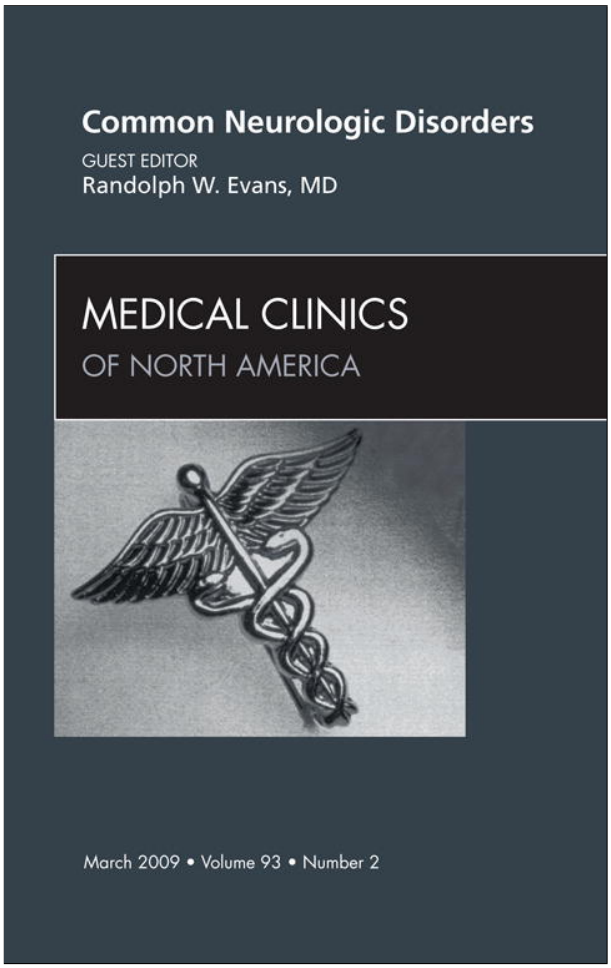

Migraine: A Question and Answer Review

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KEYWORDS

• Migraine • Clinical features • Diagnosis • Diagnostic testing
• Treatment

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

Where does the Word Migraine Originate?

Migraine comes from a Greek word meaning ''hemicrania'' or ''half the head,'' which, as discussed later, is only a partial description.

What is the Prevalence of Migraine in the United States?

The 1-year period prevalence is 11.7% (17.1% in women and 5.6% in men), some 29 million people.[1] An additional 4.5% have probable migraine, which fulfills all but one criterion for migraine with or without aura and responds to migraine medication.[2] The lifetime prevalence is 25% of women and 8% of men. Chronic migraine, which occurs on 15 or more days per month for at least 3 months, may occur in 1% to 2% of the population yearly.

Migraine prevalence is highest in those aged 30 to 39 years for both men (7.4%), and women (24.4%) and lowest in those aged 60 years or older at 1.6% in men and 5.0% in women (**Fig. 1**). The frequency of migraines per month is as follows: less than one, 23%; 1 to 4, 63%; 5 to 9, 9.6%, and 9 to 14, 4.2%.

Who are Some Famous Male Migraineurs?

Because migraine is much more common in women, including Joan of Arc and Elizabeth Taylor, men who have migraine may get ignored. Famous historical figures suspected of having migraine include Julius Caesar, Napoleon Bonaparte, Thomas Jefferson, Ulysses Grant, Friedrich Nietzsche, Sigmund Freud, Claude Monet, Alexander Graham Bell, and Lewis Carroll. Elvis Presley had migraine—the sunglasses were not just to look cool.

Probably the most witnessed migraine took place in Super Bowl XXXII in 1998. Running back Terrell Davis, who had a history of migraine, developed a migraine with visual aura after a ding on the helmet at the end of the first quarter. After

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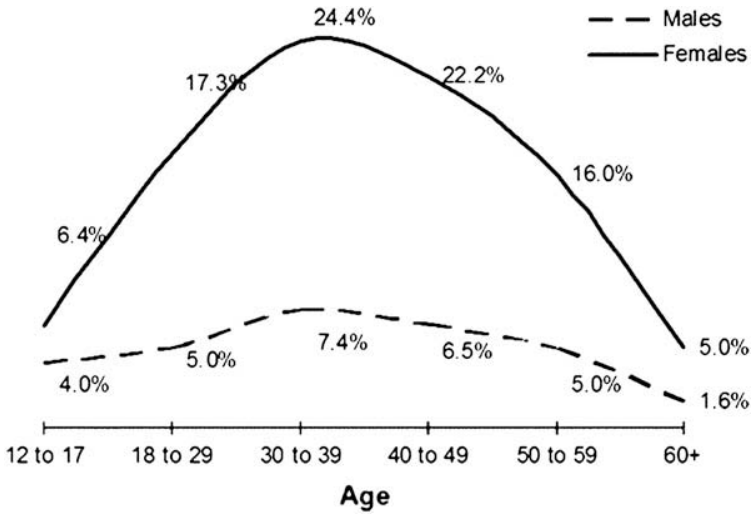

Fig. 1. One-year period prevalence of migraine by age and sex adjusted for demographics. (*Reproduced from* Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343; with permission.)

successfully using dihydroergotamine (DHE) nasal spray, he was able to return for the third quarter, scored the winning touchdown, set a Super Bowl rushing record, and was voted Most Valuable Player. Early treatment does make a difference.

It is not surprising that Freud was a migraineur because he was a psychiatrist and also a neurologist. More than 50% of neurologists and 75% of headache specialists have migraines, including this author.[3]

What is the Genetics of Migraine?

Migraine often runs in families with the risk for migraine increased in first-degree relatives by 1.5 to 4 fold. The risk is greatest for those who have migraine with aura, young age at onset, and a high attack severity and disease disability. Up to 61% of migraine is hereditable.[4] There is an unclear mode of transmission, however, which is genetically heterogeneous.

What is the Cause of Migraine?

The cause of migraine is not known. Migraine is an often inherited episodic disorder with a disturbance in the perception of normal sensory input, such as pain, light, and sound signals.[5] Migraine may be a disorder of ion channels, as suggested by the rare example of familial hemiplegic migraine. Functional imaging studies have demonstrated migraine-related activation of the dorsolateral pons. Associated neurologic symptoms (the aura) are likely to be the human homolog of the experimental phenomenon known as cortical spreading depression (in the occipital cortex in visual aura).

What Disorders are Comorbid with Migraine?

Numerous disorders are comorbid with migraine, including the following: cardiovascular and cerebrovascular (hypertension/hypotension, Raynaud, mitral valve prolapse, angina/myocardial infarction, stroke), psychiatric; neurologic (epilepsy, essential tremor, benign positional vertigo, and restless legs syndrome), gastrointestinal (irritable bowel syndrome), and other (asthma, atopic allergies, endometriosis, and fibromyalgia).

Psychiatric disorders are among the most common migraine comorbidities.[6,7] Migraineurs are from 2.2 to 4.0 times more likely to have depression. Migraine is also comorbid with generalized anxiety disorder (odds ratio [OR] 3.5 to 5.3), panic disorder (OR 3.7), and bipolar disorder (OR 2.9 to 7.3).

Is Syncope More Common in Migraineurs?

In a population-based study among migraineurs with and without aura (n = 323) and control subjects (n = 153), migraineurs had a higher lifetime prevalence of syncope (46% versus 31%; $P = .001$), frequent syncope (five or more attacks) (13% versus 5%; $P = .02$), and orthostatic intolerance (32% versus 12%; $P<.001$) compared with controls of uncertain etiology.[8] There was no association between autonomic nerve system symptoms and the severity of migraine or type of migraine. Cardiovascular measurements and the prevalence of postural tachycardia syndrome and orthostatic hypotension did not differ significantly between migraineurs and controls. Migraineurs who have syncopal episodes require diagnostic testing as appropriate.

How Often do Sufferers Know That They Have Migraine?

Only 56% of migraineurs know that they have migraine. In a recent study, sinus headache (39%), tension-type headache (31%), and stress headache (29%) were common self-reported diagnoses among migraineurs (subjects could list more than one probable diagnosis).[9]

How often do Patients who Have Self- or Physician-Diagnosed Sinus Headaches Actually Have Migraines?

In a study of 2991 patients who had a history of self-described or physician-diagnosed sinus headache, 88% were diagnosed as fulfilling migraine (80% of patients) or migrainous criteria (8% of patients).[10]

CLINICAL FEATURES

What are the International Classification of Headache Disorders Second Edition (ICHD-2) Criteria for Migraine without Aura?

The duration of untreated or unsuccessfully treated episodes ranges from 4 to 72 hours. The headaches are associated with at least two of the following pain characteristics: unilateral location, pulsating quality, moderate or severe intensity, and aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs). The pain is accompanied by at least one of the following symptoms: nausea or vomiting, sensitivity to light (photophobia), and sensitivity to sound (phonophobia). Also, the patient must have a history of at least five previous attacks that meet these criteria. If there are no indications that other primary causes may be responsible for the headaches, a diagnosis of migraine without aura can be reasonably established.[11] Migraine without aura accounts for about 70% to 80% of migraine attacks.

What are the General Features of Migraine?

Although the International Classification of Headache Disorders second edition (ICHD-2) criteria have been useful for research purposes, most clinicians recognize migraine through familiarity with the general features. Migraine pain is unilateral in 60% of cases and bilateral in 40%. About 15% of migraineurs report so-called ‘‘side-locked’’ headaches, with migraine always occurring on the same side. The pain is often more intense in the frontotemporal and ocular regions before spreading to the parietal and occipital areas. Any region of the head or face may be affected, including the parietal region, the upper or lower jaw or teeth, the malar eminence, and the upper anterior

neck. Throbbing pain is present in 85% of episodes of migraine, although up to 50% of patients describe non-throbbing pain during some attacks. Up to 75% of migraineurs report, along with the head pain, unilateral or bilateral tightness, stiffness, or throbbing pain in the posterior neck. The neck pain can occur during the migraine prodrome, the attack itself, or the postdrome.

Migraines last 4 to 72 hours if left untreated or if unsuccessfully treated. Migraine persisting for more than 72 hours is termed status migrainosus. Without treatment, 80% of patients have moderate to severe pain and 20% have mild pain. The pain, which is usually increased by physical activity or movement, is associated with nausea in about 80% of episodes, vomiting in about 30%, photophobia in about 90%, and phonophobia in about 80%.[12]

When patients deny a history of light and noise sensitivity, the questions should be asked, ''During a headache, would you prefer to be in bright sunlight or in a dark room?'' and ''During a headache, would you prefer to be in a room with loud music or in a quiet room?'' About 20% additional patients become aware of associated light and noise sensitivity by use of the follow-up questions.[13]

Forty-five percent of migraineurs have at least one autonomic symptom (ie, lacrimation, eye redness, ptosis, eyelid edema, nasal congestion, or rhinorrhea) during an attack. These symptoms are caused by parasympathetic activation of the sphenopalatine ganglion, which innervates the tear ducts and sinuses, and these symptoms can lead to confusion of migraine with sinus headaches. Of patients who have autonomic symptoms, 45% have both nasal and ocular symptoms, 21% have nasal symptoms only, and 34% have ocular symptoms only.[14]

How many Patients are Impaired During Migraine Attacks?

A large study found that 54% have severe impairment or require bed rest, 39% have some impairment, and 7% report no impairment.[1] In the prior 3 months, 25% missed at least 1 day of school or work, 28% had work or school productivity reduced by at least 50%, 34% had household productivity reduced by at least 50%, 47% did no household work, and 29% missed family or social activities.

How do you Distinguish Migraine from Other Primary Headaches?

Table 1 compares the features of migraine, tension-type, and cluster headaches.

Why are Migraines Commonly Misdiagnosed as Sinus and Stress Headaches?

Migraine can be confused with sinus headache because the pain can be referred to the face or forehead, associated with nasal or ocular symptoms, such as nasal congestion, eye redness, or lacrimation, and can be triggered by changes in the weather. Migraine can be misdiagnosed as stress or tension headaches because 75% of headaches may be referred to the neck and 50% can be triggered by stress. Again, the history of other associated symptoms makes the diagnosis.

What are Migraine Prodromal Symptoms?

Prodromal or premonitory symptoms, which may be present in up to 80% of cases and precede the migraine attack by hours or up to 1 or 2 days, include changes in mental state, such as depression, hyperactivity, euphoria, talkativeness, irritability, drowsiness, or restlessness. Neurologic symptoms may include photophobia, difficulty concentrating, phonophobia, dysphasia, hyperosmia, and yawning. General symptoms may include stiff neck, food cravings, feeling cold, anorexia, sluggishness, diarrhea or constipation, thirst, and fluid retention. Migraineurs have an average of seven prodromal symptoms per attack, including the following most common: anxiety, irritability,

Table 1
Features of some primary headaches

Feature	Migraine	Episodic Tension-Type	Episodic Cluster
Epidemiology	18% of women, 6% of men 4% of children before puberty	90% of adults 35% of children aged 3–11 y	0.4% for men 0.08% for women
Female/male	3/1 after puberty, 1/1 before	5/4	1/5
Family history	80% of first-degree relatives	Frequent	Rare
Typical age at onset (y)	92% before age 40, 2% after age 50	20–40	20–40
Visual aura	In 20%	No	Occasional
Location	Unilateral, 60%; bilateral, 40%	Bilateral > unilateral	Unilateral Especially orbital, periorbital, frontotemporal
Quality	Pulsatile or throbbing in 85%	Pressure, aching, tight, squeezing	Boring, burning, or stabbing
Severity	Mild to severe	Mild to moderate	Severe
Onset to peak pain	Minutes to hours	Hours	Minutes
Duration	4–72 h May be <1 h in children	Hours to days	15–180 min
Frequency	Rare to frequent	Rare to frequent	1–8 per d during clusters
Periodicity	Menstrual migraine	No	Yes Average bouts 4–8 weeks Average 1 or 2 bouts yearly
Associated features	Nausea in 90%, vomiting in 30%, light and noise sensitivity in 80%	Occasional nausea	Ipsilateral conjunctival injection, tearing, and nasal congestion or drainage Ptosis and miosis in 30%
Triggers	Present in 85% Present in 85%	Stress, lack of sleep	Alcohol, nitrates
Behavior during headache	Still, quiet, tries to sleep	No change	Often paces
Awakens from sleep	Can occur	Rare	Frequently

Data from Evans RW. Diagnosis of headaches. In Evans RW, Mathew NT, editors. Handbook of headache. 2nd edition. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 14–5.

yawning, unhappiness, concentration difficulties, somnolence, light and noise sensitivity, flatulence, and constipation.[15]

What are Migraine Triggers?

Migraines are often triggered by environmental or other factors; 85% of migraineurs report triggers. Patients typically have multiple triggers, with a mean of three. Up to 53% of migraineurs report that a change of weather is a trigger.[16] Other environmental triggers are heat, high humidity, and high altitude. There are numerous additional triggers, including stress (reported by up to 80% of patients), letdown after stress, vacations, and crying. Missing a meal (57%), lack of sleep, oversleeping, and fatigue are also commonly reported as triggers. Sensory triggers include bright lights, glare, flickering lights, loud noise, and strong smells, such as perfume or cigarette smoke. Up to 50% of patients report alcohol as a trigger; this can be all forms of alcohol or only one type, such as red wine or beer. Up to 45% report food triggers, such as chocolate, dairy products (particularly cheese), citrus fruit, fried foods, and nitrates and nitrites in cured meats or fish (eg, frankfurters, bacon, and smoked salmon). Other triggers include minor head trauma, exertion, and nitroglycerin.

There are triggers unique to women. Half of women who have migraine report menses as a trigger, and 14% have migraines associated only with their menses. During pregnancy, the frequency of migraines decreases (especially during the second and third trimesters) in 60%, remains the same in 20%, and increases in 20%. Migraines may occur for the first time when women start using oral contraceptives (OCs). Low-estrogen OCs usually have no effect on migraine or may even improve it, although frequency can increase. Of patients who have new-onset migraine or increased frequency of migraine associated with OCs, 30% to 40% may improve when OCs are discontinued, although improvement may not occur for up to 1 year. Two thirds of women who have prior migraine improve with physiologic menopause. Surgical menopause results in worsening of migraine in two thirds of cases.

What is Central Sensitization?

As the headache progresses, central sensitization can cause cutaneous allodynia (pain provoked by stimulation of the skin that would ordinarily not produce pain; this is seen especially in the head and face, but it can also be generalized), and triptans are unlikely to be an effective treatment.[17]

What is a Migraine Aura?

The migraine aura has a total duration of usually less than 1 hour and frequently less than 30 minutes.[18] An aura lasting more than 1 hour but less than 1 week is termed migraine with prolonged aura, or complicated migraine. The most common aura is a visual one, which is present in 99% of cases and has two types: positive visual phenomena, with hallucinations; and negative visual phenomena or scotomas, with either an incomplete or complete loss of vision in a portion or all of the visual field. Most visual auras have a hemianoptic distribution. Photopsias consist of small spots, dots, stars, unformed flashes or streaks of light, or simple geometric forms and patterns that typically flicker or sparkle.

A scintillating scotoma, also called a fortification (because of its resemblance to a medieval fortified town as viewed from above) spectrum or teichopsia (seeing fortifications), is present in about 10% of cases. The scotoma, which is frequently semicircular or horseshoe shaped, usually begins in the center of the visual field and then slowly extends laterally. The scotomatous arc or band is a shimmering or glittering, bright, zigzag border. Most visual auras consist of flickering, colored or

uncolored, unilateral or bilateral zig-zag lines or patterns, semicircular or arcuate patterns, wavy lines, or irregular patterns. Rare visual auras include metamorphopsia (objects appear to change in size and shape), macropsia, micropsia, telescopic vision (objects appear larger than normal), teleopsia (objects appear to be far away), mosaic vision, Alice in Wonderland syndrome (distorted body image), and multiple images. Headaches, when unilateral, usually occur on the side contralateral to the visual symptoms but can occasionally be ipsilateral.

What Other Type of Auras can Occur?

A sensory aura, which is present in about 30% of episodes of migraine with aura, consists of numbness, tingling, or a pins-and-needles sensation. The aura, which is usually unilateral, commonly affects the hand and then the face, or it may affect either one alone. Paresthesia of one side of the tongue is typical. Less often, the leg and trunk may be involved. A true motor aura is rare, but sensory ataxia or a heavy feeling is often misinterpreted as weakness.

Speech and language disturbances may occur in up to 20% of cases. Patients often report a speech disturbance when the spreading paresthesias reach the face or tongue. Slurred speech may be present. With involvement of the dominant hemisphere, paraphasic errors and other types of impaired language production and comprehension may occur. Rarely, other aura symptoms may be described, including déjà vu and olfactory and gustatory hallucinations.

Although visual symptoms frequently occur by themselves, combinations of aura symptoms can occur. Sensory, speech, and motor symptoms are usually associated with visual symptoms or with one or more other symptoms. When two or more aura symptoms are present, they almost always occur in succession rather than simultaneously.

Migraine aura can occur without headache (acephalgic migraine), often in patients who typically have migraine with or without aura. A visual aura is the most common in these cases. Another type of acephalgic migraine is episodic vertigo without a headache, auditory disturbances, or other neurologic symptoms, lasting minutes to days. Rarely, migraineurs may have persistent visual aura. This aura usually consists of simple, unformed hallucinations in the entire visual field of both eyes, including innumerable dots, television static, clouds, heat waves, flashing or flickering lights, lines of ants, a rainlike or snowlike pattern, squiggles, bubbles, and grainy vision. Occasionally, palinopsia (the persistence of visual images), micropsia, or formed hallucinations occur.

What are Late-Life Migraine Accompaniments?

Late-life migraine accompaniments are transient visual, sensory, motor, or behavioral neurologic manifestations of the migraine aura.[19] More than 1% of the population has a first episode of migraine aura after the age of 50 years. Headache is associated with only 50% of cases and may be mild. These accompaniments occur more often in men than in women. From most to least common, migraine accompaniments consist of visual symptoms (transient blindness, homonymous hemianopsia, and blurring of vision), paresthesias (numbness, tingling, pins-and-needles sensation, or a heavy feeling of an extremity), brain stem and cerebellar dysfunction (ataxia, clumsiness, hearing loss, tinnitus, vertigo, and syncope), and disturbances of speech (dysarthria or dysphasia).

Other causes of transient cerebral ischemia should be considered, especially when the patient is seen after the first episode or if the case has unusual aspects. The usual diagnostic evaluation for transient ischemic attacks (TIAs) or seizures is performed.

Features that help distinguish migraine accompaniments from TIAs include a gradual build-up of sensory symptoms, a march of sensory paresthesias, serial progression from one accompaniment to another, longer duration (90% of TIAs last for less than 15 minutes), and multiple stereotypical episodes. If the episodes are frequent, the usual preventive medications may be considered.

What is Basilar-Type Migraine?

Basilar-type migraine is a rare disorder that most often occurs in children and rarely presents in patients older than 50 years. According to ICHD-2 criteria, attacks are marked by two or more of the following fully reversible aura symptoms originating from the brain stem or both occipital lobes, but no motor weakness: dysarthria, vertigo, tinnitus, hypacusia, diplopia, visual symptoms simultaneously in both temporal and nasal field of both eyes, ataxia, decreased level of consciousness, and simultaneously bilateral paresthesias. There is also at least one of the following: at least one aura symptom develops gradually over 5 minutes or more or different aura symptoms occur in succession over 5 minutes or more; each aura symptom lasts between 5 and 60 minutes. Patients who have basilar-type migraine may also have other types of migraine. Visual symptoms—which usually take the form of blurred vision, shimmering colored lights accompanied by blank spots in the visual field, scintillating scotoma, and graying of vision—may start in one visual field and then spread to become bilateral. Diplopia occurs in up to 16% of cases. Vertigo may be present, either alone or accompanied by various combinations of tinnitus, dysarthria, gait ataxia, and paresthesias (usually bilateral, but sometimes affecting alternate sides in successive episodes). Impairment of consciousness is common and may include obtundation, amnesia, syncope, and, rarely, prolonged coma. A severe throbbing headache, typically with a bilateral occipital location, is present in 96% of cases. Nausea and vomiting typically occur, with light and noise sensitivity in up to 50% of cases.

DIAGNOSTIC TESTING

Is Neuroimaging Warranted in Migraineurs?

A report of the Quality Standards Subcommittee of the American Academy of Neurology makes the following recommendation: ''Neuroimaging is not usually warranted in patients with migraine and a normal neurologic examination.''[20] Numerous CT and MRI studies have been done in migraineurs, all finding a small percentage of significant abnormalities, with the most recent large study finding abnormalities in only 0.4%.[21]

What are Some Reasons to Consider Neuroimaging in Migraineurs?

Indications to consider neuroimaging include the following: unusual, prolonged, or persistent aura; increasing frequency, severity, or change in clinical features; first or worst migraine; basilar; confusional; hemiplegic; late-life migraine accompaniments; aura without headache; possibly headaches always on the same side; posttraumatic; and when patient or family and friends request. In the case of patient or their family or friend's request for imaging, often medically unnecessary imaging can be avoided with a brief discussion of their concerns (eg, brain tumor or aneurysm as the cause of the migraines) and why their headaches are typical of migraine, which is diagnosed clinically, whereas scanning has a minimal yield of incidental findings. If they are concerned about intracranial saccular aneurysm, I explain that the chance of an adult having an incidental aneurysm is about 2% but that an incidental aneurysm would not be responsible for migraines.

There are many reasons that physicians recommend diagnostic testing, including neuroimaging: aiming for diagnostic certainty, faulty cognitive reasoning, the medical decision rule that holds that it is better to impute disease than to risk overlooking it, busy practice conditions in which tests are ordered as shortcuts, patient and family expectations, financial incentives, and medicolegal issues. In the era of managed care, equally compelling reasons for not ordering diagnostic studies include physician fears of deselection and at-risk capitation. Lack of funds and underinsurance continue to be barriers for appropriate diagnostic testing for many patients.

Is it Preferable to Obtain a CT or MRI for the Evaluation of Headache?

CT detects most abnormalities that may cause headaches, which are also visualized on MRI.[22] CT is generally preferred over MRI for the evaluation of acute subarachnoid hemorrhage, acute head trauma, and bony abnormalities. There are several disorders that may be missed on routine CT of the head, including vascular disease, neoplastic disease, cervicomedullary lesions, infections, and low cerebrospinal fluid (CSF) pressure syndrome.

MRI is more sensitive than CT in the detection of posterior fossa and cervicomedullary lesions, ischemia, white matter abnormalities, cerebral venous thrombosis, subdural and epidural hematomas, neoplasms (especially in the posterior fossa), meningeal disease (such as carcinomatosis, diffuse dural enhancement in low CSF pressure syndrome, and sarcoid), and cerebritis and brain abscess. Pituitary pathology is more likely to be detected on a routine MRI of the brain than a routine CT. In addition, CT exposes the patient to ionizing radiation, which raises the long-term risk for cancer.[23] MRI is thus generally preferred over CT for the evaluation of headaches.

The yield of MRI may vary depending on the field strength of the magnet, the use of paramagnetic contrast, the selection of acquisition sequences, and the use of magnetic resonance angiography and venography. MRI has contraindications, however, such as the presence of some aneurysm clips or a pacemaker. In addition, about 8% of patients are claustrophobic and about 2% are unable tolerate the study.

What are White Matter Abnormalities and How often are they Detected in Migraineurs?

A patient wanted to be reassured that her 10-year history of typical migraines were not due to a brain tumor. She had a MRI scan and the report came back discussing a few scattered deep white matter abnormalities (WMA); you should consider microvascular ischemic disease or perhaps demyelinating disease (especially if you have an overzealous radiologist). Migraine should be listed in the differential.

WMA are foci of hyperintensity on both proton density and T2-weighted images in the deep and periventricular white matter caused by either interstitial edema or perivascular demyelination.[22] WMA are easily detected on MRI but are not seen on CT scan. The percentages of WMA for all types of migraine range from 12% to 46%, whereas the incidence of WMA in controls ranges from 2% to 14%. Although the cause of WMA in migraine is not certain, various hypotheses have been advanced, including increased platelet aggregability with microemboli, abnormal cerebrovascular regulation, and repeated attacks of hypoperfusion during the aura.

ACUTE TREATMENT

Are Over-the-Counter Medications Effective?

Over-the-counter medications are effective, especially for mild to moderate migraine pain when taken at the onset of headache. All migraine medications are more effective

if taken when the headache is mild. Aspirin, acetaminophen, and caffeine combination medications; aspirin; acetaminophen; and nonsteroidal anti-inflammatory medications can reduce the headache to mild or none 2 hours after dosing in up to 59% of patients. Use of these medications (naproxen sodium may be an exception) more than 2 to 3 days per week for several months may result in rebound headaches (the precise duration has not been determined). Isometheptene combination prescription medications may be similarly effective for some patients.

What about Butalbital Combinations and Opiates?

There is no evidence for efficacy from randomized controlled trials for the use of butalbital combinations. In addition, butalbital combinations are frequently associated with medication overuse or rebound headaches and can be habituating. In one study, use of butalbital as infrequently as 5 days per month was linked to transformation into chronic daily headache and medication overuse headache.[24] Patients on butalbital require careful monitoring with use preferably limited to no more than two to three treatment days per week or less.

Opiate combinations may be effective as rescue medication if a triptan did not work or for those who are triptan nonresponders or who have triptan contraindications. Opiates are also associated with a risk for dependency and medication overuse headaches. Preferably, patients' use should be limited to no more than 2 days per week.

What are Triptans and How Effective are They?

Triptan medications are selective 5-hydroxytryptamine (5-HT1B/1D) receptor agonists that share a basic indole ring structure with different side chains. Triptans have three potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex. These mechanisms inhibit the effects of activated nociceptive trigeminal afferents and control acute migraine attacks.

Over the past 16 years, seven triptans have become available: sumatriptan, zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan (**Table 2**).[25] Sumatriptan is also recently available in a combination with naproxen sodium, a bilayer tablet of 85 mg of rapid-release sumatriptan on the top and 500 mg of naproxen sodium on the bottom. If oral triptans are taken when the pain is moderate to severe in intensity, the 2-hour response rate (no pain or mild pain) is about 45% for naratriptan and frovatriptan and about 65% to 70% for the others. If taken when the headache is mild, the 2-hour pain-free responses are much higher for all of the triptans and may be greater than 70% depending on the drug. About 25% of patients do not respond to any of the triptans, however.[26]

The oral triptans may not be equally effective for different patients. If a patient has an unsatisfactory or inconsistent response, unpleasant side effects, or tachyphylaxis with one triptan, a different triptan may prove effective and tolerable. Patients who have prominent vomiting or nausea or who desire the quickest relief may benefit from subcutaneous sumatriptan (at 2 hours, 79% of patients show a response and 60% are pain-free) or intranasal sumatriptan or zolmitriptan. A non-triptan option is DHE nasal spray, which can be about as effective as any oral or nasal triptan and may also be effective in some patients who do not respond to any triptan.

Patients may experience recurrence, which is defined as the return of headache (usually of moderate or severe intensity) within 24 hours after an initial response to acute treatment, at which time patients may need to take a second dose of medication. When taken for moderate to severe pain, sumatriptan/naproxen sodium, naratriptan, frovatriptan, almotriptan, and eletriptan have the lowest recurrence rates of about

Table 2
Available triptan preparations

Drug	Formulation	Strengths (mg)
Almotriptan	Tablets	12.5
Eletriptan	Tablets	40
Frovatriptan	Tablets	2.5
Naratriptan	Tablets	1, 2.5
Rizatriptan	Tablets	5, 10
	Orally disintegrating preparation[a]	5, 10
Sumatriptan	Subcutaneous injection	4, 6
	Tablets	25, 50, 100
	Nasal spray	5, 20
Sumatriptan/naproxen sodium	Tablets	85/100
Zolmitriptan	Tablets	2.5, 5
	Orally disintegrating preparation[a]	2.5, 5
	Nasal spray	5

[a] Dissolves on the tongue; can be taken without water (efficacy similar to that of tablet form).

14% to 25%. The recurrence rates for the other triptans are about 30% to 40%. The time to recurrence is generally about 12 hours.[23]

What are the Contraindications for the use of Triptans?

Triptans are contraindicated in those who have ischemic heart disease, Prinzmetal angina, cerebrovascular disease, peripheral vascular syndromes, or uncontrolled hypertension and for use within 24 hours of ergotamine or dihydroergotamine.

Triptans can stimulate 5-HT1B receptors on coronary arteries and result in constriction, which may become clinically significant in patients who have coronary artery stenosis or vasospastic disease. The common triptan side effects—tightness, heaviness, pressure, or pain in the chest, neck, or throat—are not associated with electrocardiogram changes and are not caused by coronary vasoconstriction.

Should you be Concerned About Serotonin Syndrome When Prescribing Triptans and Antidepressants?

The serotonin syndrome is an adverse drug reaction that results from therapeutic single or combination medication use or overdose of medication that increase serotonin levels and stimulates central and peripheral postsynaptic serotonin receptors. Medications associated with the serotonin syndrome include selective serotonin reuptake inhibitors (SSRIs), selective serotonin/norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, tricyclic antidepressants, opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, drugs of abuse, and herbal products. The syndrome has also been associated with the withdrawal of medications. Sixty percent of patients who have serotonin syndrome present within 6 hours of medication initiation, overdose, or change in dosage, and 74% present within 24 hours.

The serotonin syndrome presents with one or a combination of mental status changes (with a range including anxiety, agitation, confusion, delirium and hallucinations, drowsiness, and coma), autonomic hyperactivity in about 50% of affected individuals (including hyperthermia, diaphoresis, sinus tachycardia, hypertension or

hypotension, flushing of the skin, diarrhea, and vomiting), and neuromuscular dysfunction (including myoclonus, hyperreflexia, muscle rigidity, tremor, and severe shivering).[27] The presentation may range from diarrhea and tremor in a mild case to life-threatening complications, such as seizures, coma, rhabdomyolysis, and disseminated intravascular coagulation. The diagnosis is one of exclusion based on the history of medication use, the physical examination, and ruling out other neurologic disorders, such as meningoencephalitis, delirium tremens, heat stroke, neuroleptic malignant syndrome, malignant hyperthermia, and anticholinergic poisoning.

In 2006, the Food and Drug Administration (FDA) issued an alert, **"**Potentially Life-Threatening Serotonin Syndrome with Combined Use of SSRIs or SNRIs and Triptan Medications"[28] stating, "The FDA has reviewed 27 reports of serotonin syndrome reported in association with concomitant SSRI or SNRI and triptan use. Two reports described life-threatening events, and 13 reports stated that the patients required hospitalization. Some of the cases occurred in patients who had previously used concomitant SSRIs or SNRIs and triptans without experiencing serotonin syndrome." The warning concluded, "The FDA recommends that patients treated concomitantly with a triptan and an SSRI/SNRI be informed of the possibility of serotonin syndrome (which may be more likely to occur when starting or increasing the dose of an SSRI, SNRI, or triptan) and be carefully followed."[28]

Through a Freedom of Information Act request, The FDA provided me with their complete reports of 29 possible serotonin syndrome cases (2 more than described in the alert), which I analyzed as previously reported.[29] Eight of the cases have been published; the rest were submitted to the FDA through the MedWatch reporting system. Of the 29 cases, 7 meet the Sternbach toxicity criteria but not the Hunter criteria. No cases meet both the Sternbach and Hunter criteria or the Hunter criteria but not the Sternbach. Even among those meeting criteria, however, there are questions as to whether other disorders were excluded in 6 cases.

During 2003 to 2004 alone, an annualized mean of 694,276 patients were simultaneously prescribed or continued use of a triptan along with an SSRI or SNRI. Millions of patients have been exposed to the triptan combinations worldwide and, according to my analysis, only 7 cases meet the Sternbach criteria, and none meet the more sensitive and specific Hunter criteria for serotonin syndrome.[30] Does this justify routinely advising our patients of this possibility as the FDA advisory recommends and perhaps unnecessarily alarming them? Some migraineurs on an SSRI or SNRI might be so alarmed that they would not want to take a triptan that could be effective, or those already taking a triptan may not want to take an indicated SSRI or SNRI. It is certainly possible that additional definite cases may be reported with greater physician awareness of these potential drug interactions and serotonin syndrome, although I am not aware of any definite cases in the 2 years since the release of the alert.

How do you Treat an Intractable Acute Migraine or Migraine Status (Persisting for more than 72 hours) in the Urgent Care Clinic or Emergency Department?

About 2% of patients in emergency rooms have migraines of the following types: first or worst attacks, those who have not taken or not responded to drugs, frequent attendees, those who have acute exacerbation of chronic migraine, and those who have migraine with neurologic symptoms and signs (with aura). These patients may receive a less-than warm welcome when they present with "just a headache." The migraines may be difficult to treat because the pain persists or recurs within 24 hours of discharge from the emergency department regardless of treatment in more than half of patients.

Intravenous fluids and electrolyte replacement may be necessary for the patient who has intractable vomiting from migraines. Evidence-based guidelines recommend the first-line use of DHE (0.5–1 mg intravenous [IV], intramuscular [IM], or subcutaneous [SC]), SC sumatriptan 4 to 6 mg (DHE and triptans should not be used within 24 hours of each other), dopamine antagonists (metoclopramide 10 mg IV, prochlorperazine 10 mg IV, and chlorpromazine 0.1 mg/kg), and ketorolac 30 mg IV or 30 to 60 mg IM, which have response rates of up to 70%.[31] Narcotic analgesics, recommended as rescue drugs, are still widely used, even though their administration may result in significantly longer stays in the emergency department compared with nonnarcotic treatments.[32] Narcotics, such as parenteral meperidine may be as effective as ketorolac but less effective than DHE and cause more sedation and dizziness.[33]

Intravenous valproate sodium (500 mg diluted in 50 mL of saline, administered intravenously over 5 to 10 minutes) and droperidol (2.5 mg IV or IM) may also be effective. Intravenous corticosteroids, such as a single dose of 10 to 24 mg of dexamethasone, are not effective for termination of the acute attack but may prevent recurrence of the headache with a number needed to treat of nine.[34]

There are the usual contraindications to the use of triptans and DHE and risk for administration with some of the drugs if the patient is pregnant. There is a small risk for prolonged QT intervals and torsade de pointes with the use of neuroleptics, such as prochlorperazine and droperidol.

PREVENTIVE TREATMENT

What are the Indications for Preventive Medications?

Indications for preventive treatment are as follows: the headaches significantly interfere with the patient's daily routine despite acute treatment; acute medications are contraindicated, ineffective, or overused, or have intolerable side effects; frequent migraines (two or more attacks a week); uncommon migraine types (hemiplegic, basilar, prolonged aura, or migrainous infarction); the cost of acute medications is significantly greater than the cost of preventive medication; and patient preference (ie, the patient is willing to risk the possibility of side effects from the preventive medication to reduce the frequency of headaches).[35]

What are the General Principles for use of Preventives?

- The clinician should start with a low dose of medication and increase it slowly, depending on the response and whether side effects occur.
- Each medication should be given a trial of 2 to 3 months at adequate doses.
- Overused medications that may be causing rebound headache and may decrease the efficacy of preventive treatment should be discontinued or tapered (depending on the drug).
- The patient should keep a headache diary to monitor his or her headaches.
- The clinician should educate the patient about the rationale for treatment and possible side effects and should address the patient's expectations for treatment. Many patients want a complete cure, and although this is certainly understandable, it is usually not possible.

Consider coexistent or comorbid conditions. Some medications may be effective for both migraine and another disorder. Other disorders, along with the migraine medications that may be effective for them, include epilepsy (divalproex sodium, topiramate, and gabapentin), hypertension (beta-blockers), depression (tricyclic antidepressants), bipolar disorder (divalproex sodium), insomnia (tricyclic antidepressants), essential tremor (beta-blockers and topiramate), and overweight or obesity

(topiramate). On the other hand, coexistent diseases, such as depression or asthma, may be relative contraindications to the use of beta-blockers. In a woman who is pregnant or may become pregnant, the potential for teratogenicity should be considered. Patients who have mild responses to one preventive agent may benefit from the addition of a second agent. Finally, when some drugs, such as tricyclic antidepressants and beta-blockers, are discontinued, they may need to be tapered off.

What Preventive Medications may be Effective?

Based on class I evidence, the beta-blocker propranolol, the tricyclic antidepressant amitriptyline, and the antiseizure medications divalproex sodium and topiramate are the most effective preventive medications, reducing the frequency of migraines by more than 50% in about 50% of patients.[36] In general, preventive medications are more effective when patients are placed on a titration schedule with a minimum target dose. Some titration schedules and minimum target doses are as follows: propranolol (either regular or long acting) 40 mg/d increased by 40 mg/wk to 120 to 160 mg; amitriptyline 10 to 25 mg at bedtime increased by 10 to 25 mg per week to 50 to 75 mg; divalproex sodium (either regular or extended release) 500 mg/d for 1 week and then 1000 mg daily; and topiramate 25 mg for the first week, increased by 25 mg/wk in divided doses to 50 mg twice daily.[37]

Other beta-blockers may also be effective (see **Table 3**). Regarding the tricyclic antidepressants, the quality of evidence for nortriptyline is not as good as that for amitriptyline, but the clinical impression is one of similar efficacy with less sedation. Venlafaxine may be as effective as amitriptyline with fewer side effects.[38] SSRIs are probably not effective for migraine prevention. Verapamil and gabapentin are only modestly effective for migraine prevention.

There are natural products that may be beneficial for migraine prevention, including the herb feverfew (*Tanacetum parthenium*; 50–82 mg daily); extract from the butterbur plant, *Petasites hybridus* (75 mg twice a day); riboflavin (200 mg twice a day); coenzyme Q10 (100 mg three times daily); and oral magnesium supplements. Botulinum toxin injections may also be of benefit in some patients who have chronic migraine but the evidence does not support the use in episodic migraine (less than 15 days per month). The relative benefit of these treatments may become clearer with additional studies, but for now, some migraineurs may prefer them because they have few if any side effects.

For many migraineurs, the avoidance of triggers may be useful. Examples include adequate sleep at set hours, routine exercise, regular meals, avoiding triggering foods and beverages, and wearing sunglasses in bright sunlight or glare. Some patients may benefit from biofeedback, relaxation training, and psychotherapy.

When Should an Effective Preventive Medication be Discontinued?

Only one randomized, placebo-controlled trial has been performed to investigate migraine frequency after preventive treatment has been discontinued. Patients were treated with topiramate for 6 months and then randomly assigned to continue this dose or switch to placebo for 6 months with 254 patients on topiramate and 258 on placebo.[39] Discontinuation ''…was associated with persistent benefits compared with values before treatment, although numbers of migraine days were higher and quality of life was lower in patients who discontinued topiramate use than in those who continued treatment. Patients should therefore be treated for 6 months, with the option to continue treatment to 12 months in some patients, particularly those whose migraine frequency decreased substantially with topiramate.''[39]

Table 3
Preventive medications for migraine

Drug Class	Agent	Dosage	Typical Side Effects
Beta-blockers	Propranolol	40–120 mg bid	Hypotension, tiredness, exacerbation of asthma
	Propranolol long acting	60–160 mg/d	
	Metoprolol	50–100 mg/d	
	Nadolol	40–160 mg/d	
	Atenolol	50–100 mg/d	
	Timolol	10–20 mg bid	
Antidepressants	Amitriptyline	25–150 mg hs	Drowsiness, dry mouth, weight gain, constipation
	Nortriptyline	25–150 mg hs	
	Venlafaxine XR	37.5 mg for 1 wk then 75 mg/d for 1 wk then 150 mg/d as tolerated	Nausea, vomiting, insomnia, drowsiness
	Divalproex sodium	500–1000 mg in divided doses or once daily with extended-release formulation	Nausea, tremor, drowsiness, weight gain, alopecia, hematologic and liver abnormalities, fetal abnormalities
Anticonvulsants	Topiramate	50–200 mg/d in divided doses	Weight loss, paresthesias, cognitive disturbances, kidney stones
	Gabapentin	300–800 mg tid	Dizziness, fatigue, drowsiness

Are you Unhappy with Current Acute and Preventive Medication Options?

Physicians and migraineurs would like to see more effective and more tolerable medications. There is some research going on at pharmaceutical companies but more needs to be done when the large number of migraineurs is considered. Physicians and migraine advocacy groups should lobby for increased government funding for migraine research, which is only about $13 million in the United States and €6 million in Europe annually.[40] Also consider joining the American Headache Society (www.ahsnet.org), which has been lobbying Congress.

WOMEN'S TREATMENT ISSUES

How do you Treat Menstrual Migraine?

Menstrual migraine is treated with the same acute medications as other migraines. Interval or short-term preventive treatment of menstrual migraine, starting 2 or 3 days before menses and continuing during the menses, may be helpful for some women who have regular menses and migraines that are poorly responsive to symptomatic medications.[41] Potentially effective medications include the following: nonsteroidal anti-inflammatory drugs, such as naproxen sodium 550 mg twice daily; ergotamine 1 mg once or twice a day; or DHE 1 mg subcutaneously or intramuscularly; naratriptan 1 mg orally twice daily for 6 days started 2 days before predicted menses; frovatriptan 2.5 mg twice daily (with double loading dose on day 1) for 6 days starting 2 days before predicted menstrual migraine; transdermal estradiol, 100 μg applied 3 days before the

expected start of menses and replaced after 3 days or a 6-day patch; continuous combined oral contraceptive use, with a lower estrogen dose given during the menses; and extended-duration oral contraceptive use.

Are Combined Estrogen Oral Contraceptives Safe for Migraineurs?

Although there is controversy whether low-estrogen OCs increase the risk for stroke, most women who have migraine without aura can safely take low-estrogen OCs if they have no other contraindications or risk factors. When taking low-estrogen OCs, women less than 35 years old who have migraine with aura, such as visual symptoms lasting less than 1 hour, have a risk for ischemic stroke of about 30/100,000 annually, which is twice the risk of those who have migraine without aura.[42] A task force of the International Headache Society to assess the use of OCs in women who have migraine concluded that ''there is a potentially increased risk of ischemic stroke in women with migraine who are using combined estrogen oral contraceptives (COCs) and have additional risk factors which cannot easily be controlled, including migraine with aura. One must individually assess and evaluate these risks. Combined oral contraceptive use may be contraindicated''[43] Women who have aura symptoms, such as hemiparesis or aphasia, or prolonged focal neurologic symptoms and signs lasting more than 1 hour, should avoid starting low-estrogen OCs and should stop the medication if they are already taking it. Progestin-only OCs and the many other contraceptive options can be considered, as appropriate. Cigarette smoking should be strongly discouraged because female migraineurs who smoke one or more packs of cigarettes per day raise their risk for ischemic stroke by a factor of about 10.

What is the Effect of Estrogen Replacement Therapy?

Estrogen replacement therapy has a variable effect on migraine: 77.5% show no change or improved and 22.5% worsen. If migraines increase when a patient starts estrogen replacement, the following strategies may be beneficial:

Reduce the estrogen dose.
Change the estrogen type to one less likely to promote migraine. From most to least likely to promote migraine, these are, in order, conjugated estrogens, pure estradiol, synthetic estrogen, and pure estrogen.
Convert from interrupted to continuous dosing, in the case of estrogen withdrawal migraine.
Convert from oral to parenteral administration (eg, a transdermal patch).
Add androgens.[44]

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