be considered.

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Issue Overview

Headache, Volume 27, Number 3, June 2021

Continuum: Lifelong Learning in Neurology® is designed to help practicing neurologists stay abreast of advances in the field while simultaneously developing lifelong self-directed learning skills.

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Learning Objectives

Upon completion of this *Continuum: Lifelong Learning in Neurology* Headache issue, participants will be able to:

- Develop a systematic diagnostic approach to the patient with headache, differentiate secondary from primary headache disorders, and diagnose some of the most common secondary and primary headache disorders
- Discuss the current understanding of the pathophysiologic basis of each phase of the migraine cycle
- Identify migraine-specific and nonspecific acute treatment options and when to consider novel agents and neuromodulation
- Describe pharmacologic and nonpharmacologic preventive treatments for migraine, outline their advantages and disadvantages, and identify when they should be considered
- Distinguish between and among primary and secondary presentations of trigeminal autonomic cephalalgias and apply evidence-based management strategies to practice
- Diagnose and manage uncommon primary headache disorders
- Discuss the differential diagnosis, evaluation, and management of neuralgic pain in the head and neck
- Describe the presentation and treatment of headache in women in relation to hormonal changes and throughout the phases of life
- Describe the differential diagnosis and treatment of headache disorders, especially migraine, in children and adolescents
- Describe the evidence, safety, risks, adverse effects, indications, and mechanisms for clinic-based procedures for headache
- Discuss the clinical presentations, diagnostic investigations, neuroimaging findings, and treatment strategies of spontaneous intracranial hypotension

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- Discuss the potential criminal and civil ramifications for not complying with the Stark Law and Anti-Kickback Statute

Core Competencies

This *Continuum: Lifelong Learning in Neurology* Headache issue covers the following core competencies:

- Patient Care
- Medical Knowledge
- Practice-Based Learning and Improvement
- Interpersonal and Communication Skills
- Professionalism
- Systems-Based Practice

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Robbins discusses the unlabeled/investigational use of onabotulinumtoxinA for new daily persistent headache and chronic posttraumatic headache.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Ailani reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Burch discusses the unlabeled/investigational use of amitriptyline and other tricyclic antidepressants, candesartan, cyproheptadine, gabapentin, lisinopril, memantine, metoprolol, venlafaxine and other serotonin norepinephrine reuptake inhibitors, and herbs and nutritional supplements for the preventive treatment of migraine.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Dodick reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Pavlović discusses the unlabeled/investigational use of medications for the treatment of menstrually related migraine and migraine and other headaches in pregnancy and lactation, none of which are approved by the US Food and Drug Administration for this indication.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Recober reports no disclosure.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Robertson discusses the unlabeled/investigational use of preventive treatments for trigeminal neuralgia, none of which are US Food and Drug Administration approved for this indication, except for carbamazepine.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Smith discusses the unlabeled/investigational use of medications for the treatment of primary headache disorders, none of which are approved by the US Food and Drug Administration.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Szperka discusses the use of various medications and devices for the prevention of migraine in children and adolescents. The only medications approved by the US Food and Drug Administration (FDA) for migraine in children and adolescents are topiramate for prevention of migraine (ages 12+); rizatriptan (ages 6+) and almotriptan, zolmitriptan nasal, and sumatriptan/naproxen (ages 12+) for acute treatment of migraine. The external vagus nerve stimulator, remote electrical neuromodulation, and single-pulse transcranial magnetic stimulation devices are FDA cleared for use in adolescents. All other medications and devices discussed in this article are unlabeled/investigational in children and adolescents.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Wang discusses the unlabeled/investigational use of theophylline for the treatment of postdural puncture headache.

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