

Diagnosing and Managing Headaches

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed, and delivered educational programming that appeals to both a medical and lay audience. (A complete biography appears at the end of this course.)

Faculty Disclosure

Contributing faculty, John J. Whyte, MD, MPH, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John M. Leonard, MD
Jane C. Norman, RN, MSN, CNE, PhD
Abimbola Farinde, PharmD, PhD

Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for physicians and will be of interest to nurses, pharmacists, and other medical personnel who may encounter patients who complain of headaches.

Accreditations & Approvals



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NetCE designates this continuing education activity for 12 hours for Alabama nurses.

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Special Approvals

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Course Objective

Given the common and difficult diagnoses associated with headaches, the purpose of this course is to educate the healthcare professional about the epidemiology and treatment of the various types of headaches so they may make early and accurate diagnoses, begin effective treatment, and/or refer patients to a specialist when necessary.

Learning Objectives

Upon completion of this course, you should be able to:

1. Illustrate the epidemiology and economic impact of headaches.
2. Demonstrate the pathophysiology of headaches.
3. Recognize the signs and symptoms of headaches, focusing on history and physical exam, and discuss the role of an interpreter in assessing non-English-proficient patients.
4. Identify the appropriate imaging modalities for headaches and their specific indications.
5. Describe the epidemiology, diagnosis, and treatment of migraine headaches.
6. Differentiate the signs and treatments for cluster and tension headaches.
7. Identify the secondary causes of headaches.
8. Compare and contrast the differences between acute and chronic headaches.
9. Recognize indications for specialist referral.
10. Analyze medico-legal issues surrounding headache diagnosis and management.

Pharmacy Technician Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology, pathophysiology, and general work-up of headaches.
2. Compare and contrast various types of primary and secondary headaches.
3. Discuss referral and medico-legal issues associated with headache.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Headaches are considered one of the most common types of pain and one of the most frequent causes of presentation to physician offices and clinics. Nearly 50 million adults seek treatment from physicians each year related to headache pain [1; 2]. As a result, headaches represent a significant cause of morbidity. It has been estimated that headaches result in billions of dollars in expenses, job absenteeism, and decreased annual productivity. They also result in decreased quality of life. Coping with a chronic headache disorder may predispose the individual to other illnesses. For example, depression is three times more common in people with migraine or severe headache than in healthy individuals [3]. A clear understanding of the types and causes of headache pain is essential for physicians and other healthcare providers to adequately address and manage the patient with headaches.

Headaches may be categorized as either primary or secondary. Most headaches are primary in origin—this includes migraine, cluster, and tension headaches. Secondary headaches, which are secondary to another cause (e.g., trauma, infections) are fewer in number; however, because most of the secondary causes have been well studied, secondary headaches generally can be effectively treated. Before assuming a diagnosis of primary headache, it is necessary to rule out headaches secondary to an underlying cause. It is important to keep in mind that malignancy is fairly unusual, even though anecdotal reports of individuals who have been diagnosed with a brain tumor following a headache abound. Many imaging technologies have become available to help in the diagnosis of headaches. These include computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), and nuclear medicine studies. It is important that physicians understand the indications and limitations of each test so that patients are not put through unnecessary and/or costly procedures.

Several therapies exist to treat headaches. These include pharmacologic medications and non-pharmacologic interventions (e.g., alternative medicines and therapies). There are also new approaches to preventing headaches for those patients who are experiencing chronic headaches. Physicians and other clinicians should familiarize themselves with the latest evidence regarding diagnosis and management of headaches. International Headache Society (IHS) diagnostic criteria have been used throughout this course; however, it should be noted that changes to these specific criteria may be made in the future.

The following case study will be referenced throughout the text to illustrate the challenges of treating a patient who presents with a headache.

Mrs. T is an African American woman, 68 years of age, with a past medical history significant for type 2 diabetes, hypertension, hyperlipidemia, osteoarthritis, and coronary artery disease. She presents to the clinic with a chief complaint of “headache.” Mrs. T describes the headache as a dull pain that has been intermittent over the past several weeks. It is not localized to any particular area, but rather seems to be more diffuse. It does not radiate to the neck, back, or any other parts of the body. It first started about a month ago.

She has taken ibuprofen and aspirin sporadically with some relief. As the headache has been persistent over the past few weeks, she thought it was important to come in and be evaluated. She states that she has been looking up information on headaches on various health websites and she now thinks she needs a “brain scan.” She has no prior history or family history of migraines; she does report a history of what she considers to be some tension-type headaches in the past few years. She believes these are due to stress at work, as they usually resolve within a day with relaxation, rest, and ibuprofen. She has never been evaluated for these episodes. The patient also remarks that over the past several days she has occasionally felt a little dizzy and light-headed, but those symptoms have largely resolved.

She denies any confusion or loss of consciousness, but her daughter, who accompanies her to the clinic, states that Mrs. T had an episode about a week ago where she seemed disoriented in the morning for approximately an hour. According to the daughter, "Lately, Mom sometimes seems in a fog."

EPIDEMIOLOGY

Almost everyone experiences a headache at some point in their life. In fact, approximately three-fourths of all adults in the United States experience some type of headache each year. The prevalence of headache varies by gender, with women having a greater incidence of headaches than men. It has been estimated that nearly nine out of ten women, and seven out of ten men, have a headache at least once during her/his lifetime [4]. In developed countries, tension-type headache is more common in women, usually by a factor of about two to one [3].

In the overwhelming majority of cases, headaches are transient and benign. People simply treat the headache with either rest and/or relaxation, or they utilize various over-the-counter analgesics. In fact, the public spends more than \$2 billion annually on over-the-counter medications to treat headaches [5]. Less than 5% of adults with headaches actually seek medical attention. Even with this small percentage, however, headaches are one of the most common complaints addressed by primary care physicians and clinicians and represent the reason for nearly 3% of all visits to the emergency department [1].

People typically seek medical care when they have increased headache frequency, an unusually intense headache, or persistent symptoms. Headaches can be one of the most difficult and challenging disorders to accurately diagnose and treat, so it is important for physicians and other clinicians to become familiar with the latest evidence on headache diagnosis and management.

ECONOMICS

Headaches are a costly condition. It has been estimated that headaches are responsible for nearly 30 million days of lost productivity, both in terms of lost days at work, as well as decreased effectiveness while at work. Headaches cost an estimated \$18 billion in both direct and indirect expenditures yearly. Most costs are indirect as the majority of headache sufferers do not seek medical attention [2; 7; 8; 9].

Although migraine is more disabling than tension-type headache, tension-type headache is more common. Each year, more than 70% of the global population has episodic tension-type headache and 1% to 3% has chronic tension-type headache (i.e., headache occurring at least 15 days per month). The World Health Organization (WHO) has confirmed that the problem of lost productivity in the workplace is worldwide, with headache disorders being the third most common cause of years lost to disability and migraine alone being the sixth most common cause [2; 3; 6; 10].

Headaches also represent a significant socioeconomic burden. Along with lost and reduced work, headaches also affect other activities, such as one's ability to perform effectively in school or enjoy time with family and friends. In essence, headaches reduce the quality of life.

BASIC PATHOPHYSIOLOGY

The pathophysiology of headaches is multifactorial and complex. When lesions of the brain cause headache (e.g., mass, fluid, hemorrhage), they do so by involving pain-sensitive structures inside the skull, such as arteries at the base of the brain, the dura area blood vessels, and certain cranial nerves (e.g., CN V, VII, IX, X) that carry pain fibers. In addition, the external structures of the head are all pain-sensitive and give rise to a variety of headaches.

TYPES OF HEADACHES

As noted, headaches may be categorized as either primary or secondary in nature. Primary headaches are pure headache syndromes, meaning they are self-originating and not triggered or produced by other disorders. Primary headaches include migraine, cluster, and tension-type headaches [11]. Nearly 90% of all headaches are primary in nature [12]. Although migraine headaches receive a great deal of press in medical and lay literature, of the primary headaches, tension-type is the most common, followed by migraines, and then cluster [13]. It is important to note that primary headaches are diagnosed only when other underlying disease processes have been eliminated.

Secondary headaches, as the name indicates, occur secondary to another cause (i.e., they are a symptom of other diseases). These may include vascular, traumatic, neoplastic, infectious, pressure, and metabolic disorders [11]. Secondary headaches account for only 10% of headaches. Although some causes of secondary headache are common, others are important to recognize because they are dangerous and may require specific treatment [12]. For example, patients with chronic tension headaches may present with an epidural hematoma, and patients with migraine may actually have a brain tumor. Primary and secondary headaches should not be considered mutually exclusive when evaluating a patient with headache. It is helpful to consider secondary headaches in terms of etiologic categories. Some of the more common causes of secondary headaches are as follows [13]:

Traumatic

- Epidural hematoma
- Subdural hematoma

Vascular

- Subarachnoid hemorrhage
- Giant cell arteritis
- Arterial dissection
- Stroke

Neoplastic

- Primary brain tumor
- Metastatic brain tumor

Infectious

- Meningitis
- Encephalitis
- Sinusitis
- Abscess

Pressure

- Hypertension
- Idiopathic intracranial hypertension

Metabolic

- Toxic ingestions (e.g., carbon monoxide, lead poisoning)

Other

- Syringomyelia
- Dental and myofascial
- Cervicogenic
- Medication overuse
- Herbal medications

WORK-UP OF HEADACHES

The work-up of headaches includes the patient's history and a thorough physical examination and may also include laboratory studies, imaging procedures, and a lumbar puncture.

ASSESSING HEADACHES IN PATIENTS WITH THE ASSISTANCE OF AN INTERPRETER

As a result of the evolving demographics in the United States, interaction with patients for whom English is not a native language is inevitable. Because patient history is such a vital aspect of the assessment of headaches, it is each practitioner's responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication

process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures, and assisting in promoting culturally competent communication and practice [15]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [16]. They are also well-versed in interpreting both the overt and the latent content of information without changing any meanings and without interjecting their own biases and opinions [16]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [17].

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options, and medication/treatment measures is being provided, the use of an interpreter should be considered.

HISTORY

As with any disease, history-taking is critical in determining the correct diagnosis. The goals of history taking are to classify the headache type(s) and screen for secondary headache. An inadequate history is the probable cause of most misdiagnoses of the headache type [11; 18; 19].

It is important to focus on the following characteristics when interviewing a patient who presents with a headache [13; 20]:

Position/Location

- Where on the head does the pain occur?
- Is the headache unilateral or bilateral?
- Does the pain radiate anywhere (e.g., neck, back, jaw)?
- Is the face involved?

Quality/Character

- What does the headache feel like? Is it pounding, throbbing, aching, piercing, squeezing, etc.?
- How intense is the headache on a scale of 1 to 10? Is it mild, moderate, severe, or incapacitating? Is it the worst headache one has ever had?

Frequency/Duration

- How often do the headaches occur?
- How long do they last?
- What time of day do the headaches occur?
- What time of year do the headaches occur?
- If the headaches are recurrent, what is the interval between headaches?
- What is the minimum, maximum, and usual duration?
- How long has this particular type of headache been affecting the patient?

Associated Factors

- Is there a fever?
- Any nausea, vomiting, congestion, flushing, arthralgia, depression, weight loss, etc.?
- Is there photophobia?
- Any neck stiffness?
- Any dental problems?

Aggravating Factors

- What makes the headache worse?
- Does head or body position make the headache better?
- Does coughing, sneezing, or bending affect the headache?
- Is the headache associated with menses?

Alleviating Factors

- What makes the headache better?
- Does ice or compression minimize the headache?
- Does a dark, cool room make it better?
- How does movement affect the headache?
- What types of medications have been tried? Have they been effective?

Environmental Exposures

- How does the environment affect the headache? For example, does exposure to bright light, loud noises, odors, cigarette smoke, temperature, foods, or alcohol affect the headache?
- Does the patient work around any metals or an industrial plant?

Associated Neurologic Symptoms

- Any visual, sensory, or motor abnormalities?
- Any dizziness or confusion?
- Any loss of consciousness?
- Is there any weakness?
- Does the patient exhibit ataxia?

Current and Past Medical History

- At what age did headaches first occur?
- What other medical conditions does one currently have (e.g., coronary artery disease, hypertension, depression, psychiatric disorder)?
- What are the current medications, including over-the-counter medications as well as supplements and herbal medicines? Is caffeine ingested on a regular basis?
- What medications have been recently terminated?
- Any recent trauma?
- Any recent falls?

Family History

- Does anyone else in the family have these types of headaches?
- Do any diseases or other medical conditions (e.g., cancer, stroke, diabetes, hypertension) run in the family?

Social History

- How are matters at home and at work?
- Is there any significant current stress?
- Are any illicit drugs used?
- Does the patient engage in unprotected sexual intercourse? In the past?

The above sample list of questions may seem daunting, especially in the context of a brief office visit. However, it is critical that a detailed history be obtained. It may be more efficient to have a questionnaire available for patients to fill out while they are waiting, or even prior to the office visit.

Upon further questioning, Mrs. T denies any fever, nausea, or vomiting. She denies depression or weight loss. She has not had visual disturbances. She does not recall any environmental exposures. Her current medications include metformin, lisinopril, simvastatin, and celecoxib. She remarks that her job is going quite well, and she does not feel particularly stressed from work. She works as a senior account manager at a consulting firm.

She has not had any change in medications and does not use any herbs or supplements. She drinks two cups of coffee a day, and there has been no recent change in her coffee consumption. There is neither family history of headaches nor family history of cancer. Both parents died of heart disease. She does note that she recently tripped and fell outside (almost a month ago) while playing with her grandson, but denies any serious consequences from the fall other than a sore left wrist. She denies any residual weakness. She notes that she does not feel "quite 100%" but does not feel confused or "in a fog."

PHYSICAL EXAM

A thorough physical exam is necessary for all patients who present to either the physician's office or the emergency department with a headache. The goal of the history and physical evaluation is to rule out findings that may suggest a headache of secondary pathology [13; 18; 19; 20; 21; 22]. All parts of the physical exam are important, but consider paying particular attention to the following:

- **Vital signs:** Carefully check blood pressure, respirations, heart rate, and temperature. Determine whether the patient is orthostatic.
- **Skin:** Observe color and texture, and carefully inspect for any rashes, petechiae, bruising, or lesions.
- **Head, eyes, ears, nose, and throat (HEENT):** Note the size, symmetry, and shape of the head. Inspect for bruises, masses, and/or nodules while palpating the head and neck. Palpate the temporal arteries. Be sure to auscultate for bruits over the scalp, eyes, and carotids. Assess the temporomandibular joint for clicking. Check for nuchal rigidity. Palpate the thyroid gland. Determine any decreased arterial pulsations. Check for sinus tenderness, especially frontal and maxillary areas.
- **Eyes:** Check visual function and extra-ocular movements, specifically looking for ptosis or miosis. Perform funduscopy to evaluate disc margins, papilledema, and any evidence of retinal hemorrhages.
- **Oral cavity:** Check for decay, abscesses, loose teeth, etc.
- **Cardiac:** Listen carefully for murmurs or abnormal heart sounds.
- **Extremities:** Assess thoroughly range of motion.
- **Neurologic:** Assess all cranial nerves, muscle strength, reflexes, and cerebellar function. Consider performing the Mini-Mental Status Exam.

WARNING SIGNS OF SIGNIFICANT DISEASE

Although most headaches are benign, clinicians should be aware of the following “red flags” or warning signs that should prompt an immediate and exhaustive work-up and possible referral to an appropriate specialist for further assessment [5; 13; 20; 21; 23]:

- Onset in or after middle age (>50 years of age)
- Sudden onset, rapid time to peak headache intensity (i.e., seconds to five minutes)
- First or worst sudden, severe headache
- Accelerating pattern, progressively worsening
- Fever
- Seizure
- Change in level of consciousness
- Abnormal neurologic, physical, or systemic findings
- New headache in patients with cancer, immunosuppression, or pregnancy

On physical exam, Mrs. T's blood pressure is 135/82 mm Hg, heart rate is 78 BPM, respirations are 18/minute, temperature is 98 degrees, height is 5'5", and weight is 135 lbs. The physical exam is largely unremarkable. There are no masses appreciated, no petechiae noted, no sinus pain or tenderness, no scalp tenderness, and no neck stiffness. There are no visual defects and no focal neurologic deficits with the exception of minimal decrease in muscle strength in lower extremities bilaterally. She scored a 26 (maximum score: 30) on the Mini-Mental Status Exam, with some difficulty remembering three objects as well as performing serial 7s.

Given the patient's age and the fact that the headache has been persistent, a clinician should order a more extensive work-up. The patient seems to be dismissive of the minor fall, but this should be explored further. Although it would be easy to attribute this headache complaint to a tension-type headache, secondary causes should be excluded.

LAB STUDIES

In general, most headache diagnoses will be made based upon the history and physical exam [13; 20]. However, laboratory studies may aid in the diagnosis. For example, clinicians may want to measure basic serum chemistries, complete blood count with differential, liver function tests, and thyroid function tests. These tests will provide a general overview of the patient's health and help guide diagnosis and treatment choices.

A resting electrocardiogram (EKG) should be considered if the history or cardiac exam is abnormal or if the patient has signs of an arrhythmia. Some headaches may have a cardiac etiology, and some treatments for headaches may have an impact on cardiac function.

Mrs. T's laboratory tests are as follows:

Na 138; Cl 100; K 4.0; CO₂ 26; BUN 15; Creatinine 0.9; Glucose 125; Hgb 12.5; Hct 38; WBCs 5,000; Platelets 200,000; TSH 0.9; T3 120; ALT 30; AST 32; Alk phos 70; Total bili 1.0; LDH 120; GGT 22; ESR 35

EKG: normal sinus rhythm at 78 BPM; left axis deviation; evidence of old anterior infarct. No acute changes.

ELECTROENCEPHALOGRAM

Electroencephalogram (EEG) is not frequently used and not recommended in the routine work-up of headaches. It has minimal value in determining any structural causes of headaches. It may be useful, however, when patients present with encephalopathy, focal neurologic deficits, atypical aura symptoms, or altered consciousness [21; 22; 24].

LUMBAR PUNCTURE

In general, lumbar puncture is indicated when there is clinical suspicion of central nervous system (CNS) infection, cancer, hemorrhage, or conditions that result in a change in cerebrospinal fluid (CSF) pressure; it is not recommended in the routine evaluation of headaches [13; 21; 23]. Examples of indications include meningitis, encephalitis, idiopathic intracranial hypertension, meningeal

carcinomatosis, or subarachnoid hemorrhage [5; 25]. If an intracranial mass lesion is suspected, or if the patient has papilledema on fundoscopic exam, lumbar puncture should be deferred until after CT evaluation to reduce the possibility of cerebellar herniation [23; 25; 26].

When lumbar puncture is performed, it is helpful to measure the opening pressure and perform a complete analysis of CSF, including glucose, protein, and differential blood count. In addition, opening pressure, supernatant color, and latex agglutination are sometimes useful. CSF examination is helpful in diagnosing subarachnoid bleeding, infection, and high and low CSF pressure syndromes [27]. It is important to avoid a traumatic tap. Such a tap, which leads to bleeding, could make it more difficult in establishing the diagnosis of subarachnoid hemorrhage [5]. In addition, the procedure itself may actually cause a headache [28; 29]. This usually occurs 48 to 72 hours following the procedure if too much fluid has been removed [30].

IMAGING

In general, routine neuroimaging, such as CT, MRI, MRA, or positron emission tomography (PET), of people with headaches and normal physical examinations has a very low yield and is not considered to be cost-effective. However, it is important to remain cognizant of the strengths and weaknesses of each imaging modality when considering and ordering such studies [31; 32]. MRI may be more sensitive than CT for identifying clinically insignificant abnormalities. However, MRI may not be more sensitive for identifying clinically significant pathology that is relevant to the cause of headache [22].

CT scans may be performed either with or without contrast. Unless there is a contraindication to the use of contrast agents, most scans are performed with contrast in the diagnostic work-up of headaches. A contrast-enhancing CT scan can be an effective test for identifying several serious lesions that may be causing headaches [33; 34].

CT is usually obtained in the setting of trauma or the abrupt onset of headache [27]. Primary indications include acute head trauma, suspected acute intracranial hemorrhage, mental status changes, headache, acute neurologic deficits, suspected intracranial infection or hydrocephalus, brain herniation, and suspected mass tumor. It may also be used in cases in which MRI is primarily indicated but unavailable, contraindicated, or delayed [34].



According to the American College of Radiology, the imaging mode of choice for patients who present with sudden onset of severe headache (“worst headache of one’s life” or “thunderclap headache”) is CT without contrast.

(<https://acsearch.acr.org/docs/69482/Narrative>. Last accessed April 5, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

In general, CT scans are widely available, quickly performed, and well-tolerated by patients. The technology has been around for quite some time, and most patients are familiar with it [34]. In addition, there are “open” CT scanners that help minimize the feeling of claustrophobia some patients experience. This scan detects most space-occupying lesions such as brain tumors, subdural hematomas, and CNS abscesses. It can also show fluid from hydrocephalus and cerebral edema, and it can reveal bleeding and structural abnormalities such as some arteriovenous malformations. However, CT scanning can miss aneurysms, and it also does not provide adequate views of the sphenoid sinus. Adding “bone windows” on CT provides much better detection of skull fractures, especially as compared to plain films.

MRI is the diagnostic test of choice for most patients [27]. However, it is not as readily available as CT [34]. MRI is more sensitive for detecting lesions within the posterior fossa (specifically because of bony artifacts that limit CT’s visualization), pituitary area, paranasal sinuses, and leptomeninges [34; 35]. It has also proven effective

in identifying some otherwise occult tumors and infarcts. MRI is also more sensitive for detecting vascular abnormalities, although it is not as sensitive as CT in revealing early subarachnoid bleeding. In addition, special MRI images can evaluate problems with the orbit or optic nerve areas. When abnormalities of the cervical spine are suspected, MRI is the preferred imaging technique, especially compared to plain films. “Open” MRI scanners may be used to help diminish claustrophobia or to accommodate obese patients [34].

MRA is essentially an MRI of the blood vessels. MRA can be useful when suspecting circulatory causes of headache. For example, it provides increased sensitivity for unruptured aneurysms, as well as arterial stenosis. It is rarely useful, however, as a first-line study but rather helps to determine who may ultimately require an angiogram. This technology is not universally available. Many institutions also lack the appropriate staff for this procedure [32].

Plain films are rarely useful for diagnosing the etiology of headache unless CT and MRI are unavailable [34]. These films can demonstrate bony defects, such as fractures or other skeletal abnormalities, but usually there are other sources to obtain this data. In addition, the use of plain films for most cases of sinusitis is not usually cost effective in the work-up of headaches. In some institutions, nuclear medicine brain scans, or PET imaging scans, have been used with success as an ancillary procedure.

The choice of a specific imaging study depends on numerous factors, including clinical suspicion, availability of a given test, time necessary to perform the test, and the amount of time available to make a treatment decision. A patient should not undergo a test simply because it is available, but rather the information obtained from an imaging study should impact decision making. Ideally, one wishes to avoid additive tests, such as a situation in which an MRI is a better study (e.g., for posterior fossa infarcts), but a CT is ordered because it is more rapidly available.

The U.S. Headache Consortium has issued guidelines relating to neuroimaging in patients with nonacute headache. The guidelines include three consensus-based general principles of management [22]:

- Testing should be avoided if the test results will not lead to a change in management.
- Testing is not recommended if the individual is not significantly more likely than anyone else in the general population to have a significant abnormality.
- Testing that normally may not be recommended as a population policy may make sense at the individual level, resources notwithstanding. For example, exceptions might be made for patients who are disabled by their fear of serious pathology.

The Consortium additionally has issued the following specific recommendations regarding neuroimaging [22]:

- Neuroimaging should be considered in patients with nonacute headache and an unexplained abnormal finding on the neurologic exam.
- Neuroimaging is not usually warranted for patients with migraine and normal neurologic examination. For patients with atypical headache features or patients who do not fulfill the strict definition of migraine, or have some additional risk factor(s), a lower threshold for neuroimaging may be applied.

Relating to CT and MRI, the panel did find that MRI appears to be more sensitive in finding white matter lesions and developmental and/or venous anomalies than CT. However, it noted that this difference had little clinical relevance, and thus did not make any recommendations on preferred testing methods in the evaluation of headaches [22].

PRIMARY HEADACHES

As noted earlier, there are three types of primary headaches: migraine, cluster, and tension-type (*Table 1*).

MIGRAINE HEADACHES

A migraine is a type of neurovascular headache that is initiated by a neurologic event that causes vasodilation, which in turn is interpreted by the brain as pain. It is important to realize that the event that initiates this cascade is not dilation of the blood vessels in the brain but rather a primary neural event. The exact neural event that is occurring is not completely understood, but it seems to involve the dysfunction of an ion channel in the brain stem that normally controls sensory input and exerts influences on cranial vessels [36]. Migraine is believed to have a genetic basis [3].

Adults with migraine headache describe episodic attacks with pain of moderate-to-severe intensity that are often throbbing in quality, unilateral in position, and aggravated by physical exertion. Migraines are usually associated with nausea, vomiting, and sensitivity to light and sound. Nausea is the most common characteristic. The duration of these attacks, when not treated, may last anywhere from 4 to 72 hours [3].

The prevalence of migraine headache in developed countries is in the range of 16% to 25%, with women approximately two to three times more likely to have migraines than men [3; 6; 37]. In children, however, prevalence is equal between males and females. It is during adolescence that a female predominance occurs. The incidence of migraine is highest among individuals 35 to 45 years of age, but it may affect much younger people, including children [3; 38]. The prevalence of migraine in children has increased in the past 20 to 30 years. Environmental factors may precipitate migraine attacks in persons with a predisposition to migraine [38].

CHARACTERISTICS OF PRIMARY HEADACHES			
Characteristics	Migraine	Cluster	Tension
Position	Unilateral	Unilateral	Bilateral
Quality	Throbbing, pulsating, pounding; moderate to severe	Burning, piercing, sharp; severe	Tightness, aching, pressure; mild to moderate
Radiation	None	None	None
Duration	4 to 72 hours	15 to 180 minutes	30 minutes to seven days
Triggers	Foods, oversleeping, stress, depression, decreased barometric pressure, hormonal variations, caffeine withdrawal	Alcohol, change in temperature, breezes on the face, a change in physical, mental, or emotional activity	Stress
Associated symptoms	Nausea, vomiting, photophobia	No nausea, vomiting, or photophobia	No nausea/vomiting; occasional photophobia or phonophobia
Therapies	Lifestyle modification, biofeedback, acupuncture, medications, exercise, consistent sleep schedule	100% oxygen, medications	Hot/cold packs, ultrasound, exercise, consistent sleep schedule, medications
Source: Compiled by Author			Table 1

Data from the American Migraine Study II showed that the overall prevalence of migraine was higher in whites than in blacks, highest in middle life, and inversely related to household income. The frequency of severe headache was similar for males and females, with 62% reporting one or more severe headaches per month, and 36.8% reporting one to three severe headaches per month. The results of this and other studies have also indicated that the burden of migraine in the United States remains substantial (more than \$13 billion per year) due to misdiagnosis, underdiagnosis, and improper treatment [37; 38; 39; 40; 41].

A study published in 2003 has suggested the use of the following three screening questions to identify migraine sufferers. A “yes” response to two of the questions can effectively identify patients who have true migraines [42]:

- Has a headache limited your activities for a day or more in the last three months?
- Are you nauseated or sick to your stomach when you have a headache?
- Does light bother you when you have a headache?

Although this set of questions has been validated, more studies are still necessary to determine its general applicability. It may be helpful, however, in identifying complicated cases. Additionally, the IHS has incorporated the criteria into their guidelines.

Migraine headaches are essentially a syndrome with a range of neurologic and non-neurologic characteristics. They are classified into two major categories (*Table 2* and *Table 3*):

- Migraine without aura
- Migraine with aura

These were formerly referred to as “common” and “classic” migraines [43].

Migraines without aura are migraine headaches without an associated neurologic disturbance. Typical characteristics include headache of unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. These are the most common type of migraine, accounting for nearly 80% of migraines. They have a higher average attack frequency and are usually more disabling than migraine with aura [43].

CRITERIA FOR DIAGNOSIS OF MIGRAINE WITHOUT AURA

At least five attacks with the following characteristics:

1. Episodic attacks of headache lasting 4 to 72 hours
2. At least two of the following headache characteristics:
 - Unilateral location
 - Throbbing or pulsating quality
 - Pain of moderate or severe intensity
 - Aggravated by or causing avoidance of routine physical activity
3. At least one of the following symptoms during headache:
 - Nausea
 - Vomiting
 - Photophobia
 - Phonophobia
4. Not better accounted for by another diagnosis

Source: [43]

Table 2

CRITERIA FOR DIAGNOSIS OF MIGRAINE WITH AURA

At least two attacks not better accounted for by another diagnosis (particularly transient ischemic attack) fulfilling two criteria:

1. One or more of the following fully reversible aura symptoms:
 - Visual
 - Sensory
 - Speech and/or language
 - Motor
 - Brainstem
 - Retinal
2. At least two of the following four characteristics:
 - At least one aura symptom spreads gradually over five or more minutes and/or two or more symptoms occur in succession.
 - Each individual aura symptom lasts 5 to 60 minutes.
 - At least one aura symptom is unilateral.
 - The aura is accompanied, or followed within 60 minutes, by headache.

Source: [43]

Table 3

Migraines with aura, seen in approximately 15% to 20% of patients with migraine, are preceded or accompanied by transient focal neurologic symptoms that usually develop gradually over 5 to 20 minutes and last for less than 60 minutes [43]. Aura symptoms may be sensory, motor, or visual but most commonly present as visual symptoms. The visual symptoms tend to manifest as scintillating scotomata, such as flashing lights, zigzags of light, and small blind spots [13]. On average, they last 20 to 30 minutes.

Premonitory symptoms occur hours to a day or two before a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, irritability, neck stiffness, sensitivity to light or sound, nausea, blurred vision, yawning, and pallor. The IHS has recommended that the terms “prodrome” and “warning symptoms” be avoided because they are often mistakenly used to include aura [43]. Migraines with aura have been additionally subdivided into typical migraine, migraine with brainstem aura, hemiplegic migraine, and retinal migraine [43].

Additional types of migraines include episodic syndromes that may be associated with migraine, chronic migraine, complications of migraine, and probable migraine [43].

Familial hemiplegic migraine (FHM) is a type of hemiplegic migraine that is often earlier in onset than typical migraine, frequently beginning in the first or second decade. These attacks are characterized by visual disturbance, dysphasia, and severe unilateral weakness and may also be accompanied by unilateral numbness of the face, arms, and legs. The attacks tend to be prolonged and may last for hours or days [43; 44]. The diagnosis of FHM requires at least one affected first-degree or second-degree relative, and most individuals diagnosed with FHM have an affected parent [44]. Three subtypes of FHM have been identified: FHM1, FHM2, and FHM3 [44]. In approximately 50% of FHM1 families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks. FHM is often mistaken for epilepsy and (unsuccessfully) treated as such [43]. Molecular genetic testing is available for the three genes known to be associated with FHM [44]. In many cases, FHM1 additionally has brainstem symptoms [43].

Sporadic hemiplegic migraine is migraine with aura including motor weakness but no affected first- or second-degree relative. Sporadic cases occur with approximately the same prevalence as familial cases and have similar clinical characteristics. Sporadic cases require neuroimaging and other tests to rule out other cause. A lumbar puncture is also necessary to rule out pseudomigraine with temporary neurologic symptoms. This condition is more prevalent in males and is often associated with transient hemiparesis and aphasia [43].

Migraines with brainstem aura (previously referred to as basilar migraines) occur in adolescence and young adulthood. The origin of the neural event is in the brain stem; as a result, the basilar artery dilates and causes a variety of bilateral aura symptoms. The aura of these migraines includes two or more of the following symptoms: diplopia, vertigo, tinnitus, hypoacusis, ataxia, and decreased level of

consciousness [43]. These migraines are associated with a slightly increased risk of migrainous infarction when compared to other migraine types.

Retinal migraine is a type of migraine with aura associated with repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness [43]. Diagnosis is confirmed with a clinical visual field examination and/or the patient's drawing (made after clear instruction) of a monocular field defect.

Approximately 3% to 5% of patients with migraine experience an aura without headache. This presentation, formerly known as a "migraine equivalent," tends to occur in older individuals who have had a history of migraines with aura in their earlier years [45]. They predominantly occur in men of advanced age.

The symptoms of a migraine do not always end with resolution of the headache. Following a migraine, individuals tend to have continued symptoms. These symptoms are quite varied in scope and may manifest as impaired concentration, fatigue, irritability, listlessness, muscle weakness, anorexia, food cravings, and euphoria. Keep in mind that migraine headaches are quite heterogeneous and vary widely in scope. Not only do they vary from patient to patient, they even vary in the same individual [46].

Triggers

Many different factors work to trigger migraines. These factors vary greatly from one individual to another and often no precipitating events can be clearly identified. Trigger factors increase the probability of a migraine attack in the short term (i.e., usually in less than 48 hours) in a person with migraine. Some of the more common triggers include stress, sleep disturbances, depression, low barometric pressure, food, hormonal variations, and caffeine withdrawal. Some trigger factors have been reasonably well studied epidemiologically (e.g., menstruation) or in clinical trials (e.g., chocolate, aspartame); however, causal attribution in individual patients may be difficult [43].

For individuals who are not certain of what triggers their headaches, it may be helpful to recommend keeping a headache diary. This diary allows individuals to chronicle their headaches and document details, such as warning signs, time duration of headache, location of pain, intensity of pain, and treatment attempts/effects, along with details of their diet, sleep patterns, medications, stress, and menstrual cycle (if applicable). This is a useful tool in elucidating the relationship between events, environment, and migraines. The headache diary has been shown to improve diagnostic accuracy and allow a more precise judgment of medication consumption. It may also help in judging the quantity of two or more different headache types or subtypes, and it teaches the patient how to distinguish between different headaches.

Migraine headaches in premenopausal women often correlate with menses, when estrogen and progesterone levels precipitously drop. These same women, when on birth control pills, develop a similar headache pattern with initiation of their placebo pills, when estrogen and progesterone levels are low. It has been suggested that altering the schedule of birth control pills may significantly reduce the number and severity of the headaches; however, women who experience migraine with aura should not use a combined oral contraceptive pill [11; 47]. Despite the increased prevalence of headache and migraine in premenopausal women, migraine is underdiagnosed in this population [48].

Approximately two-thirds of women with migraines experience headache improvement during the course of a pregnancy [49]. Usually, symptoms during the first trimester determine whether pregnant patients will experience relief—if symptoms resolve during the first trimester, patients usually remain headache-free throughout the pregnancy; if symptoms persist during first the trimester, they usually remain throughout the pregnancy [13]. Keep in mind that although most headaches during pregnancy are typically migraine or tension, secondary causes should be ruled out.

People who are prone to migraines also find that caffeine, which can acutely help with headaches, may work to precipitate headaches if it is withdrawn after a period of continuous daily use. Many different foods contain chemicals that may act to initiate the headache cascade (*Table 4*).

In addition to determining what may trigger a headache, it is important to have an understanding of the impact of a headache on an individual's quality of life and productivity. One way to get a fast yet effective understanding is with the use of the validated questionnaire called the Migraine Disability Assessment Scale (MIDAS) (*Table 5*) [50]. The MIDAS was developed to measure headache-related disability and improve communication between patient and physician about the functional consequences of migraine. Scores on the MIDAS have been highly correlated with physician judgments about the severity of illness and need for treatment. It may play a role in improving the care of patients with migraine and other types of headache [51].



The Institute for Clinical Systems Improvement asserts that migraines occurring in association with menses and not responsive to standard cyclic prophylaxis may respond to hormonal prophylaxis with use of estradiol patches, creams, or estrogen-containing contraceptives.

(<https://www.icsi.org/wp-content/uploads/2019/01/HeadacheRR.pdf>. Last accessed April 5, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

COMMON FOOD TRIGGERS	
Trigger	Causal Factor
Food	Chemical trigger
Cheese	Tyramine
Chocolate	Theobromine
Citrus fruits	Phenolic amines
Hot dogs, ham, cured meat	Nitrites, nitric oxide
Dairy products, yogurt	Allergenic proteins (casein)
Chinese food	Monosodium glutamate
Coffee, tea, cola	Caffeine
Artificial sweeteners	Aspartame
Wine, beer	Histamine, tyramine, sulfites
Source: Compiled by Author	

Table 4

MIGRAINE DISABILITY ASSESSMENT SCALE (MIDAS)
<ul style="list-style-type: none"> On how many days in the last three months did you miss work or school because of your headaches? How many days in the last three months was your productivity at work or school reduced by half or more because of your headaches? On how many days in the last three months did you not do household work because of your headaches? How many days in the last three months was your productivity in household work reduced by half or more because of your headaches? On how many days in the last three months did you miss family, social, or leisure activities because of your headaches? On how many days in the last three months did you have a headache? On a scale of 0–10, on average how painful were these headaches?
Source: [50]

Table 5

Treatment Goals

The goals of both pharmacologic and nonpharmacologic long-term migraine treatment are to [52; 53]:

- Reduce attack frequency, severity, and disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improve quality of life
- Avoid acute headache medication escalation
- Educate and enable patients to manage their disease to enhance personal control of their migraine
- Reduce headache-related distress and psychologic symptoms

Behavioral and physical interventions are used for preventing migraine episodes rather than for alleviating symptoms after an attack has begun. Although these modalities may be effective as monotherapy, they are more commonly used in conjunction with pharmacologic management [52].

Nonpharmacologic Treatment for Migraines

The cornerstone of nonpharmacologic therapy for treating migraine headaches involves empowering patients with knowledge. Educating patients about their diagnosis allows them to have a better understanding of what is occurring and what factors may be contributing to their headaches. Patients should be involved in formulating a management plan. Regular re-evaluation of therapy is also important [54; 55].

Migraine is a chronic neurologic disorder that may require patients to undergo some level of lifestyle change. Lifestyle modification is one of the most important aspects of nonpharmacologic therapy. Lifestyle modification includes dietary changes, stress management techniques, establishment of regular sleeping and eating habits, and moderate exercise. These may help ease both the severity and frequency of migraine headaches. After the early signs of headaches are identified, additional attempts may be made to further reduce symptoms.

As noted, patients' headaches are often precipitated by food triggers. Patient education includes teaching patients to recognize these triggers and then avoid them, which may help patients to become headache-free. A headache diary, as discussed previously, may help patients to identify these food triggers [20; 55]. Consultation with a nutritionist may help patients find alternative foods. In addition, patients should be counseled to maintain a regular diet and avoid skipping meals. Moreover, they should consume at least eight 8-ounce glasses of water daily [56].

It has been estimated that more than 85% of headache patients use complementary and alternative medicine (CAM) therapies. Some CAM techniques have been shown to be beneficial and effective in preventing migraine. Behavioral interventions (e.g., biofeedback, stress management, psychotherapy) should be part of the standard

of care for a difficult migraine patient, especially when stress is a major trigger or when analgesics are being overused [13; 55]. Stress management techniques, including biofeedback and acupuncture, have been successful for some patients and have been recommended to help patients reduce the frequency and severity of migraine headache [11; 23]. These techniques are most successful with a motivated patient, especially one who is trying to avoid pharmacologic therapy. It should be considered, particularly for pregnant patients and those not easily treated with pharmacologic agents. However, it is time-consuming and requires a commitment on the part of the patient [20].

Acupuncture is another therapy with which some patients have found success. It may be used as preventive management in patients with migraine and tension headache but should be used with caution in patients with severe bleeding disorders, who are pregnant, or who wear a cardiac pacemaker [11; 23]. Available studies have suggested that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, with fewer adverse effects [57]. It can be a valuable nonpharmacologic tool and should be considered a treatment option for patients willing to undergo this treatment [58; 59; 60].

Sleep disturbances are a well-known cause of headaches [61]. Insomnia has been identified as a risk factor for tension-type headache, and sleep problems have been reported as a trigger of headaches [62]. Therefore, it is important for patients to maintain regular sleep habits. This involves going to sleep and awaking at about the same time every day. It also includes avoiding stimulants around bedtime and trying to receive at least six to eight hours of sleep daily [13; 56]. Patients should avoid sleep fragmentation, if possible. Interestingly, patients with a family history of hypersomnia may also experience headache [63].

Moderate exercise has also been found to be helpful in decreasing headache frequency and intensity for some migraine patients [56; 64]. Exercise that decreases stress and concurrently improves cardiovascular fitness seems to be the most effective. Simply walking 30 minutes per day during a lunch hour or after work can make quite a difference in terms of decreasing headache frequency. Other migraine patients have found some relief with regular yoga classes, especially those that focus on breathing and relaxation. At a minimum, patients should be encouraged to engage in an exercise program, especially because exercise improves overall health. Ideally, patients should exercise 30 to 60 minutes, at moderate intensity, at least three times per week.

All patients who smoke should be encouraged to quit smoking. Nicotine is a well-known vasoconstrictor, and carbon monoxide is a vasodilator. Combined they can trigger the migraine process. Therefore, current smokers should be counseled to quit.

Often, a multidisciplinary approach can be effective for some patients and may lead to a decrease in migraine pain, frequency, and intensity; improved overall health status and quality of life; and improved functional status [65]. Treatment choices should be based on the severity and frequency of the headache as well as on associated symptoms and comorbidities [24].

Pharmacologic Treatment for Migraines

Unfortunately, even if a patient has some success with nonpharmacologic options, many will still need medications. Some data have suggested an enhanced effect with a combination of treatments [66].

The pharmacologic options for migraine headache fall into two main categories: acute attack treatment (also known as abortive treatment) and preventive therapies.

Acute Attack Treatments

The U.S. Headache Consortium has identified goals for the successful treatment of acute attacks of migraine [53]:

- Treat attacks rapidly and consistently without recurrence.
- Restore the patient's ability to function.
- Minimize the use of back-up and rescue medications.
- Optimize self-care and reduce subsequent use of resources.
- Be cost-effective for overall management.
- Have minimal or no adverse events.

To meet these goals, the Consortium has recommended that clinicians [52; 53; 54]:

- Educate migraine sufferers about their condition and its treatment; encourage patients to participate in their own management.
- Use migraine-specific agents (i.e., triptans, dihydroergotamine [DHE]) in patients with moderate or severe migraine or whose mild-to-moderate headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) or combinations such as aspirin plus acetaminophen plus caffeine. Note: The American Academy of Family Physicians/American College of Physicians-American Society of Internal Medicine has recommended the use of migraine-specific agents only when a first-line therapy of NSAIDs (e.g., aspirin, ibuprofen, naproxen sodium, acetaminophen-aspirin-caffeine combination) has failed.
- Select a non-oral route of administration for patients with migraine associated with severe nausea or vomiting.
- Consider a self-administered rescue medication for patients with severe migraine who do not respond to (or fail) other treatments.
- Guard against medication-overuse headache.

The goal of acute attack treatment should be for the patient to be pain-free within two to four hours. The patient should be able to return to full function after this time. In addition, the headache should not return within 24 hours of being pain-free. A stepwise approach is typically recommended [38]. This approach suggests that patients are to be treated with the safest, least expensive medication during the first migraine attack, and subsequently progress to more expensive medications for subsequent attacks, if the initial ones are not effective [53; 67]. As a general rule, medications used to alleviate the pain of a migraine attack should be taken early after onset, when the headache is still mild, if possible.

In 2015, the American Headache Society (AHS), in cooperation with the American Academy of Neurology (AAN), provided an updated assessment of the evidence for individual pharmacotherapies for acute attack treatment (**Table 6**). This assessment will form the basis of new treatment guidelines [173]. The assessment was based on a systematic review of clinical trials published from 1998 to 2013 that compared the efficacy of various acute attack treatments versus placebo. It did not compare the efficacy of individual therapies [173]. Where no new studies for a particular drug were found, classifications were based on previous AAN guidelines.

Acute attack pharmacologic options are used at the onset of the attack. They can be divided into nonspecific and specific drugs. The nonspecific therapies are single or combination analgesics. Routes of administration include oral, nasal, parenteral, and rectal. Appropriate situations for use, including potential side/adverse effects, drug-drug interactions, and patient-specific contraindications, should be addressed. Opioids are generally avoided, if possible, due to concerns about tolerance and dependence [54; 173].

The more common analgesics used include acetaminophen, NSAIDs (e.g., aspirin, ibuprofen, naproxen sodium), and narcotics (e.g., oxycodone, morphine sulfate) [38]. Acetaminophen-aspirin-caffeine combination may also be used to treat migraines. The evidence for efficacy is most consistent for aspirin, ibuprofen, naproxen sodium, and the acetaminophen-aspirin-caffeine combination. Acetaminophen alone has been found to be ineffective [53; 66; 173].

In the 2000 AAN guidelines, the NSAID diclofenac was considered “probably effective” for the acute treatment of migraine. Class I studies conducted since that time resulted in the agent being reassessed by the AHS as “effective” (Level A) [14; 176; 177].

The nonspecific therapeutic drugs may be used to relieve the pain through many different mechanisms, although most typically work by dulling pain receptors. These are usually considered first-line therapeutic options for many individuals who find these adequate in obliterating headaches [54]. In order to increase the likelihood of efficacy it is important that these are taken as early as possible in the headache cycle [38]. In addition, a large single dose tends to be more effective than repeated smaller doses. When any of these medications are used, many clinicians add an antiemetic or pro-motility agent to increase the chance of absorption, especially during an attack when nausea is a major component [53].

Over-the-counter analgesics are often effective in treating migraine. In an observational study of the impact of over-the-counter analgesics for migraines on a patient’s quality of life, nearly 100 patients who used over-the-counter medications, such as acetaminophen-aspirin-caffeine combination, and who also received educational migraine materials over a four-month period completed a general health status questionnaire. At the end of the study, patients reported significant improvements in several quality-of-life measures and increased frequency of relief [69].

AHS EVIDENCE ASSESSMENT OF ACUTE MIGRAINE PHARMACOTHERAPIES	
Drug Class	Specific Agents and Doses
Level A (Effective)	
Analgesics	Acetaminophen 1,000 mg (for non-incapacitating headache)
Ergots	DHE nasal spray 2 mg ^a
NSAIDs	Aspirin 500 mg ^a Diclofenac 50 mg, 100 mg Ibuprofen 200 mg, 200 mg Naproxen 500 mg, 550 mg ^a
Opioids	Butorphanol nasal spray 1 mg ^a
Triptans	Almotriptan 12.5 mg Eletriptan 20, 40, 80 mg Frovatriptan 2.5 mg Naratriptan 1, 2.5 mg ^a Rizatriptan 5, 10 mg ^a Sumatriptan (oral 25 mg, 50 mg, 100 mg ^a ; nasal spray 10 mg, 20 mg; subcutaneous 4 mg, 6 mg) Zolmitriptan (nasal spray 2.5 mg, 5 mg; oral 2.5 mg, 5 mg ^a)
Combinations	Acetaminophen/aspirin/caffeine 500 mg/500 mg/130 mg ^a Sumatriptan/naproxen 85 mg/500 mg
Level B (Probably Effective)	
Antiemetics	Chlorpromazine 12.5 mg IV ^a Droperidol 2.75 mg IV Metoclopramide 10 mg IV ^a Prochlorperazine 10 mg IV/IM ^a
Ergots	DHE 1 mg IV, IM, SC ^a Ergotamine/caffeine 1 mg/100 mg ^a
NSAIDs	Flurbiprofen 100 mg ^a Ketoprofen 100 mg Ketorolac 30–60 mg IV/IM
Other	Magnesium sulfate 1–2 g IV (for migraine with aura) Isometheptene 65 mg ^a
Combinations	Codeine/acetaminophen 25 mg/400 mg ^a Tramadol/acetaminophen 75 mg/650 mg
Level C (Possibly Effective)	
Antiepileptics	Valproate 400–1,000 mg IV
Ergots	Ergotamine 1–2 mg ^a
NSAIDs	Phenazone 1,000 mg
Opioids	Butorphanol 2 mg IM ^a Codeine 30 mg PO ^a Meperidine 75 mg IM ^a Methadone 10 mg IM ^a Tramadol 100 mg IV ^a
Steroids	Dexamethasone 4–16 mg IV
Other	Butalbital 50 mg ^a Lidocaine intranasal ^a

Table 6 continues on next page.

AHS EVIDENCE ASSESSMENT OF ACUTE MIGRAINE PHARMACOTHERAPIES (Continued)	
Drug Class	Specific Agents and Doses
Combinations	Butalbital/acetaminophen/caffeine/codeine 50 mg/325 mg/40 mg/30 mg ^a Butalbital/acetaminophen/caffeine 50 mg/325 mg/40 mg ^a
Level U (Conflicting or Inadequate Evidence)	
NSAIDs	Celecoxib 400 mg
Other	Lidocaine IV ^a Hydrocortisone 50 mg IV ^a
For an agent to be classified as Level A, it must be supported by at least two Class I studies (randomized controlled trials in the representative population). Level B requires one Class I study or two Class II studies (randomized controlled trials not meeting the standards of Class I), and Level C required one Class II study or two Class III studies (nonrandomized controlled studies). An agent was classified Level U when evidence to support its use was either conflicting or inadequate. ^a Based on 2000 American Academy of Neurology evidence review.	
Source: [173]	

Table 6

Ergotamines

The specific therapies include ergotamines and triptans. The ergotamines and triptans both work as vasoconstrictors. Ergotamine derivatives, although less expensive, are more nonspecific and tend to increase the likelihood of rebound headaches after their use [53; 67].

The U.S. Headache Consortium reviewed the results from 23 controlled trials of ergotamine tartrate, ergotamine-containing compounds, and ergostine-containing compounds and has recommended the following regarding the use of ergot alkaloids and derivatives, all of which are supported by the recent AHS evidence assessment of migraine pharmacotherapies [53; 173]:

- In the treatment of selected patients with moderate-to-severe migraine, ergot derivatives may be considered.
- Because of their inability to tolerate or take oral medication, patients with nausea and vomiting may be given DHE subcutaneous, IV, or intramuscular (IM). Initial treatment with DHE subcutaneous or IM is a reasonable choice when the headache is moderate-to-severe or an adequate trial of NSAIDs or other nonopioid analgesics has failed to provide adequate relief in the past. The

use of DHE IM or subcutaneous may be considered in patients with moderate-to-severe migraine.

- DHE IV plus antiemetics is an appropriate treatment choice for patients with severe migraine.
- The use of DHE nasal spray is an appropriate treatment choice and should be considered for use in patients with moderate-to-severe migraine. Because of their inability to tolerate or take oral medications, patients with nausea and vomiting may be given intranasal DHE. Initial treatment with DHE nasal spray is a reasonable choice when the headache is moderate-to-severe or an adequate trial of NSAIDs or other nonopioid analgesics has failed to provide adequate relief in the past.

Triptans

The triptans are serotonin 5-HT_{1B/1D} receptor agonists and act through three possible mechanisms: vasoconstriction of intracranial vessels, inhibition of neuropeptide release from the trigeminal nerve, and inhibition of central pain transmitters. The newer triptans have fewer side effects and are much less likely to cause rebound headaches as compared to their predecessors.

Although many of the serotonin 5-HT_{1B/1D} receptors are located in the brain, some 5-HT_{1B} receptors are located in the heart, as determined by anatomical studies using selective antibodies [70]. Triptans have been shown to constrict coronary arteries and prevent the release of pro-inflammatory neuropeptides [71]. In rarer circumstances, they may actually cause myocardial infarction [72]. Because of this, it is contraindicated to use these drugs in the setting of ischemic heart disease, uncontrolled hypertension, pregnancy, and cerebrovascular disease, such as ischemic stroke [36; 38; 53; 73]. They should also be avoided in the treatment of FHM and basilar migraine. Triptans should not be prescribed to patients who are also taking monoamine oxidase inhibitors (MAOIs), nor should they be given within 24 hours of use of ergotamines [73]. No evidence has supported the use of triptans during the aura phase of a migraine attack [53].

Several triptan drugs are available. The drugs may be taken orally as tablets or capsules, sublingually as quick-dissolving wafers, or intranasally as a spray. Sumatriptan is also available in subcutaneous injection form [71; 74].

The U.S. Headache Consortium has found that triptans are effective and relatively safe for the acute treatment of migraine headaches. They are an appropriate initial treatment choice in patients with moderate-to-severe migraine who have no contraindications for their use [52]. Patient-reported satisfaction with triptans is modest [75]. It is advisable to switch from one oral triptan to another if three migraine attacks have been treated without success [192].

Almotriptan: Almotriptan is available in oral form. It has the highest oral bioavailability of the triptans, with approximately 70% of the dose absorbed within the first hour [73; 76]. A meta-analysis of 53 randomized controlled trials demonstrated almotriptan 12.5 mg to be of comparable efficacy to sumatriptan 50 mg or 100 mg [77]. Side effects include dizziness, dry mouth, paresthesia, nausea, and somnolence [53; 73].

Eletriptan: Eletriptan is available in oral form. It has been suggested as one possible therapy for those patients who have a poor response to NSAIDs. In an open-label treatment study, 113 patients who suffered from migraines and did not experience a satisfactory response to NSAIDs were given eletriptan 40 mg for one migraine attack [78]. Headache, pain-free response, absence of associated symptoms, and functional response were assessed at 1, 2, 4, and 24 hours after receiving the medication. By four hours post-dose, the pain-free response rate was greater than 40% and relief of baseline symptoms was 82%. By 24 hours post-dose, only 24% of patients had headache recurrence. In a randomized double-blind study comparing eletriptan 40 mg to naratriptan 2.5 mg and placebo, 548 patients with migraines were evaluated [79]. At four hours post-dose, 67% of patients taking naratriptan experienced headache relief versus 80% for patients taking eletriptan and 44% for placebo. Patients taking eletriptan also used fewer rescue medications. Side effects include asthenia, dizziness, dysphagia, abdominal pain/discomfort, and chest tightness [53; 73]. Diagnosis should be re-evaluated if the first dose is ineffective.

Frovatriptan: Frovatriptan, available in oral form, appears to have the highest potency of the triptans and may be cerebro-selective [76]. It has one of the lowest rates of headache recurrence after use. In a review of three randomized placebo-controlled trials involving almost 2,700 patients, patients using frovatriptan 2.5 mg experienced greater headache relief than placebo [80]. Side effects include fatigue, dizziness, flushing, dyspepsia, skeletal pain, and chest tightness [73].

Naratriptan: Naratriptan has the longest half-life of all the triptans. As a result, it may be particularly effective in reducing recurrence headaches in some patients. The use of naratriptan 2.5 mg was compared to naproxen 500 mg in a small, double-blind crossover study [81]. At six hours post-dose, naratriptan was more effective in relieving headache, nausea, and vomiting and did so more quickly than naproxen. Side effects include dizziness, drowsiness, malaise, paresthesias, and throat tightness [73].

Rizatriptan: Rizatriptan is one of the quickest acting oral preparations, typically reaching peak concentration in 1 to 1.5 hours. It is also available as an orally-disintegrating wafer [73; 76]. In a study comparing rizatriptan 10 mg versus zolmitriptan 2.5 mg versus placebo, both drugs showed improvement in headache relief compared to placebo but there was no significant difference in symptom relief between the two drugs [82]. When taken orally, rizatriptan 10 mg is superior to sumatriptan 100 mg and naratriptan 2.5 mg on some, but not all, efficacy outcomes [71; 74]. Compared to sumatriptan 100 mg and naratriptan 2.5 mg, greater proportions of patients taking rizatriptan 10 mg have measurable pain relief one hour after taking medication and/or are completely pain-free after two hours. There is insufficient evidence to determine whether rizatriptan (or any triptan) is superior overall [71; 74]. Side effects include asthenia, dry mouth, nausea, paresthesia, dizziness, and chest discomfort. The wafer preparation contains phenylalanine [53; 73].

Sumatriptan: Sumatriptan is available in oral, subcutaneous, and intranasal preparations and in combination with naproxen [73]. It was the first triptan on the market and thus has been the most studied. Oral sumatriptan has been found to be significantly more effective than placebo at relieving migraine headache pain within two hours [83]. A systematic review of 61 studies involving 37,250 participants found that oral sumatriptan (100 mg) significantly improved headache relief compared to placebo [83].

Side effects include tingling/flushing, dizziness, fatigue, muscle pain or weakness, and chest discomfort [73]. There may be taste disturbance with the use of the nasal spray [53; 73]. Although sumatriptan is the most commonly prescribed treatment for migraine, current formulations may be associated with limitations (e.g., difficulty taking oral medication) that can result in patients' delaying or avoiding treatment. Transdermal patches have proved effective for the delivery of sumatriptan. In 2013, the U.S. Food and Drug Administration

(FDA) approved Zecuity, a sumatriptan iontophoretic transdermal system [84; 85]. In 2016, the manufacturer of Zecuity suspended sale of the drug pending an FDA evaluation of reports of burns and scars associated with the patch [86]. Additional novel formulations include needle-free injectable sumatriptan [75].

Zolmitriptan: Zolmitriptan is available in oral form, nasal spray, and orally disintegrating wafers [73]. In a randomized controlled trial of nearly 1,200 patients comparing oral zolmitriptan to placebo, zolmitriptan 2.5 mg was found to significantly decrease headache symptoms, resulting in headache relief in the majority of patients [87]. Of note, a dose response effect was observed, with lower doses resulting in fewer adverse events. In a randomized controlled trial comparing the use of zolmitriptan to sumatriptan of nearly 1,500 patients with migraines, there was no significant difference in headache relief [87]. Side effects include asthenia, nausea, paresthesia, dizziness, and chest discomfort. The use of the nasal spray can cause taste disturbances. The wafer preparation contains phenylalanine [53; 73].

The triptans are all closely related although they differ slightly in terms of half-life, oral bioavailability, and metabolism. Side effects vary but in general they are mild and include tingling, flushing, dizziness, somnolence, and the sensation of pressure in the head; their safety profiles are all quite similar [36]. Because sumatriptan was the first on the market and the most commonly prescribed, it is often used as a comparison in studies with newer triptans [53].

A comparative review of the safety and efficacy of the triptans has indicated that [71; 73; 74]:

- Indirect comparisons from placebo-controlled trials of oral triptans suggest that sumatriptan 100 mg, almotriptan 12.5 mg, eletriptan 40 mg, and zolmitriptan 5 mg all have similar efficacy, whereas frovatriptan 2.5 mg is probably inferior.

- Evidence remains inconclusive as to how the orally disintegrating wafer, nasal, and injectable forms of triptans compare in efficacy to the more conventional oral capsule or tablet forms.
- For the oral forms of eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan, there are no differences in adverse effects (e.g., chest tightness, CNS symptoms); data are lacking for almotriptan and frovatriptan.
- For all the triptans, the safety of treating an average of more than four headaches in a 30-day period has not yet been established.

Note that, like NSAIDs, failure with one triptan does not imply that the patient will not find relief with another triptan. At least two medications in a class should be tried before the class of medications is considered unsuccessful in headache treatment. Ultimately, individuals will need to try the different triptans and determine what works best for them. One might also consider adding an NSAID to a triptan to potentially enhance effectiveness. The first combination product of a triptan and an NSAID (Treximet) was approved by the FDA in 2008. Treximet contains sumatriptan (85 mg) and naproxen sodium (500 mg) and has found to be more effective than placebo or either sumatriptan or naproxen sodium alone [38; 74].

Treating pregnant patients with migraines can be particularly challenging. In general, most medications should be avoided, and patients should be treated with behavioral intervention and nonpharmacologic measures. The triptans are considered FDA Pregnancy Risk Category C, which means risk to humans has not been ruled out [73].

Management of Acute Attack in the Emergency Department

Acute migraine attack results in 1.2 million visits to emergency departments in the United States each year [174]. While more than 20 different parenteral medications and combinations of medications are used to treatment acute migraine in U.S. emergency departments, fewer than 25%

of patients experience sustained freedom from headache after treatment [175]. The ideal parenteral treatment should offer rapid, sustained freedom from headache, no short- or long-term sequelae, a rapid return to normal activities, and no adverse effects; however, no such treatment exists. This led the AHS to develop a guideline on the management of acute migraine in the emergency department, with the goal of determining which injectable medications should be considered first-line treatment for acute migraine in the emergency setting, and whether parenteral corticosteroids can prevent recurrence of migraine in adults discharged from the emergency department (**Table 7**) [175].

Other Medications

Although the triptans provide effective relief from migraine for many patients, a substantial number will be unresponsive. Calcitonin gene-related peptide (CGRP) is believed to contribute to pain transmission and inflammation and, for these reasons, to the mechanisms of migraine. CGRP receptor antagonists have been shown to terminate migraine with efficacy similar to triptans by inhibiting neurogenic vasodilatation and inflammation. Four CGRP receptor antagonists (erenumab, fremanezumab, galcanezumab, and ubrogepant) have been tested in clinical trials and have shown clinical benefit and excellent tolerability [88; 89; 90; 91].

Selective serotonin reuptake inhibitors (SSRIs) block the passage of serotonin, a neurotransmitter, in brain cells and are typically used to treat depression. In view of research suggesting that serotonin may play a role in the genesis of headache pain, SSRIs have been tested for their potential benefit in preventing headaches. Results suggest, however, that SSRIs are no better than placebo for preventing migraine or tension-type headaches [92]. Additionally, the FDA has issued a public health advisory regarding the combined use of 5-hydroxytryptamine receptor agonists (triptans), SSRIs, or selective serotonin/norepinephrine reuptake inhibitors (SNRIs). A life-threatening condition called “serotonin syndrome” may occur

AHS RECOMMENDATIONS FOR MANAGEMENT OF ACUTE MIGRAINE IN THE ED			
Medication, Dose, Route of Administration	Pharmacologic Category	Efficacy	Recommendation
First-Line Treatment			
Acetaminophen, 1 g, IV	Analgesic	Possibly effective	May offer
Acetylsalicylic acid, 0.5–1.8 g, IV	NSAID	Likely effective	May offer
Chlorpromazine, 0.1–25 mg, IV	Antimanic, antipsychotic	Possibly effective	May offer
Diclofenac, 75 mg, IM	NSAID	Possibly effective	May offer
Droperidol, 2.5–8.25 mg, IM	Antiemetic	Likely effective	May offer
Haloperidol, 5 mg, IV	Antipsychotic	Likely effective	May offer
Ketorolac, 30–60 mg, IM/IV	NSAID	Likely effective	May offer
Metoclopramide, 10–20 mg, IV	Antiemetic	Highly likely to be effective	Should offer
Prochlorperazine, 10 mg, IV	Antiemetic	Highly likely to be effective	Should offer
Sumatriptan, 6 mg, SC	Triptan	Highly likely to be effective	Should offer
Valproic acid, 500–1,000 mg, IV	Anticonvulsant; antimanic	Possibly effective	May offer
Migraine Recurrence Prevention			
Dexamethasone, 8–24 mg, IV	Corticosteroid; antiemetic	Highly likely to be effective	Should offer
Source: [175]			Table 7

MEDICATIONS IMPLICATED IN SEROTONIN SYNDROME
SSRIs
Citalopram
Fluvoxamine
Escitalopram
Paroxetine
Fluoxetine
Olanzapine/fluoxetine
Sertraline
SNRIs
Duloxetine
Venlafaxine
Sibutramine ^a
Triptans
Naratriptan
Almotriptan
Frovatriptan
Sumatriptan
Rizatriptan
Eletriptan
Zolmitriptan
Ditans
Lasmiditan
^a Sibutramine, a drug approved for weight loss but not depression, is an SNRI and should therefore be used with caution with triptans and other serotonergic drugs.
Source: [93]

Table 8

when triptans are used together with an SSRI or an SNRI (**Table 8**). Symptoms may include restlessness, hallucinations, loss of coordination, tachycardia, rapid changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea. Serotonin syndrome may be more likely to occur when starting or increasing the dose of a triptan, SSRI, or SNRI. The FDA has requested that all manufacturers of triptans, SSRIs, and SNRIs update their prescribing information to warn of the possibility of serotonin syndrome when triptans and SSRIs or SNRIs are taken together [93].

In 2019, lasmiditan, a ditan, was approved for the treatment of migraine [73]. Lasmiditan is similar to a triptan but is a high-affinity, highly selective 5-HT_{1F} receptor agonist. The selective targeting of the 5-HT_{1F} receptor is hypothesized to decrease stimulation of the trigeminal system and treat migraine pain without causing vasoconstriction. In a phase 3 study, patients reporting being free of headache after two hours with lasmiditan 200 mg (32.2%) or 100 mg (28.2%) compared with placebo (15.3%). Patients who received lasmiditan were

also significantly more likely to report alleviation of their most bothersome symptom compared with placebo [193]. Adverse events were mostly mild or moderate in intensity.

Botulinum Toxin

Botulinum toxin type A (Botox) injections were discovered as a treatment for migraines after individuals who had injections for cosmetic purposes found that it lessened or obliterated their migraine headaches. These observations subsequently led to a series of clinical research studies designed to assess the value of botulinum toxin type A therapy for headache prevention; however, the results from these studies have been mixed [68; 94; 95; 96; 97].

For example, a review of botulinum toxin studies was performed by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The Subcommittee examined evidence of the toxin's effectiveness for a variety of conditions, including migraine. According to the Subcommittee's report, the evidence indicated that botulinum toxin may be useful in the treatment of lower back pain but that it is probably not effective against episodic migraine and chronic tension-type headache. The report also stated that the available evidence was not strong or consistent enough to determine botulinum toxin's usefulness in the treatment of chronic daily headache (primarily, transformed migraine) [95; 96].

In a double-blind, randomized, placebo-controlled study, researchers compared the number of headache-free days experienced by patients four weeks prior to injections of botulinum toxin type A with the number of such days occurring four to eight weeks after treatment. The number of headache-free days increased for the study's placebo and nonplacebo groups, but the difference in increase between the two groups was not significant. The researchers did find, however, that when compared with the placebo group, the patients who received botulinum toxin type A injections experienced a significant reduction in the duration of their headaches [95]. Additionally, pooled results from

two large trials indicated that treatment with up to five cycles of botulinum toxin type A at 12-week intervals was effective in reducing headache symptoms, decreasing headache-related disability, and improving health-related quality of life in patients with chronic migraine [97].

It is generally recommended that use of botulinum toxin type A be restricted to patients who fail to respond to conventional preventative therapy or experience intolerable side effects from such therapy. It is important to note that botulinum toxin type A is not FDA-approved for migraine treatment [73; 94]. Because its effects on a developing fetus are unknown, women who are pregnant should not receive botulinum toxin type A [73; 94].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

The American Academy of Neurology has stated that botulinum toxin type A injections should be offered as a treatment option to patients with chronic migraine (but not episodic migraine) to increase the number of headache-free days and reduce headache impact on health-related quality of life.

(<http://n.neurology.org/content/86/19/1818.full>.
Last accessed April 5, 2022.)

Strength of Recommendation: A (Established as effective for the given condition in the specified population)

The mechanism of action of botulinum toxin type A is thought to be secondary to relieving pressure on certain nerves, such as branches of the trigeminal nerve, and thus reducing the release of neuropeptides. The actual process involves 20 to 30 injections in the forehead, temple, and neck. Side effects may include pain and bleeding at the site, exacerbation of the headache, and ptosis (eyelid droop) [73]. In those patients for whom it works, the effect typically lasts three to six months, at which time the headaches often return. This necessitates repeat injections every three to six months. This treatment is still considered to be experimental. Much more research is needed before this therapy can be considered effective.

Neuromodulation Devices

In recent years, there has been more research and development of neuromodulation devices for the treatment and prevention of headache disorders. Benefits of this type of device include proven efficacy, non-invasive nature, and very limited side effects. Due to the limited amount of time these devices have been available, ongoing research is needed to determine long-term safety and efficacy for headache disorders.

Cerena

In 2013, the Cerena transcranial magnetic stimulation (TMS) device was approved to treat migraine with aura. Patients use both hands to hold the device against the back of the head, then press a button to release a pulse of magnetic energy to stimulate the occipital cortex in the brain, which may stop or lessen the pain associated with migraine headaches. The maximum recommended dosage is one treatment in 24 hours [191].

Approval for Cerena was based on a study in which 39% of users were pain-free two hours post-treatment, compared with 22% of the control group. At 24 hours post-treatment, 34% of patients were pain-free, compared with 10% in the control group. However, studies and research on Cerena are limited [191].

Cefaly

In 2014, the first neuromodulation device received approval from the FDA for prevention of episodic migraines and received approval for acute treatment in 2017 [182; 183]. The Cefaly is a prescription external trigeminal nerve stimulation (e-TNS) device that is placed on the forehead. A self-adhesive electrode transmits electrical impulses to specific areas of the trigeminal nerve, generating an analgesic effect. The Cefaly device is used 20 minutes daily at a frequency of 60 Hz to prevent migraine or can be used for acute treatment during migraine with or without aura at a frequency of 100 Hz [183].

Results of a trial published in 2019 showed that patients using Cefaly as a preventive treatment for three months experienced a 16.21% reduction in headache days and a 30.81% decrease in acute medication intake compared with a group assigned to a sham device. Minor adverse events included skin irritation under the electrode and headache worsening with vertigo [184]. Another study published in 2019 examined the efficacy in acute treatment of migraine with or without aura. One hour after beginning the Cefaly treatment, 79% of patients achieved significant pain relief and 29% reported being pain free [185]. According to results of these and other studies, the Cefaly device is considered safe and effective for both prevention and acute treatment of migraine. In 2020, Cefaly was made available over-the-counter without the need for a prescription [194].

gammaCore

In 2017, the gammaCore device was cleared by the FDA for the acute treatment of migraine and cluster headache, and as a preventive treatment for cluster headache. This device is a handheld, non-invasive vagus nerve stimulator (nVNS) that produces mild electrical stimulation to the vagus nerve through the neck, thereby reducing and preventing pain [186]. Stimulation is controlled by the user, and treatment sessions consist of 2 to 3 two-minute stimulations. Patients that have a metallic device (e.g., a stent, bone plate, or bone screw) implanted at or near their neck should not use gammaCore.

A four-week study published in 2018 examined the effects of nVNS using the gammaCore device on episodic migraine headache with or without aura. Researchers found 12.7% of patients were pain free after 30 minutes of initiation of treatment (vs. 4.2% in the sham group) and 21% after 60 minutes (vs. 10%). The only adverse event was vertigo, seen in 1% of patients. Researchers indicate that nVNS is a safe treatment that may possibly decrease the risk of medication overuse in some patients [187].

Another study published in 2018 examined the effects of nVNS on episodic and chronic cluster headache over the course of two weeks. Compared with the sham group, 16.7% of patients with episodic cluster headaches achieved pain-free status at 15 minutes for greater than 50% of their attacks (vs. 6.8%), and 64.3% of patients reported significant improvement (vs. 15.4%). Comparison of patients with chronic cluster headaches were insignificant, with patients reporting free of pain at 8.8% (vs. 6.5% in the sham group) and patients with significant improvement at 29.4% (vs. 12.9%) [188].

Clinical trials for prophylactic treatment of cluster headaches using nVNS showed that there was a significantly greater reduction in the number of cluster attacks per week versus the control (5.9 vs 2.1, respectively). Forty percent of patients reported pain relief of 50% or greater, compared with 8.3% of the control group. nVNS also led to a reduction in the use of abortive medications. There was no change in cluster headache duration or severity of acute attacks reported in this trial [186].

Nerivio Migra

Nerivio Migra received FDA *de novo* clearance in 2019 for acute treatment of migraine with or without aura. It is a prescription trunk and limb electrical stimulator that is used on the upper arm. Electrical pulses are controlled through a smartphone for 30 to 45 minutes. This device is expected to be available in the United States in late 2019 [189].

A study of the efficacy of Nerivio Migra was published in 2019 and included patients who experience two to eight migraines per month. Two hours post-treatment with active stimulation, Nerivio Migra provided complete pain relief to 37.4% of patients (vs. 18.4% of sham participants), significant pain relief in 66.7% of patients (vs. 38.8%), and relief of most bothersome symptoms in 46.3% of patients (vs. 22.2%). For many, pain relief was sustained 48 hours post-therapy [190].

Relivion

In 2021, the FDA cleared Relivion, a transcutaneous electrical nerve stimulator that can be self-applied at home [195]. This device consists of a headset controlled by a smartphone app and delivers stimulation to six branches of the occipital and trigeminal nerves. It is indicated for the treatment of migraine with or without aura in patients 12 years of age or older.

Preventive Therapies

The initiation of a preventive agent is a decision that can be made only when a variety of factors have been considered. For example, if an individual is using abortive medications more than two times per week with only moderate success, if there are more than two seriously disabling attacks per month, if there is failure of or contraindication to abortive treatments, if there is occurrence of uncommon features, or if there is a pattern being established of medication overuse, physicians should consider the initiation of a preventive medication [38; 113]. Additional factors that should be considered include the patient's preference, adverse events associated with treatments for acute migraine attacks, and how much treatment costs for acute attacks and migraine prevention [54]. Most treatment is effective within the first month.

Although the precise mechanism of action is unknown, it is believed that preventive therapies act on the CNS by raising the threshold of a migraine headache, producing "resistance" for the system to develop headaches. They also work by inhibiting the propagation of the migraine process early on.

When considering preventive agents, keep in mind the following points [98; 113]:

- Start with the lowest possible dose.
- Give the medication an adequate trial, which typically is two to three months.
- Increase the dose slowly until either benefits or unacceptable adverse reactions are observed.

MEDICATIONS AND STANDARD DOSES FOR MIGRAINE PREVENTION	
Medication/Therapy	Standard Dose
Beta Blockers	
Propranolol ^a	160–240 mg daily
Timolol ^a	10–30 mg daily
Metoprolol	25–100 mg daily
Tricyclic Antidepressants	
Amitriptyline	10–150 mg daily
Antiepileptics	
Divalproex sodium ^a	250–1,000 mg daily
Topiramate ^a	25–100 mg daily
CGRP Antagonists	
Erenumab-aooe ^a	70 mg monthly
Fremanezumab-vfrm ^a	225 mg monthly
Galcanezumab-gnlm ^a	120 mg monthly
Neuromodulation Devices	
Cefaly ^a	100 Hz, for 20 minutes daily
gammaCore	50–60 Hz, for 4 to 6 minutes daily
^a FDA-approved for migraine prevention	
Source: [73; 98; 178; 179; 180; 113] Table 9	

- Try to use long-acting formulations; these may help improve patient compliance.
- Choose an agent that may treat co-existing conditions, such as depression or hypertension.
- Encourage the patient to use a headache diary for better evaluation of effectiveness.

The proven and/or well-accepted drugs used for prevention of migraines include beta blockers (e.g., propranolol, metoprolol), tricyclic antidepressants, triptans, and antiepileptics (**Table 9**) [98; 113]. When antiepileptic drugs are used to treat or prevent migraine, the dose is typically much lower than the dose used to treat seizures. Also, divalproex sodium and topiramate are the only antiepileptic drugs approved by the FDA for migraine prevention [73]. Antiepileptic drugs

have been shown to be effective in reducing the frequency of migraine attacks by 38% to 50% or more with antiepileptics than with an inactive placebo [99; 100; 101]. It should be noted that, although the drug may be beneficial, the FDA has issued a warning regarding the risk of metabolic acidosis in patients receiving topiramate as well as a warning of increased risk of development of oral clefts in infants born to women treated with the drug during pregnancy [76; 102].

Gabapentin has demonstrated some effectiveness in the prevention of migraine; however, more research is needed to determine long-term effectiveness [98; 101; 103; 104]. The preventive treatments are often helpful but will not eradicate headaches altogether. Preventive therapy may reduce the frequency of migraines by 38% or more; such improvement is considered successful [36; 99; 100; 101; 105].

In 2018, the FDA approved three once-monthly medications for migraine prevention — erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm [178; 179; 180]. These CGRP antagonists are self-administered once per month with an autoinjector.

Physicians and other clinicians should also be cognizant that migraine sufferers often must try as many as five different medications (both acute and preventive) before they find one that is effective for their symptoms. It is important to be patient and not become frustrated during these trial periods.

CLUSTER HEADACHES

Cluster headaches are one of several types of trigeminal autonomic cephalalgias, primary headaches characterized by unilateral pain in the trigeminal nerve region. As defined by the IHS, cluster headaches are attacks of severe unilateral pain in the orbit and/or the surrounding region of the eye that last 15 to 180 minutes [43; 53]. The term “cluster” refers to the headache attacks occurring in daily episodes. The patient is headache-free in between the clusters.

DIAGNOSTIC CRITERIA FOR CLUSTER HEADACHES

At least five attacks with the following characteristics:

1. Severe or very severe unilateral pain in the orbit, surrounding area, or both, lasting 15 to 180 minutes untreated
2. Either or both of the following:
 - At least one of the following signs on the side of the pain:
 - Conjunctival injection and/or lacrimation
 - Sensation of fullness in the ear
 - Nasal congestion and/or rhinorrhea
 - Facial and forehead sweating
 - Miosis and/or ptosis
 - Facial and forehead flushing
 - Eyelid edema
 - A sense of restlessness or agitation
3. Frequency of attacks from every other day to eight times a day
4. Not better accounted for by another diagnosis

Source: [43]

Table 10

The attacks may occur anywhere from every other day to eight times per day and are accompanied by one or more of the following symptoms: ipsilateral conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, ptosis and/or miosis, eyelid edema, forehead/facial sweating, forehead/facial flushing, or sensation of fullness in the ear (**Table 10**). Attacks occur in series lasting for weeks or months separated by remissions lasting for months to years [43].

Cluster headaches are divided into two subclasses: episodic and chronic [43]. The episodic cluster occurs at a rate six times higher than chronic cluster [106]. Episodic cluster headache attacks occur in periods lasting seven days to one year, separated by pain-free periods lasting one month or longer [43]. The chronic cluster headache occurs for more than one year without remission or with remissions lasting less than one month. Chronic cluster headache may arise de novo or evolve from the episodic subtype. Some patients may switch from chronic to episodic cluster headache [43].

Cluster headaches are typically described as an excruciating burning or piercing pain. The pain comes on quickly and reaches its peak quickly. The location is typically retro-orbital and unilateral.

Although people do not experience an aura, per se, some individuals report brief warning signs prior to the headache such as a “fuzzy” feeling in the head, spasm of the neck muscles, or a general feeling of discomfort. Interestingly, when a patient is in the throes of a headache, rather than resting and remaining still (as is the characteristic “migraine” behavior) the individual will likely be seen rocking, pacing, or even banging his or her head against a wall in an attempt to somehow divert the pain. The pain is often so excruciating that it has been called the “suicide headache.” Each episode lasts from 15 minutes to three hours. Nausea and vomiting are rarely present [43; 107].

Prevalence varies by gender. Men are more likely to get this type of headache than women with an approximate 3:1 ratio [43]. Cluster headaches tend to start in individuals 20 to 40 years of age and often remit by 55 years of age. They may be inherited in about 5% of cases [43]. Attacks often begin during sleep, implicating a disorder of circadian rhythm. An increased incidence of sleep apnea in patients with cluster headache suggests that periods of reduced oxygenation of key tissues may trigger an attack [106].

TREATMENT OF CHRONIC CLUSTER HEADACHE		
Therapy	Dosage and Route	Comments
Verapamil	120 mg PO three times/day	—
Lithium	Start at 300 mg PO three times/day; use blood levels to achieve therapeutic dose	Need close monitoring of lithium levels; test 12 hours after last dose. Side effects include tremor and dysuria. Check thyroid and renal function before and during treatment.
Microvascular decompression	NA	Only used for intractable cases
Source: [73; 107; 109; 181]		Table 11

TREATMENT OF ACUTE CLUSTER HEADACHE		
Therapy/Drug	Dosage and Route	Reported Adverse Effects
Oxygen	100% oxygen at least 7 L/min over 15 minutes	None
gammaCore (non-invasive vagus nerve stimulator)	Stimulation level between 1–40 using device on side of neck over vagus nerve at maximum level tolerable for a treatment consisting of 3 two-minute stimulations applied consecutively at the onset symptoms; additional treatment may be administered if symptoms are not aborted; use for up to four attacks (or eight separate treatments) per day (for a total of up to 24 stimulations per day).	Local skin reactions, muscle contractions, dizziness
Triptans		
Sumatriptan	Up to 6 mg subcutaneously; may repeat in 24 hours OR 25–100 mg PO; repeat after two hours if significant relief not attained Maximum: 200 mg/day	Local skin reactions, fatigue, nausea, vomiting, dizziness, burning sensations, paresthesias
	20 mg nasal spray	None
Zolmitriptan	2.5 mg PO at onset (includes orally disintegrating wafer) Maximum: 10 mg/day	Chest pain, palpitation, dizziness, somnolence, vertigo, nausea, paresthesia, warm/cold sensation
	One nasal spray (5 mg) at onset	None reported
Intranasal dihydroergotamine	0.5 mg nasal spray bilaterally	Abuse potential; contraindicated in patients with cardiovascular disease
Intranasal lidocaine	1 mL of 4% lidocaine placed with a cotton swab bilaterally for 5 minutes	Unpleasant taste
Source: [73; 76; 107; 108; 111; 112; 188]		Table 12

Although the symptoms for cluster headache are quite dramatic and for the most part pathognomonic, tumors in the vicinity of the internal carotid artery may induce symptoms that mimic those seen in cluster headaches. For this reason, some clinicians advocate a CT scan or MRI for patients who are initially presenting with this type of headache [108].

Cluster headaches are quite rare, affecting only 0.1% of adults [107]. Interestingly, there are some associated risk factors. Most individuals with cluster headaches are smokers, yet smoking cessation rarely, if ever, brings relief. A history of head trauma also seems to convey an increased risk of developing cluster headaches. Headache triggers include smoking, alcohol consumption, changes in

PROPHYLAXIS OF EPISODIC CLUSTER HEADACHE			
Drug/Therapy	Dosage and Route	Reported Adverse Effects	Comments
gammaCore (non-invasive vagus nerve stimulator)	Stimulation level between 1–40 using device on side of neck over vagus nerve at maximum level tolerable for a prophylaxis treatment consisting of 2 two-minute stimulations; first daily treatment should be applied within 1 hour of waking; second treatment should be applied at least 7 to 10 hours later; additional treatment may be administered if symptoms are not aborted; use for up to four attacks (or eight separate treatments) per day (for a total of up to 24 stimulations per day).	Local skin reactions, muscle contractions, dizziness	Intended to be used as an adjunctive therapy; first FDA-cleared device
Galcanezumab-gnlm	Loading dose of 240 mg subcutaneous (SQ) injection, followed by 120 mg SQ monthly	Antibody development, injection site reaction	Given by patient self-injection, FDA-approved
Verapamil	120–160 mg PO three times/day	Hypotension, bradycardia, atrioventricular block, dizziness, fatigue, nausea, constipation	In doses of 360–480 mg/day, has been found to be effective in reducing attack frequency
Prednisone	100 mg PO/day, up to 500 mg IV (methylprednisolone or equivalent corticosteroid) titrated over five days	Increased appetite, insomnia, nervousness, hyperglycemia, dizziness, headache	Recurrences frequent toward the end of the taper; take concurrently with another prophylactic medication
Divalproex sodium	600–2,000 mg/day	Nausea, somnolence, dizziness, insomnia, anorexia, weakness, thrombocytopenia, alopecia, weight gain	Small studies indicate efficacy; use with caution in patients with renal or hepatic insufficiency; contraindicated in pregnant women
Topiramate	25 mg PO/day for seven days, then increase by 25 mg/day every week to maximum dosage of 200 mg/day	Paresthesias, cognitive effects, drowsiness, dizziness	Small studies indicate efficacy
Ergotamine	2–4 mg/day in divided doses	Vertigo, pruritus, nausea, paresthesias, weakness, cardiac valvular fibrosis, retroperitoneal or pleuropulmonary fibrosis, angina, myocardial infarction	Best for nocturnal attacks; should not be taken concurrently with sumatriptan May cause withdrawal symptoms if suddenly discontinued
Melatonin	10 mg PO at bedtime	None reported	May be useful in some patients; drug of third choice

Source: [107; 111; 186]

Table 13

temperature, breezes on the face, and changes in physical, emotional, or mental activity [43; 107].

PET scanning and functional MRI are helping to clarify the poorly understood etiology of cluster headaches. It is thought to be multifactorial and likely involves alterations in the hypothalamus [107]. It is generally believed that the trigeminal system is involved in these headaches [107].

Treatment of cluster headache involves a dual strategy of abortion (during the acute stage) and concurrent prophylaxis, which is initiated to suppress the expected recurrent headaches [109]. Patients with chronic cluster headache require long-term prophylaxis (**Table 11**). Patients with intractable headaches may require more aggressive intervention, including combination therapy or surgery [107; 110].

The treatments of choice for acute cluster headache are oxygen, a triptan, or a combination of the two (**Table 12**). There has been some data suggesting the use of melatonin in patients who suffer from cluster headaches, especially those who have concomitant sleep disorders; however, the effectiveness of melatonin remains unclear because of conflicting studies [107; 108].



EVIDENCE-BASED
PRACTICE
RECOMMENDATION

According to the Institute for Clinical Systems Improvement, oxygen inhalation is a highly effective treatment for cluster headaches when delivered at the beginning of an attack with a non-rebreathing facial mask (7–15 L/min).

Most patients will obtain relief within 15 minutes.

(<https://www.icsi.org/wp-content/uploads/2019/01/HeadacheRR.pdf>. Last accessed April 5, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

Preventive therapies are usually initiated when the cluster headache series begins. Preventive medications include antidepressants, antiepileptics, ergotamine, and calcium channel blockers (**Table 13**).

TENSION HEADACHES

Tension headaches are among the most common headache type seen in practice today; however, it is the least studied of the primary headache disorders, despite the fact that it has the highest socioeconomic impact. The lifetime prevalence ranges from 30% to 78%, with a rate of 63% seen in men and 86% in women [21; 43].

The etiology of tension headaches is multifactorial. Although once thought to be simply secondary to muscle spasm, it is now felt that other factors play important roles. In fact, although tension headaches may arise from sustained contraction of pericranial muscles, no correlation exists between muscle contraction and the presence of a tension headache. It seems that, just as in migraine headaches, tension headaches arise in part from centrally mediated neural dysfunction. This abnormality may in part be due to central sensitization in the trigeminal area [43; 67].

The IHS has categorized tension headaches into two categories: episodic and chronic (**Table 14**). Episodic tension-type headache is further divided into infrequent (i.e., episodes that occur less than once per month) and frequent subtypes. The infrequent subtype has little impact on the individual. Frequent sufferers, however, may encounter considerable disability that requires the use of expensive drugs and prophylactic medications. The chronic subtype is always associated with disability and high personal and socioeconomic costs [43].

Episodic tension headaches are usually associated with a stressful event. They are of moderate intensity, typically are self-limited, and usually respond well to over-the-counter headache treatments. They are usually described as soreness, tightness, or a band-like pressure around the entire head. They are often accompanied by stiffness in the neck and shoulders [114].

IHS diagnostic criteria for infrequent episodic tension-type headache include at least ten episodes occurring on less than 1 day per month on average (i.e., less than 12 days per year), lasting from 30 minutes to 7 days, with at least two of the

DIAGNOSTIC CRITERIA FOR TENSION HEADACHE

A. Infrequent Episodic Tension Headache

1. At least 10 episodes occurring less than 1 day per month on average or less than 12 days per year
2. Duration from 30 minutes to seven days
3. At least two of the following pain characteristics:
 - Pressing or tightening (non-pulsating) sensation around the head
 - Mild-to-moderate severity
 - Bilateral location
 - No aggravation by walking, climbing stairs, or similar physical activity
4. No nausea/vomiting and no more than one photophobia or phonophobia
5. Not better accounted for by another diagnosis

B. Frequent Episodic Tension Headache

1. At least 10 episodes of headache occurring on 1 to 14 days per month on average for more than three months (≥ 12 and < 180 days per year)
2. Duration from 30 minutes to seven days
3. At least two of the following pain characteristics:
 - Bilateral location
 - Pressing or tightening (non-pulsating) quality
 - Mild-to-moderate severity
 - No aggravation by routine physical activity such as walking or climbing stairs
4. No nausea/vomiting and no more than one of photophobia or phonophobia
5. Not better accounted for by another diagnosis

C. Chronic Tension Headache

1. More than 180 days of headache in a given year or at least 15 headaches per month for an average of greater than three months
2. Duration may be from hours or it may be continuous
3. At least two of the following pain characteristics:
 - Pressing or tightening sensation around the head
 - Mild-to-moderate severity
 - Bilateral location
 - No aggravation by walking stairs or similar physical activity
 - May include one of the following: nausea, photophobia, or phonophobia
4. No evidence of organic disease

Source: [43]

Table 14

following characteristics: a pressing or tightening (non-pulsating) sensation around the head, mild-to-moderate severity, bilateral location, and no aggravation by walking stairs or similar routine physical activity. There is no nausea, but either photophobia or phonophobia may be present [43].

Chronic tension headaches generally have the same pain characteristics as episodic tension headaches, including phonophobia or photophobia. They occur more frequently, with an incidence of at least 15 headaches per month on average for greater than three months, or greater than 180 days in a given year. The headache may last hours, or it may be continuous [43; 53].

As with migraines, there are both nonpharmacologic and pharmacologic treatments. Nonpharmacologic measures tend to be more effective for tension headaches than for migraines or clusters. These measures include the use of hot or cold packs, ultrasound, electrical stimulation, improvement of posture, trigger point injections, regular exercise, and consistent sleep schedules [114]. Forward head posture and neck mobility have been associated with tension-type headache [115].

Tension headaches also tend to respond well to medications. Some commonly used medications that are effective include aspirin, acetaminophen, and NSAIDs in the standard prescribed doses [114]. Combination treatments with the above medications and caffeine, butalbital, and muscle relaxants are also effective. However, overuse of these medications, especially those containing caffeine, may lead to rebound headaches. The use of butalbital also may result in dependency, and for this reason, it is not recommended for prolonged use [53; 73]. In general, narcotics should be avoided because tension headaches are typically mild-to-moderate in pain intensity. Botulinum has also been suggested for the treatment of tension headaches; however, not all researchers agree that it should be used for chronic tension-type headache [11; 116]. As discussed, however, more study regarding efficacy and safety is required.

Some chronic tension headaches may not respond as well to the above modalities and may require preventive medication. Before preventive medication is initiated, it is important, as in the case with migraine headaches, to have the individual keep a headache diary to determine what factors, if any, are triggering the headache [114]. Use of nonpharmacologic measures may also be initiated. Some clinicians may try a drug-free holiday, whereby all headache drugs are stopped for at least two weeks. If none of these modalities prove effective, preventive medications may be helpful. The same preventive medications used for migraine are used for chronic tension headache. These tend to be helpful especially if the patient experiences both migraine and tension headaches.

OTHER PRIMARY HEADACHES

Primary Exercise Headache

As the name implies, primary exercise headache (formerly referred to as a primary exertional headache) is a headache that occurs with exertion, is benign in nature, and is unassociated with any structural lesions. On first occurrence of this headache type, it is mandatory to exclude subarachnoid hemorrhage (SAH) and arterial dissection [43; 117].

The headache is typically described as a diffuse, bilateral pain, throbbing in quality and acute in onset. It is precipitated by strenuous physical exercise. The headache lasts from five minutes to 48 hours and occurs particularly in hot weather or at high altitude [43; 117].

Primary exercise headache is believed to be vascular in origin. Strenuous physical activity increases intracranial venous sinus pressure, which leads to an increase in intracranial pressure and decreases blood flow. This results in the occurrence of the headache. Effective treatment includes ergotamines and NSAIDs. Indomethacin has been found effective in the majority of cases [43; 117].

Hypnic Headache

Hypnic headaches are relatively brief in duration (15 to 240 minutes), mild-to-moderate (severe pain is reported in 20% of patients), usually dull in quality, and bilateral in about two-thirds of cases. Hypnic headaches occur during sleep and are related to the REM stage. The headaches typically awaken patients from sleep, but there are few other associated symptoms [43]. They usually occur almost every night and may last for months until patients ultimately present for evaluation. These types of headaches primarily affect the elderly [118].

The etiology is considered idiopathic, and thus, the diagnosis is primarily one of exclusion. Other causes of headache associated with sleep, such as sleep apnea and drug withdrawal, should be excluded.

One of the most effective treatments for hypnic headaches includes the use of lithium; however, it is often limited by side effects and interactions and requires monitoring of plasma concentrations to avoid toxicity. Indomethacin, atenolol, prednisone, and caffeine have also been shown to be useful [43; 118].

Headache Associated with Sexual Activity

These headaches have been previously referred to as benign sex headaches, coital cephalalgias, benign vascular sexual headaches, or benign orgasmic headaches. They may be provoked by activities besides coitus and not necessarily with orgasm. Headache associated with sexual activity affects men more than women [119; 120].

Two subforms (preorgasmic headache and orgasmic headache) were previously described, but further research was unable to clearly delineate the two separate entities [43]. Therefore, headache associated with sexual activity is now a single diagnosis with variable presentation. The condition is characterized by at least two episodes of pain in the head and/or neck brought on by and occurring only during sexual activity [43]. The pain becomes more severe with increasing sexual excitement and/or may be experienced as abrupt explosive intensity just before or with orgasm. The duration of severe pain is from 1 minute to 24 hours; more mild presentations may last up to 72 hours [43].

Diagnosis cannot be made until secondary causes (e.g., SAH or arterial dissection) have been excluded. For most patients, these are self-limited disorders. Patients often can lessen the severity of an impending attack by ceasing the sexual activity. Frequent, recurrent episodes may require preventive strategies, such as propranolol or indomethacin [119].

SECONDARY HEADACHES

As noted, it is helpful to think of secondary headaches in terms of etiologic categories, such as vascular, traumatic, neoplastic, infectious, pressure, metabolic/toxic ingestions, and medication overuse. A secondary headache may be diagnosed when another disorder known to cause headache has been demonstrated; headache occurs in close temporal relation to the other disorder and/or there is other evidence of a causal relationship; and headache is greatly reduced or resolves within three months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder. The IHS has divided secondary headaches into subtypes attributed to specific causes [43]. **Table 15** shows a summary of several causes of secondary headache.

TRAUMATIC CAUSES OF HEADACHES

Epidural Hematoma

Epidural hematomas occur between the dura and skull, and thus separate the dura from the skull. In the majority of cases, there is an associated skull fracture. Typically, there is a history of head trauma, although an epidural hematoma occurs in less than 2% of all serious head injuries. Epidural hematomas are not a frequent occurrence in the elderly, partly because as one ages, the dura becomes more firmly attached to the inner part of the skull [121].

Classically, there is a brief period of unconsciousness and then a return to a normal mental status. This is known as the “lucid interval.” Roughly 10% to 33% of patients demonstrate the classic presentation of a lucid interval, and alterations in the level of consciousness may have a variable presentation. After a period of hours, the hematoma expands and pushes the dura inward. Signs of rising intracranial pressure manifest as a severe, diffuse, constant headache, which develops within minutes to 24 hours after development of the hematoma [121]. Other symptoms may include papillary dilatation, hemiplegia, and eventually obtundation. Often there is weakness on the side of the body opposite the hematoma [121].

CHARACTERISTICS OF SECONDARY HEADACHES					
Type of Headache	Position	Quality	Radiation	Duration	Therapy
Subarachnoid hemorrhage	Diffuse	Sharp	Neck, back	Several days	Surgery, hypertension management, volume expansion
Giant cell arteritis	Temporal area, unilateral or bilateral	Soreness/burning	No	Days to weeks	High-dose steroids
Arterial dissection	One-sided, nonthrobbing pain in the eye	Pounding	Neck	Days	Anticoagulants, stenting, surgery
Stroke	Diffuse	Dull	No	Hours	Supportive
Epidural hematoma	Diffuse	Severe	No	Hours to days	Surgery
Dental	Occipital, temporal	Squeezing	No	Varies	Dental referral for care
Subdural hematoma	Diffuse	Mild	No	—	Diuretics, anticonvulsants, surgical evacuation
Brain tumor	Diffuse or unilateral	Mild ache	No	—	Surgery, radiation, chemotherapy
Meningitis	Diffuse	Mild to moderate	Neck	—	Rest, fluids, electrolyte balance, antibiotics
Encephalitis	Diffuse	Dull	No	—	Rest, fluids, electrolyte balance, antiretrovirals
Sinusitis	Sinus area	Heavy fullness	No	Duration of illness	Antibiotics
Abscess	Hemicrania	Moderate to severe	Neck	—	Evacuation, antibiotics

Source: [43]

Table 15

Hemorrhages usually occur in the temporal fossa from middle meningeal artery tears; they may also occur in the posterior fossa as a result of a transverse sinus tear. Posterior fossa epidural hematoma may exhibit a rapid and delayed progression from minimal symptoms to even death within minutes. Overall mortality has been estimated to be as high as 50%, so prompt evaluation and treatment is critical [43].

With respect to diagnosis through neuroimaging, in the acute setting, unenhanced CT scan is more useful than MRI imaging. Epidural hematomas have a characteristic white lenticular shape adjacent to the bone, while focal hypodense or isodense areas on CT indicate active bleeding.

Because the temporal fossa is often involved, one must be careful that bony artifacts do not obscure a hemorrhage [121].

Subdural Hematoma

As the name implies, subdural hematomas occur between the surface of the brain and the dura. The source of bleeding is the venous system (i.e., bridging veins) as opposed to the arterial system. Because the subdural space is continuous, these types of hemorrhage may have significant mass effect. Subdural hematomas are more common than epidural hematomas. They tend to evolve more slowly based on the slower rate of venous bleeding compared to arterial hemorrhage. As a result, there may be a progression of symptoms over two to four weeks; the rate of progression depends upon the severity of the injury [122].

Patients often present with a mild persistent headache. There may be drowsiness and confusion, although focal neurologic signs are often absent. Symptoms may be followed by a brief lucid interval with subsequent deterioration. Subdural hematomas are seen in approximately 15% of all head traumas. Automobile accidents are a typical cause of subdural hematomas [122].

Different types of subdural hematomas should be differentiated according to their temporal profile. In acute and subacute hematomas, which usually occur after obvious head trauma, headache is frequent (11% to 53% of cases) but commonly overshadowed by focal signs and disorders of consciousness. In chronic subdural hematomas, headache is more frequent still (up to 90%) and, though moderate, may be the leading symptom [122]. The diagnosis can be difficult because the causative head trauma is often trivial and may have been forgotten by the patient [43].

Subdural hematomas are more common in the elderly than epidural hematomas, and patients on anticoagulants are at increased risk of developing a subdural hematoma. Chronic subdural hematoma should always be considered in an elderly patient with a progressive headache, particularly if there is some cognitive impairment and/or mild focal signs [43; 122; 123].

Patients with suspected subdural hematoma should undergo CT scanning. CT scan findings depend on the age of the hemorrhage but typically demonstrate an abnormality in the entire hemisphere, causing a shift of the midline structures. Early on, there are hyperdense areas demonstrated on CT, followed by isodense areas after a week and hypodense areas after a month [122; 123].

Prompt treatment is critical because mortality can reach 60%. Treatment may include diuretics to reduce swelling. Because there is a high frequency of seizures, antiepileptics are frequently used to either control or prevent seizures. For more serious hematomas, surgical evacuation may be necessary. The long-term prognosis is actually worse than that for epidural hematomas [122; 123; 124].

Upon further history taking, it becomes clear that Mrs. T did experience a significant fall a few weeks ago, even though she minimized it when mentioning it. Sequelae are present. Therefore, a contrast-enhanced CT should be ordered.

The CT scan demonstrated hypodense areas in both hemispheres, consistent with subdural hematoma. There was no evidence of mass effect. The subdural hematoma is likely a result of the fall approximately one month earlier. Mrs. T was admitted to the hospital for observation and given diuretics and anticonvulsants. Her clinical course was good with resolution of the hematoma without the need for surgery.

VASCULAR HEADACHES

Subarachnoid Hemorrhage

Typically, headache due to an SAH is described as a sharp pain that usually involves the entire head. Patients classically describe it as the “worst headache of their life.” It often radiates into the neck and even into the back. There is usually nausea and vomiting. In general, there are no focal neurologic deficits early on, but as it progresses, there may be loss of consciousness and altered mental state. Seizures during the acute phase occur in 10% to 25% of patients [125].

The course of this headache is abrupt in its onset and maximum intensity at its origin; it is typically incapacitating in its severity. It is exacerbated by neck and head movements. It usually remains severe for several days and then gradually diminishes [43]. An often overlooked aspect is that the acute headache may be preceded days to weeks earlier by a similar but less severe headache due to slow bleeding. Therefore, a high index of suspicion is necessary for accurate diagnosis [125].

The headache results most often (approximately 80% of cases) from rupture of an aneurysm, although this condition may also result from trauma, arteriovenous malformations, venous thrombosis, blood dyscrasias, cocaine use, amphetamine use, and a variety of metabolic conditions [43; 125]. Types of aneurysms include berry aneurysms, fusiform aneurysms, atherosclerotic lesions, and mycotic

aneurysms from septic emboli. Approximately 80% of nontraumatic SAHs are due to a ruptured berry aneurysm; rupture of arteriovenous malformations is the second most identifiable cause (10%) [126]. The initial pain is actually produced by tearing and distortion of the blood vessel and its adjacent arachnoid membrane. The incidence of headache in ruptured aneurysms is 90% [122].

The prevalence of SAH increases with age in a linear relationship. The mean age is 50 years [125; 126; 127]. On physical examination, the patient is typically in severe pain. The pain is sometimes referred to as a “thunderclap” headache [126]. Symptoms of meningeal irritation, such as nuchal rigidity and pain, back pain, and bilateral leg pain, occur in as many as 80% of patients with SAH but may take several hours to manifest [126]. Focal neurologic deficits, such as facial droop or weakness in a specific extremity, are present in 25% of patients. However, if the hemorrhage is associated with infarction it will likely involve the brain parenchyma, which may lead to hemiparesis, aphasia, or visual field abnormalities. Loss of consciousness is transient [43; 125].

Patients with suspected SAH should undergo CT scanning without contrast or MRI (flair sequences) [43; 122]. The CT typically demonstrates blood localized to the basal cisterns or extended into the ventricles [122]. Unenhanced CT detects SAH in about 90% of cases; however, sensitivity drops to 80% after three days. As a result, a normal CT does not exclude a small SAH [125].

If the CT is negative, equivocal, or technically inadequate, a lumbar puncture should be performed [43]. Most cases not detected on CT are identified on lumbar puncture by red blood cells (RBCs) that do not clear in three samples of CSF. A decrease in RBCs from the first to the last tube represents an artificially bloody tap, whereas an increase count in RBCs suggests SAH. The fluid is then centrifuged and examined for xanthochromia. Xanthochromia is often characterized as a yellow-tinged superna-

tant, although it may also be pink or orange. It represents enzymatically derived breakdown products, oxyhemoglobin, methemoglobin, and bilirubin, of in vivo red blood cells. It is always seen within 12 hours of SAH but is absent after a traumatic tap. Its presence may be helpful in the diagnosis [43]. Of note, blood in the CSF after a traumatic tap will also result in an artificial increase in white blood cells (WBCs). WBCs will increase by one for every 500 to 1,000 RBCs in the CSF. This assumes a normal WBC count, which is typically the case in SAH [126]. Ultimately, angiography may be necessary to determine aneurysm size and location, as well as to determine surgical or medical management. Treatment options include a surgical clip, management of hypertension, and volume expansion [124; 126]. In 2013, the FDA approved a new oral nimodipine solution for the treatment of patients with SAH from ruptured intracranial berry aneurysms. The solution is administered enterally (e.g., oral, nasogastric tube, gastric tube route) within 96 hours of the SAH at a starting dose of 20 mL every four hours for 21 consecutive days [73; 128].

SAH is a serious condition. Prompt diagnosis of SAH is critical because 50% of patients die following SAH, often before arriving at hospital, and 50% of survivors are left disabled [43; 125].

Giant Cell Arteritis

Giant cell (temporal) arteritis is systemic large and medium-sized vessel vasculitis. Most often, it involves the external carotid arteries [43; 129]. This headache typically begins as an intermittent soreness or burning discomfort and steadily escalates over several weeks or months to become a constant, well-localized pain. On rare occasions, it can be explosive. Many patients report that the pain is worse at night. Although the pain is usually unilateral, it may also be bilateral. Pain is classically confined to the temples. Between 70% to 90% of patients with giant cell (temporal) arteritis complain of headache [53; 129].

The typical presentation is a new-onset headache in patients older than 50 years of age. Incidence is higher in females than males (ratio 3.7:1), as well as in persons of northern European descent. It represents the most common vasculitis in adults. Nearly 50% of patients with polymyalgia rheumatica also have giant cell arteritis [129].

On exam, the affected scalp artery is sometimes prominent. It may be tender and is often pulseless. The scalp itself is usually tender as well. Depending upon the progression, visual field defects and decreased acuity may be noted, although the patient does not usually exhibit focal neurologic deficits. Typically, the headache occurs in someone who is febrile, has malaise, and feels aches in the back and shoulders. Claudication of the jaw occurs commonly and is virtually pathognomonic for this condition when present during talking or chewing [129].

Giant cell arteritis involves not only the arteries of the scalp causing headache, but also other vessels, including those supplying the eye and occasionally the brain. Nearly half of patients with giant cell arteritis develop blindness, if untreated, due to ischemia of the optic nerve or retina. Because blindness can be prevented by immediate steroid treatment, prompt and accurate diagnosis is critical [43; 129].

Laboratory studies often show patients to have an elevated erythrocyte sedimentation rate (ESR), typically >80 mm/hour. (In general, a normal rate would be less than or equal to the patient's age, divided by two.) Given the lack of sensitivity and specificity of this test, however, a normal ESR does not exclude the diagnosis [129]. Platelets may also be elevated, as well as liver function tests (especially alkaline phosphatase). These are nonspecific but may provide more information to make a clinical diagnosis [129].

Diagnosis is confirmed by biopsy of the temporal artery, which should be performed as an outpatient procedure within one week after the initiation of corticosteroid therapy [129]. The biopsy demonstrates skip lesions, which are due to the disease's segmental process. When ocular symptoms exist, emergency medical treatment is necessary. High-dose corticosteroids are an effective treatment. Headache usually resolves or greatly improves within three days of high-dose steroid treatment [43; 129]. A maintenance dose of prednisone may be required to be administered for one to two years in some patients [129].

Arterial Dissection

Arterial dissection may cause headache. Dissection of the cervical carotid or vertebral artery typically causes sudden, nonthrobbing pain around the eye, piercing pain in the neck, and a "pounding" one-sided headache. Headache with or without neck pain may be the only manifestation of cervical artery dissection. It is by far the most frequent symptom (55% to 100% of cases), and it is also the most frequent inaugural symptom (33% to 86% of cases). Headache and facial and neck pain are usually unilateral, severe, and persistent, averaging four days in duration. However, it has no constant specific pattern and may sometimes be misleading [43]. The headache is often mistaken to be due to migraine or tension. However, the time, course, and associated symptoms are considerably different.

The cause of arterial dissection is multifactorial and may involve some sudden neck movement, causing hyperextension or significant pressure in the area. This may be a result of trauma; however, cases of dissection have been reported after patients cough or sneeze, undergo spinal manipulation, shave a beard, or place their necks in the sink at beauty salons. Underlying arteriopathies, alone or in combination with the mechanical forces, account for most of the pathophysiology [130]. Therefore, it is important to determine what a patient was doing when the headache occurred.

The dissection may begin when the rotation/hyperextension of the neck causes a small lesion in the lining of an artery. This causes bleeding, which then leads to the formation of a clot. Over time, the clot expands restricting blood flow to the brain [130].

Dissection is more common in patients younger than 50 years of age. It accounts for nearly a quarter of all strokes in that age range [130]. Diagnosis is confirmed by Duplex scanning, MRI, MRA, and/or helical CT and, ultimately, arteriography. Several of these investigations are commonly needed as any of them may be normal. Once detected, the majority of patients survive, and most dissections heal without surgery. Treatment includes the use of anticoagulants (heparin followed by warfarin for three to six months), stenting, and bypass surgery on rare occasion [43].

Stroke

Headache, migraine, and stroke are common and can be temporally related, but a direct causal association has not been definitively proven in clinical studies. Headache may be coincidental with stroke (also referred to as cerebrovascular accident or stroke syndrome), including both ischemic and hemorrhagic stroke, or it may be a consequence of stroke. Headache or migraine may increase the risk of stroke [131]. Results of the Women's Health Study, presented at the 2013 International Headache Congress, reported that migraine with aura is a strong risk factor for any type of stroke [132; 133; 134]. Headaches associated with stroke are typically reported as dull but diffuse (35%) [135]. They are not localized to a particular side. In addition, headache presentation of a stroke is more common in patients younger than 40 years of age [135]. Headache is more likely to occur in combination with other signs and symptoms of stroke [132]. Depending upon the type of stroke, there may be a focal neurologic deficit, such as aphasia or dysarthria. Young patients should be evaluated carefully to avoid misclassification of stroke as a complicated migraine [135].

Diagnostic work-up necessitates a CT scan or MRI to identify the location of the stroke. Treatment focuses on preventing further ischemia and bleeding [132; 135]. For ischemic strokes, recombinant tissue plasminogen activator may be given within 3 to 4.5 hours of symptoms. Aspirin and other antiplatelet medications are also frequently used. For hemorrhagic stroke, most care is supportive, unless there is a large hematoma, in which case surgery may be necessary [124].

NEOPLASTIC CAUSES OF HEADACHES

Brain tumors are either primary or metastatic, and both types may have headaches as a symptom. Primary brain tumors arise from CNS tissue and account for approximately 50% of all cases of intracranial neoplasms; most do not metastasize. The remainder of brain neoplasms are caused by metastatic lesions. Gliomas, meningiomas, acoustic neuromas, and pituitary adenomas account for 95% of all primary brain tumors [136].

Estimates of the annual incidence rate of primary brain tumors range from 7 to 19.1 cases per 100,000 population. Metastatic tumors to the brain are more common, affecting more than 200,000 patients per year in the United States. Brain tumors are the second most common cancer in children, comprising 15% to 25% of all pediatric malignancies [136]. The most common primary tumors that metastasize to the brain are lung, breast, melanoma, and kidney [137]. Although the overall incidence remains low, it is increasing. This increase appears to be independent of improved diagnostic capabilities. However, it could be due to the aging population; approximately 60% of brain tumor patients are 50 to 70 years of age. Men are slightly more affected than women [136; 137].

Headache (42%) and seizure (21%) are the two most common presenting symptoms of brain tumors [137]. The headache is generally described as a dull ache and nonpulsating. It may be localized to one area early on, but often it is generalized. It tends to be mild and intermittent, but it is recurrent. Over a period of days, weeks, or months, it becomes more persistent and more intense. This is due to the fact

that most brain tumors tend to grow slowly over time and cause progressive symptoms. Headache is often a late complaint, not an isolated finding, and the worst presenting symptom in only one-half of patients. Most headaches in patients with brain tumors are nonspecific and resemble tension-type headaches. New onset of headaches in middle-aged or older patients is cause for concern as is a change in any patient's headache pattern [136].

The headache is typically associated with nausea. Depending upon the type, size, and location of the tumor, there may also be neurologic, visual, and/or hearing impairment. The location of the headache reliably indicates the side of the head affected, but it does not indicate the precise site of the tumor. The cause of the headache is a progressively enlarging mass causing displacement of, or traction on, pain-sensitive intracranial structures, producing a worsening headache [136; 137].

Headaches are more common with posterior fossa tumors [136]. Colloid cysts of the third ventricle may produce explosive paroxysmal headaches that last minutes to several hours and may be brought on or alleviated by sudden changes in position. This occurs because they produce position-dependent intermittent obstruction.

Diagnosis is made by contrast-enhanced CT or MRI. MRI is most helpful for identifying tumors in the posterior fossa [136]. Scans should then be followed by histologic analysis (hence the phrase "tissue is the issue" in oncology). Depending upon several factors, including tumor type, degree of any metastasis, and comorbidities, treatment options include surgery, radiation, and/or chemotherapy.

INFECTIOUS CAUSES OF HEADACHES

In general, headaches related to infections tend to be painful, accompanied by nausea, and gradual in onset. Infections may be bacterial, viral, or fungal. The most common types of infections that cause headaches are meningitis, encephalitis, sinusitis, and brain abscess.

Meningitis

Meningitis is an inflammation of the meninges. The etiology of the meningitis may be bacterial, viral, or fungal.

Bacterial meningitis causes an abrupt diffuse headache associated with a high fever, altered consciousness (most commonly lethargy), focal neurologic deficits, and nuchal rigidity [43]. The severity of the headache and the acuteness of the infection are directly proportional. Focal neurologic deficits and papilledema are uncommon. Classically, a patient would show Kernig sign (i.e., resistance to knee extension following flexion of hips and knees) and Brudzinski sign (i.e., rapid flexion of the neck elicits involuntary flexing of the knees in a supine patient). However, a prospective study of 297 adults with suspected meningitis documented very low sensitivities for these signs (5% for Kernig sign; 5% for Brudzinski sign) indicating that their absence should not defer the performance of lumbar puncture [138]. In general, whenever the diagnosis of meningitis is strongly considered, a lumbar puncture should be promptly performed [139]. Laboratory studies reveal a CSF with more than 100 WBCs per mL and a protein level >100 mg/dL. CSF cell counts above 2,000/mL, a protein above 100 mg/dL, and a CSF-serum glucose ratio of <0.40 are all 99% specific for bacterial meningitis [139]. Treatment with antibiotics is usually empiric but may be modified by gram stain results. Typical organisms are *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*.

Viral meningitis causes a less severe headache that may develop over several days with a low-grade fever. The headache is usually frontal or retro-orbital. Other symptoms may include fever, irritability, nausea, vomiting, stiff neck, rash, or fatigue within the previous 18 to 36 hours. Meticulous history taking is essential and should include evaluation of exposure to ill contacts; mosquitoes, or ticks; outdoor activity in areas of endemic Lyme disease; travel history; history of medication use, including intravenous drug use; and risk of sexually transmitted disease [140]. Diagnosis may be made

with the assistance of a CSF viral culture or the absence of a positive bacterial culture. Most cases of viral meningitis are caused by enteroviruses, such as coxsackieviruses and echoviruses. Herpes viruses and human immunodeficiency virus (HIV) may also cause viral meningitis. Therapy consists of bed rest, analgesics, fluids, and other conservative treatment [140].

Fungal meningitis gives a more chronic picture and may not be associated with fever or fever may be below normal. The headache is temporal, frontal, or retro-orbital. It becomes more frequent and severe over time and may be accompanied by irritability, nausea, vomiting, stiff neck, and hallucinations. Diagnosis is made by CSF analysis (fungal stain and culture, increased CSF pressure, elevated protein, decreased glucose [45% of blood glucose], and leukocytosis [40–400/mm³—mostly mononuclear cells]). The most common organism is *Cryptococcus neoformans* [139]. Blastomyces and coccidioides may also cause fungal meningitis. The most common treatment is with amphotericin B, an intravenous therapy. Intrathecal medication is given to patients through the spinal cord who do not respond positively to IV therapy. Rarely, treatment may also consist of oral antifungal drug therapy [141].

Encephalitis

Encephalitis is an inflammation of the brain parenchyma. Encephalitis may be due to either infectious or noninfectious causes. Noninfectious causes include toxins, tumors, and connective tissue disorders.

Viral encephalitis is the most common infectious type. Examples include herpes, arboviruses, HIV, and cytomegalovirus. Typically, there is acute onset of low-grade fever, altered consciousness, vomiting, and sometimes seizures. There is often disorientation and some speech disturbances. Encephalitis may occur as a secondary complication after the administration of certain vaccines or during the course of an acute illness, such as measles. Dull, diffuse headache may also be present, although it is neither common nor prominent as a symptom.

When present, the headache typically does not radiate. Headache is not as common a symptom as in meningitis [142].

Most cases of encephalitis are mild and benign in nature, with symptoms resolving over one to two weeks. When neurologic symptoms are present, it may take up to two months for symptoms to completely resolve. If associated with HIV, such infections may be life-threatening.

CSF examination is critical to establish the diagnosis and reveals moderate monocytosis and erythrocytosis with a variably elevated protein level. EEG is sensitive but not specific, and contrast CT is only 60% sensitive. It may be used, however, to evaluate acute disease progression and to follow up on complications. MRI is more sensitive than CT scan [142]. MRI with gadolinium enhancement is the preferred imaging study. One should keep in mind certain seasonal and geographic issues when differentiating specific etiologic agents.

Depending upon the etiology, treatment is mostly supportive (e.g., rest, fluid, electrolyte balance). For some conditions, antiretrovirals are available [142].

Sinusitis

Although the term “sinus headache” is widely used, sinus headaches are uncommon. Headaches due to sinusitis are confined to a small percentage of patients who have acute frontal sinusitis or sphenoiditis. Sinusitis rarely causes headache, let alone facial pain, except when there is an acute bacterial infection and the sinus in question cannot drain, and it is usually unilateral due to increased pressure and inflammation caused by pus trapped within the sinus cavity.

In acute rhinosinusitis, the patient may present with purulent nasal discharge, which is frequently associated with fever and leukocytosis [43]. The pain is felt as a deep, dull, heavy fullness that sometimes may be pulsatile. Shaking or flexion of the head, coughing, and sneezing exacerbate the pain. Sinus headache is seldom associated with nausea. In addition, it does not reach the same pain intensity of cluster headache or migraine.

The vast majority of patients with acute sinusitis respond to antibiotics [143]. Plain radiography is generally obsolete, but exceptions include its use in confirming air-fluid levels in acute sinusitis [144]. MRI is generally reserved for the evaluation of any complications of local sinus infections, particularly suspected intracranial extension. A CT scan is highly sensitive and is the examination of choice in the evaluation of sinusitis, particularly in cases of chronic sinus disease [144]. However, it is usually not useful in acute sinusitis, as diagnosis in these cases is primarily based on clinical findings. Coronal CT imaging is the preferred initial procedure [144].

Diagnosis may be made by Gram stain of the discharge directly from the sinuses. This is a technique that is not commonly performed in the primary care office setting. The most common organism is *Streptococcus*. The treatment, therefore, is appropriate antibiotics, typically for 10 to 14 days. The use of local corticosteroids may offer the allergic individual added relief when nasal symptoms are prominent [145]. Decongestants are often added.

It is important to note that more than 90% of self- or physician-diagnosed sinus headaches meet the IHS criteria for migraine or probable migraine [145; 146]. In those patients with migraine, the most common reasons for misdiagnosis include headache triggers, pain location, and associated features commonly attributed to sinus headache. The clinician should be aware of these unique presentations of migraine so that a correct diagnosis can be made and effective treatment instituted [145]. Additionally, a portion of patients with self-diagnosed sinus headache suffer from a headache type that is unclassifiable by the IHS criteria. These headaches are characterized by bilateral maxillary pressure, mild-to-moderate pain intensity, cranial autonomic symptoms, and the complete absence of migraine features [145].

Abscess

Brain abscesses are quite uncommon; however, when they do occur they are life-threatening. They may originate from a contiguous site of infection (e.g., sinusitis, dental infections, otitis media), hematogenous spread, or trauma. In at least 15% of cases, the source of the infection is unknown [43; 146; 147]. They occur usually in the first three decades of life. They are also more prevalent in immunocompromised patients [146].

A moderate-to-severe headache, frequently hemispherical, is a common complaint (70%) [147]. The level of pain remains constant and may be aggravated by straining [43]. Often, there is nuchal rigidity. Frontal lobe abscesses tend to present with headache more often than other regions. In more than half of the cases, patients present with fever, altered mental status, nausea, and vomiting. There may also be papilledema and seizures [146; 147].

The time course of an abscess is reflected in the symptoms and usually progresses over one to two weeks [147]. Diagnosis is aided by CT, MRI, and nuclear medicine studies. In general, MRI provides better brain parenchymal differentiation than CT and shows the edema from the abscess in better detail [147]. The abscess is also better demonstrated because the routine brain MRI generally is multiplanar, as opposed to the routine CT, which is usually axial. However, MRI may not be useful in an acutely ill patient [146]. MR spectroscopy and some nuclear medicine studies may also be helpful to differentiate abscess from brain tumor [146]. Diffusion weighted MR may also give early indication of an infarction because this may be part of the sequelae of the abscess. Lumbar puncture is contraindicated due to its poor diagnostic yield and possible risk of herniation of the cerebellar tonsils [146; 147].

The typical treatment is evacuation/drainage and an antibiotic regimen based on cultures. The most common organisms are *Staphylococcus aureus*, *Streptococcus*, *Bacteroides* species, and *Enterobacter*. Occasionally, intracranial tuberculosis or fungal infections may present as an abscess. Therefore, cultures for acid-fast bacilli and fungi should be done in all cases [43; 146].

PRESSURE HEADACHES

Hypertension

High blood pressure is an infrequent cause of headaches. In general, it does not become a cause of headaches until diastolic blood pressure exceeds 120 mm Hg [43; 148]. The association between blood pressure and headache is most clearly manifested in patients with systolic blood pressure greater than 200 mm Hg [148]. Whether moderate hypertension predisposes to headache at all remains controversial, but there is some evidence that it does [43].

Headaches associated with high blood pressure usually appear in the morning. Typically, the headache eases as the patient gets up and about [43; 148]. It is usually dull, although sometimes throbbing, and is either diffuse or bioccipital in location. Infrequently, it is bifrontal in location. As blood pressure increases, there is often nausea, vomiting, and visual disturbances. As elevation of blood pressure progresses further, seizures and confusion may develop.

Malignant hypertension occurs when there is evidence of end-organ damage. On funduscopy, one will see papilledema and retinal hemorrhages. A diagnosis of malignant hypertension is based on the association of severely elevated blood pressure (e.g., >130 mm Hg) with severe hypertensive retinopathy [149]. The average age at diagnosis is 40 years, although a wide range of ages has been observed. Men are affected more often than women and black individuals more often than whites [150; 151]. Despite progress in the overall management of hypertension, the prevalence of malignant hypertension has remained stable over the past 30 to 40 years [149].

Routine screening consists of a chest radiograph, which is useful for assessment of cardiac enlargement, pulmonary edema, or involvement of other thoracic structures. Other tests (e.g., head CT scan, transesophageal echocardiogram, renal angiography) may be indicated if directed by the initial workup. An EKG is an essential part of the evaluation to screen for ischemia, infarct, or evidence of electrolyte abnormalities or drug overdose [151]. Treatment consists of slowly reducing pressure. Too rapid a decline may cause cerebral hypoperfusion and coronary insufficiency. Recommendations advise reduction of mean arterial pressure by 25% over the first 24 to 48 hours [151]. Nitroprusside has been the drug of choice [151].

It is important not to misdiagnose the normal reactive hypertension that follows an ischemic stroke as hypertensive encephalopathy. In addition, a sudden increase in blood pressure may be the result of illicit drugs, such as cocaine or methamphetamine; this sudden increase may cause a headache [151]. Patients using MAOIs who ingest tyramine may also exhibit a precipitous rise in blood pressure that will cause a headache.

Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH) (formerly referred to as pseudotumor cerebri or benign intracranial hypertension) is characterized by increased intracranial pressure without evidence of a tumor, obstruction, infection, or encephalopathy [43; 152]. The etiology is unknown [153]. Although benign, it is not without morbidity.

A majority of patients present with papilledema (although IIH without papilledema has been observed), progressive visual loss, sixth-nerve palsies (10% to 40%), and headache [43; 152]. Headache is the most common symptom and is usually pulsatile and of mild severity. It is usually chronic in duration and can either be bilateral or unilateral; the most common presentation is bifrontotemporal. Overall, the patient appears in relatively reasonable health, although there may be some gastrointestinal upset [153; 154].

Incidence is greatest in young obese females. Risk factors include corticosteroid use, pregnancy, large doses of vitamin A, adrenal and parathyroid disease, and venous sinus thrombosis [43; 153].

The diagnosis is one of exclusion. Brain MRI with gadolinium enhancement is the study of choice for most patients with IIH because it provides sensitive screening for hydrocephalus, intracerebral masses, meningeal infiltrative or inflammatory disease, and dural venous sinus thrombosis. MR venography may be useful for patients who are at greater risk for dural venous sinus thrombosis. Brain CT scan is less expensive than MRI and is adequate to rule out larger tumors or lesions, but it is not as sensitive as MRI for meningeal infiltration and/or dural venous sinus thrombosis. On lumbar puncture, CSF pressure is elevated with a low protein level [153].

This condition may resolve spontaneously, although it may take several months to a year to completely resolve. Analgesics typically are given for the headache. Acetazolamide, or other diuretics, may be considered as well as serial lumbar punctures to drain fluid. Corticosteroids are sometimes used if there is impending visual loss. In rare circumstances, surgery consisting of lumboperitoneal shunting may be performed when the condition is refractory [153].

METABOLIC/TOXIC CAUSES OF HEADACHES

Carbon Monoxide

Numerous toxins may cause headache as a sequela. Carbon monoxide is one of the more common causes of poisoning and represents the most frequent cause of toxin-induced death. This poisoning most commonly occurs when there is inadequate or faulty ventilation. Examples of sources include car exhausts, propane heaters, and gasoline-powered generators [153; 155; 156; 157].

Patients typically present with headache, altered mental status (most commonly confusion), nausea, chest pain, and dizziness. Cherry-red discoloration of the skin and lips has been described but is a rare manifestation. The acuity and time of exposure determine the degree of symptoms [43]. High levels may cause loss of consciousness and death [153; 155; 156].

High clinical suspicion is necessary as this condition mimics other illnesses with nonspecific symptoms, including significant myocardial damage. A complete blood count and arterial blood gas analysis are helpful in aiding the diagnosis. Often, there is a metabolic acidosis with an anion gap; in addition, there may be neutrophilia. Diagnosis is made through measuring venous or arterial carboxyhemoglobin, which will be elevated (>2% nonsmokers, >9% smokers). Treatment involves 100% oxygen. Some patients may need to undergo hyperbaric treatment. In severe cases of poisoning, there may be residual brain damage [158].

Lead Poisoning

Lead poisoning is fairly uncommon in adults. In general, it takes years of exposure before symptoms become apparent. Whereas children usually become exposed due to lead-based paint in old homes, adults can develop lead poisoning through occupational exposures [159].

Symptoms include headache, which generally is diffuse and nonspecific, irritability, confusion, mood disorders, and sleep problems. As levels become toxic, patients develop ataxia and convulsions [159].

Diagnosis is based on symptoms and blood or urine tests for lead. Treatment involves chelation therapy in severe cases, as well as removal of the source of exposure [159].

OTHER CAUSES OF SECONDARY HEADACHES

Syringomyelia

Syringomyelia is an uncommon presentation of headache. It is a condition in which a cyst forms within the spinal cord, either congenitally or due to trauma, malignancy, infection, or hemorrhage. In most cases, the disorder is related to a congenital abnormality of the brain called a Chiari malformation. This malformation occurs during the development of the fetus and causes the lower part of the cerebellum to protrude from its normal location in the back of the cranium into the cervical portion of the spinal canal [160].

The cyst, or syrinx, gradually expands and elongates over time, eventually resulting in destruction of the cord's center. As a result, patients may present with a variety of symptoms, although they typically present with headache, back pain and stiffness, and numbness of the extremities [160]. Symptoms usually begin between 25 and 40 years of age; they are more common in men than women and may worsen with straining (e.g., heavy lifting) or any activity that causes CSF pressure to fluctuate [160].

Signs of the disorder tend to develop slowly, although sudden onset may occur with coughing or straining. In addition, there are often long periods of stability. The preferred imaging modality is MRI, which shows dilation of the central canal and may reveal contributing factors (e.g., a tumor). The usual treatment when significant symptoms are present is surgery, which involves drainage of the syrinx. If not treated surgically, syringomyelia may lead to progressive weakness in the arms and legs, loss of hand sensation, and chronic, severe pain [160].

In the absence of symptoms, syringomyelia is usually followed by observation over time. Patients are advised to avoid activities that involve straining [160].

Dental and Myofascial Causes

There may be times when referral to a dentist is appropriate for headache management. Disorders of the teeth usually cause toothache and/or facial pain; those causing headache are rare. Pain from the teeth may be referred, however, and cause diffuse headache. The most common cause of headache is periodontitis or pericoronitis as the result of infection or traumatic irritation around a partially-erupted lower wisdom tooth [43].

Myofascial pain dysfunction (MPD) syndrome (formerly called temporomandibular joint or TMJ syndrome) originates in the muscles that move the jaw. Symptoms include dull, aching pain in and around the ear, which may radiate to the side of the scalp, back of the head, or down into the neck. In the majority of instances, the source of pain is an overuse of the masticatory musculature through parafunction. The most common dental parafunctional habits are bruxism and clenching. The patient is often unaware of the habit, which may take place while asleep [161].

Initial therapy is directed at relief of muscle spasms and involves use of heat, massage, a soft and non-chewy diet, muscle relaxing, and pain-reducing medications. For many patients, one or two weeks of such treatment is sufficient to eliminate the symptoms. Early treatment is important to prevent shifting of the jaw and arthritic changes in the jaw joint [161].

Cervicogenic Headache

Cervicogenic headache is often a sequela of head or neck injury but may also occur in the absence of trauma [162]. With this type of headache, the pain is perceived to be in the head but is actually referred from the cervical spine. Typically, the pain may be characterized as insidious in nature and unilateral in position [163]. The parietal and occipital areas are most commonly affected. The pain is usually fairly constant and may last for days to weeks. It is aggravated by neck movements. On exam, there is usually cervical paraspinal tenderness. The source of pain is usually the cervical ligaments or intervertebral discs [162].

The mean age of patients with this condition is 43 years, and it is four times more prevalent in women than in men [162; 163]. Diagnostic criteria have been established, but the presenting characteristics of cervicogenic headache are often difficult to distinguish from primary headaches disorders, such as tension-type headache [43; 162]. Additionally, there are significant differences, especially with respect to quality of life. In a study comparing responses on a medical outcomes questionnaire for patients with cervicogenic headache, episodic tension-type headache, and patients with migraine without aura, domain scores for physical functioning for patients with cervicogenic headache were lower than the tension-type and migraine groups [164].

Diagnostic imaging cannot confirm the diagnosis of cervicogenic headache but may lend support to its diagnosis. Successful treatment requires a multifaceted approach, including using pharmacologic, nonpharmacologic, manipulative, anesthetic, and occasionally surgical interventions. Medications alone have proven to be ineffective or, at best, to provide only modest benefit [162; 163].

Medication Overuse

Medication overuse headache, also known as rebound headache, results from misuse of drugs, most notably over-the-counter analgesics or migraine medications. It is most common in patients with frequent migraine attacks or tension-type headaches [165]. Chronic tension-type headache is less often associated with medication overuse; however, episodic tension-type headache has commonly become a chronic headache through overuse of analgesics [43]. The headache is caused

by frequent use of anti-headache medications for more than 15 days per month. Evidence suggests that this occurs sooner with triptan overuse than with ergotamine overuse [43; 166]. The mean period of time that elapses before this type of headache evolves ranges from one to two years for the triptans, three to five years for ergotamines, and up to 5 to 10 years for over-the-counter analgesics [167]. The pathophysiology of this syndrome remains unknown.

The diagnosis of medication-overuse headache is clinically extremely important because patients rarely respond to preventative medications while overusing acute medications [43]. Treatment is withdrawal from the medication. If tapered, this may take more than two weeks, depending on the medication. Improvement should occur within two months after cessation of overuse in order for the diagnosis to be definite [43]. This is followed by prophylactic treatment of the primary headache [165; 166].

Herbal Medications

It is important to consider the use of herbal medications as a possible cause of headaches. Approximately 38% of adults in the United States use at least one herbal medicine [168]. Many patients do not admit use to physicians, either because they do not consider them to be a “medication,” because they do not need a prescription to obtain them, or because they are embarrassed to admit they use a medication that most physicians do not consider scientific. Herbal medications that have been reported to cause headaches include valerian root, ginkgo biloba, and ginseng [169].

ACUTE VERSUS CHRONIC

Although chronic headache is a term often used by patients, as well as some clinicians, it is no longer a recognized diagnosis. Patients either have a chronic primary headache or a chronic secondary headache. Chronic daily headache occurs in approximately 4% to 5% of the population [170; 171]. The overwhelming majority of chronic headaches are primary headaches, typically migraine or tension. Chronic headache is not a separate syndrome. The general time frame for chronic is when the headache occurs on more than 15 days of each month, whether or not the patient is taking any medication.

REFERRAL

One of the most important decisions in managing patients with headaches, especially chronic headaches, is when to continue care and when to refer care. In general, most patients with benign headaches can be managed by primary care physicians and other clinicians. There are several factors involved when one should consider referral to a specialist. These include, but are not limited to:

- Minimal physician expertise in headache management
- Unable to determine diagnosis
- Failure of the patient to respond to appropriate treatment
- Worsening symptoms
- Development of rebound cycles
- Dependence on opioids
- Significant comorbidities

When one or more of these conditions exist, referral to a specialist should be considered. Specialists typically are neurologists, although some are internists and family practitioners who focus their clinical practice on headache management. Headaches represent the most common reason for neurology visits [172]. Therefore, physicians should not view referral as failure on their part.



The decision to seek a specialty consultation will depend upon the practitioner's familiarity and comfort with headache and its management. The Institute for Clinical Systems Improvement recommends considering specialty consultation when:

- The diagnosis cannot be confirmed.
- Etiology cannot be diagnosed or warning signals are present.
- Headache attacks are occurring with a frequency or duration sufficient to impair the patient's quality of life despite treatment or the patient has failed to respond to acute remedies or is in status migrainosus.

(<https://www.icsi.org/wp-content/uploads/2019/01/HeadacheRR.pdf>. Last accessed April 5, 2022.)

Level of Evidence: Expert Opinion/Consensus Statement

MEDICO-LEGAL ISSUES

With rising malpractice premiums, the threat of malpractice remains high on the minds of many healthcare professionals. With respect to headaches, physicians are fearful of missing that rare brain tumor or other catastrophic cause of headache. When such a misdiagnosis occurs, a malpractice claim may ensue. Any malpractice action falls under tort law.

Tort law allows injured persons to recover damages through the civil (i.e., noncriminal) judicial system. It is important to note that injury is a necessary but not sufficient requirement for recovery and most injuries do not give rise to a legal action. In the context of medical malpractice suits, the most relevant aspect of tort law is negligence as that is the claim most plaintiffs raise. A common claim for headache management is "failure to diagnose."

Not all bad outcomes, however, support a claim for negligence. There are several necessary components to negligence, all of which must be present for a plaintiff to prevail. First, the defendant must have owed some duty to the plaintiff to adhere to a specific standard of conduct and protect the plaintiff from unreasonable risk of injury. In the context of the doctor-patient relationship, this duty is for the physician to meet the standard of care for his or her profession. Generally the standard of care is the knowledge and skill held by a member of the profession in the same community or a similar community. The standard of care for specialists is somewhat higher as it is based on the knowledge and skill held by specialists.

Second, the defendant must have breached this duty by deviating from the standard of care. Such a deviation may be either an act or an omission. Finally, this breach of duty must be the actual and proximate cause of the plaintiff's injury. This means that a physician might make a clear medical error but if that error proves harmless and does not actually cause any injury to the patient, there is no legitimate claim for negligence.

In order to minimize malpractice, physicians and other clinicians should document their actions and thought processes in the medical record. In addition, it is imperative that physicians keep up-to-date on the management of the conditions that they treat. If one has little expertise in headache management and the patient's condition is not improving, one should then consider referral.

CONCLUSION

Headaches represent one of the most common medical conditions and are a frequent reason for physician visits. They produce a significant socioeconomic cost in terms of lost work and decreased quality of life. In general, most headaches will be benign; however, there should be a thorough history and physical exam each time a patient presents with headaches. The majority of headaches will be primary in origin (i.e., migraine, tension, cluster), but secondary causes need to be excluded. Physicians should be aware of the warning signs that warrant an immediate and thorough work-up and realize that a patient may have more than one headache disorder. Various imaging modalities, such as CT, MRI, and PET, exist but should be used prudently, based on clinical presentation and clinical suspicion of disease.

Numerous treatment modalities exist to treat the various headache syndromes. Therapies for primary headaches include both pharmacologic and nonpharmacologic interventions. Preventive therapies also should be explored for patients with repeat headaches. Finally, primary care physicians and clinicians should know when to refer patients to a specialist.

ADDITIONAL SOURCES OF INFORMATION

American Migraine Foundation

<http://americanmigrainefoundation.org>

American Headache Society (AHS)

<https://americanheadachesociety.org>

Help for Headaches

<http://www.headache-help.org>

International Headache Society

<https://ihs-headache.org>

National Headache Foundation

<https://headaches.org>

FACULTY BIOGRAPHY

John J. Whyte, MD, MPH, is currently the Director of Professional Affairs and Stakeholder Engagement at the FDA's Center for Drug Evaluation and Research. Previously, Dr. Whyte served as the Chief Medical Expert and Vice President, Health and Medical Education at Discovery Channel, part of the media conglomerate Discovery Communications. In this role, Dr. Whyte developed, designed, and delivered educational programming that appeals to both a medical and lay audience.

Prior to this, Dr. Whyte was in the Immediate Office of the Director at the Agency for Healthcare Research Quality. He served as Medical Advisor/Director of the Council on Private Sector Initiatives to Improve the Safety, Security, and Quality of Healthcare. Prior to this assignment, Dr. Whyte was the Acting Director, Division of Medical Items and Devices in the Coverage and Analysis Group in the Centers for Medicare & Medicaid Services (CMS). CMS is the federal agency responsible for administering the Medicare and Medicaid programs. In his role at CMS, Dr. Whyte made recommendations as to whether or not the Medicare program should pay for certain procedures, equipment, or services. His division was responsible for durable medical equipment, orthotics/prosthetics, drugs/biologics/therapeutics, medical items, laboratory tests, and non-implantable devices. As Division Director as well as Medical Officer/Senior Advisor, Dr. Whyte was responsible for more national coverage decisions than any other CMS staff.

Dr. Whyte is a board-certified internist. He completed an internal medicine residency at Duke University Medical Center as well as earned a Master's of Public Health (MPH) in Health Policy and Management at Harvard University School of Public Health. Prior to arriving in Washington, Dr. Whyte was a health services research fellow at Stanford and attending physician in the Department of Medicine. He has written extensively in the medical and lay press on health policy issues.

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