

# Migraine Headache

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## Introduction

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### Background

Although migraine is a term applied to certain headaches with a vascular quality, overwhelming evidence suggests that migraine is a dominantly inherited disorder characterized by varying degrees of recurrent vascular-quality headache, photophobia, sleep disruption, and depression.

### Pathophysiology

The mechanisms of migraine remain not completely understood. However, the advent of new technologies has allowed formulation of current concepts that may explain parts of the migrainesyndrome. See also Pathophysiology and Treatment of Migraine and Related Headache.

### Vascular theory

For many years, headache pain during a migraine attack was thought to be a reactive hyperemia in response to vasoconstriction-induced ischemia during aura. This explained the throbbing quality of the headache, its varied localization, and the relief obtained from ergots; however, it did not explain the prodrome and associated features, the efficacy of some drugs used to treat migraines that have no effect on blood vessels, and the fact that most patients do not have an aura.

Also, intracarotid and single-photon emission computed tomography (SPECT) studies revealed that the headache is dissociated from hyperperfusion at its onset and termination in patients suffering from migraine headache with aura. They also revealed that regional cerebral blood flow (rCBF) decreases in the posterior area of the relevant cerebral hemisphere even before the aura is noted and that headache occurred while rCBF remained decreased; rCBF gradually increased throughout the remainder of the headache phase. No consistent flow changes have been identified in patients suffering from migraine headache without aura, but rCBF remains normal in the majority. However, bilateral decrease in rCBF beginning at the occipital cortex and spreading anteriorly has been reported. More recently, Perciaccante has shown that migraine is characterized by a cardiac autonomic dysfunction.<sup>1</sup>

### Cortical spreading depression

The spread of hypoperfusion propagates at a speed similar to that of cortical spreading depression (CSD) and migraine aura. This suggests not only that CSD is the disturbance resulting in the clinical manifestation of migraine aura but also that this spreading oligemia can be clinically silent (ie, migraine without aura). Perhaps a certain threshold is required to produce symptoms in patients having aura but not in those without aura. CSD with or without clinical manifestation (aura) may be a key trigger for the headache of migraine. Although this question is unsettled, CSD has been postulated to directly excite trigeminovascular afferents by promoting release of nociceptive substances from neocortex into the interstitial space, causing direct firing of the nociceptive stimulus.

### Vasoactive substances and neurotransmitters

Perivascular nerve activity also results in release of substances such as substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), and nitric oxide (NO), which interact with the blood vessel wall to produce dilatation, protein extravasation, and sterile inflammation, stimulating the trigeminocervical complex as shown by induction of c-fos antigen by positron emission tomography (PET) scan. Information then is relayed to the thalamus and cortex for registering of pain. Involvement of other centers may explain the associated autonomic symptoms and affective aspects of this pain.

Is the neurologically mediated sterile plasma extravasation the cause of this pain? Neurogenic plasma extravasation is inhibited by 5-HT<sub>1</sub> agonists, GABA agonists, neurosteroids, prostaglandin inhibitors, SP antagonists, and the endothelin antagonist bosentan; the latter 2 are ineffective as antimigraine drugs, showing that blockade of neurogenic plasma extravasation is not completely predictive of antimigraine efficacy in humans. Neurogenically induced plasma extravasation may play a role in expression of pain in migraine, but whether this in itself is sufficient to cause pain is not

clear; the presence of other stimulators may be required. Also, the pain process needs not only the activation of nociceptors of pain-producing intracranial structures but also reduction in the normal functioning of endogenous pain control pathways that gate the pain.

### **Migraine center**

What generates a migraine episode? A potential "migraine center" in the brain stem has been proposed based on findings on PET of persistently elevated rCBF in the brain stem (ie, periaqueductal gray, midbrain reticular formation, locus ceruleus) even after sumatriptan produced resolution of headache and related symptoms in 9 patients who had experienced spontaneous attack of migraine without aura. This increased rCBF was not observed outside of the attack, suggesting that this activation is not due to pain perception or increased activity of the endogenous antinociceptive system.

That sumatriptan reversed the concomitant increased rCBF in the cerebral cortex but not the brainstem centers suggests dysfunction in the regulation involved in antinociception and vascular control of these centers. Thalamic processing of pain is known to be gated by ascending serotonergic fibers from the dorsal raphe nucleus and from aminergic nuclei in the pontine tegmentum as locus ceruleus and that the latter can alter brain flow and blood-brain barrier permeability. Perhaps when these modulatory controls are timed to dysfunction, the migrainous process ensues.

### **Frequency**

#### **United States**

More than 23 million people in the United States suffer from migraine. This roughly corresponds to 17.6% of females and 6.0% of males.

### **Mortality/Morbidity**

Headaches may serve as a warning: not all severe headaches are due to migraine; they can be a warning sign of more serious conditions. Headache characteristics that should raise concern include the following:

- Change in character of the headache over the time should raise a red flag. Headaches associated with other neurological signs or symptoms (eg, diplopia, loss of sensation, weakness, ataxia) or those of unusually abrupt onset.
- Headaches that are persistent (especially beyond 72 hours), that first occur after the age of 55 years, or that develop after head injury or major trauma. Headaches that are persistent on one side of the head (persistent one-sided throbbing headaches mimicking like migraines: arteriovenous malformation should be excluded with imaging).
- Headaches that are associated with stiff neck or fever
- Headaches without a clear family history of migraine headache

### **Race**

The prevalence of migraine appears to be lower among African Americans and Asian Americans than among whites.

### **Sex**

- Migraine headaches are reported to affect women more than men.
- Approximately 75% of all persons who experience migraines are women.

### **Age**

- The prevalence of migraine appears to be similar for boys and girls in the prepubescent years.
  - The prevalence of migraine is higher in adolescent girls than in boys of similar age.
  - By early adulthood, migraine is 3 times as frequent in women as it is in men.
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# Clinical

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## History

The typical headache of migraine is throbbing or pulsatile. It is initially unilateral and localized in the frontotemporal and ocular area, then builds up over a period of 1-2 hours, progressing posteriorly and becoming diffuse. It typically lasts from several hours to a whole day. Pain intensity is moderate to severe, prompting the patient to remain still as it intensifies even with routine physical activity.

- The attack commonly occurs when the patient is already awake, although it may have already started upon awakening and less commonly may awaken the patient at night.
- Nausea and vomiting usually occur later in the attack in about 80% and 50% of patients, respectively, along with anorexia and food intolerance.
- Some patients have been noted to be pale and clammy, especially if nausea develops.
- Photophobia and/or phonophobia also commonly are associated with the headache.
- The headache usually subsides gradually within a day and after a period of sleep; a majority of patients report being tired and weak afterwards.
- About 60% of people who experience migraines report a prodrome, often occurring hours to days before headache onset. Patients describe a change in mood or behavior that may include psychological, neurological, constitutional, or autonomic features.
  - These symptoms may be difficult to diagnose as part of the migraine complex if they occur in isolation from the headache or if they are mild. The prodrome of migraine has yet to receive significant investigational attention.
  - Because of the set periodicity of migraine, linkage to the suprachiasmatic nucleus of the hypothalamus that governs circadian rhythm has been proposed. Discovering the central trigger for migraine would help identify better prophylactic agents.
- The migraine aura is a complex of neurologic symptoms that may precede or accompany the headache phase or may occur in isolation.
  - It usually develops over 5-20 minutes and lasts less than 60 minutes.
  - The aura can be visual, sensory, motor, or any combination of these.
  - The most characteristic visual aura of migraine is a scintillating scotoma (occurring in about 64% of cases), beginning as a hazy spot from the center of a visual hemifield followed by shimmering light of different patterns expanding peripherally to involve a greater part of the hemifield with scotoma.
  - Paresthesias, occurring in 40% of cases, constitute the next most common aura; they are often cheiro-oral with numbness starting in the hand then migrating to the arm and then jumping to involve the face, lips, and tongue.
  - As with visual auras, positive symptoms typically are followed by negative symptoms; paresthesias may be followed by numbness.
- Sensory aura rarely occurs in isolation and usually follows visual aura.
  - The rate of spread of sensory aura is helpful in distinguishing it from transient ischemic attack (TIA) or a sensory seizure.
  - Just as a visual aura spreads across the visual field slowly, the paresthesias may take 10-20 minutes to spread, which is slower than the spread of sensory symptoms of TIA.
  - The migrainous aura generally resolves within a few minutes and then is followed by a latent period before the onset of headache, although merging of the 2 also is reported.
- Motor symptoms may occur in 18% of patients and usually are associated with sensory symptoms.
  - Motor symptoms often are described as a sense of heaviness of the limbs before a headache but without any true weakness.
  - Speech and language disturbances have been reported in 17-20% of patients, commonly associated with upper extremity heaviness or weakness.
- Whether migraine with and without aura (prevalences, 36% and 55%, respectively) represent 2 distinct processes remains debatable; however, the similarities of the prodrome, headache, and resolution phases of the attacks, similarity in therapeutic response, and the fact that 9% of patients experience both suggest that they are the same entity.
- When an aura is not followed by a headache, it is called a migraine equivalent or acephalic migraine. This is reported most commonly in patients older than 40 years who have a history of recurrent headache. Scintillating

scotoma has been considered to be diagnostic of migraine even in the absence of a headache; however, paresthesias, weakness, and other transient neurologic symptoms are not. In the absence of a prior history of recurrent headache and first occurrence after age 45 years, TIA should be considered and must be investigated fully.

- Although headache is a very common reason for seeking medical care, the majority of headache complaints are benign in origin. However, migraine with its protean manifestation may simulate or be simulated by primary and secondary headache disorders. Also, it can coexist with a secondary headache disorder. When headache is episodic, recurrent, and with a well-established pattern, a primary headache disorder is likely. Differentiating between migraine, tension-type, and cluster headaches is important, as optimal treatment may differ.
- Any of the following features suggest a secondary headache disorder and warrant further investigation:
  - Atypical history or unusual character that does not fulfill the criteria for migraine
  - Occurrence of a new, different, or truly "worst" headache
  - Change in frequency of episodes or major characteristics of the headache
  - Abnormal neurologic examination
  - Inadequate response to optimal therapy
- When patients are seen shortly after the initial headache and their level of anxiety is such that more than reassurance is needed, further diagnostic studies may be necessary.
- Severe headache of sudden onset is a concern despite its occurrence in primary headache disorders. Typically, migraine is gradual in onset, peaking within 2 hours, although some have abrupt onset; these are termed "crash" migraine and are similar to a "thunderclap" headache.
  - Cluster headache also may be sudden and excruciating, but it lasts only 15-180 minutes and is recognized easily if the patient has had previous attacks. Exertional headache builds in intensity over minutes and occurs with sustained physical exertion. Coital headache can develop at the height of orgasm or it may build up through intercourse.
  - Despite these possibilities, a ruptured intracranial aneurysm is the primary consideration if the headache is severe with sudden onset and reaches maximum intensity in minutes. The classical presentation of an aneurysmal subarachnoid hemorrhage (SAH) is a severe headache with sudden, explosive onset, stiff neck, photophobia, nausea and vomiting, and possibly alteration of consciousness. An extensive evaluation is indicated in this case, including initial CT scan of the head without contrast. Lumbar puncture (LP) should be considered if CT scan is negative, as 25% of cases are missed by CT.
  - The question persists of whether an angiogram should be performed after normal findings of neurologic examination, cerebrospinal fluid (CSF) examination, and CT or MRI. In one study, acute severe thunderclap headache comparable to that of SAH without the nuchal rigidity occurred in 6.3% of patients with unruptured aneurysm. Other studies have revealed that in patients with severe thunderclap headache with normal CT and CSF findings, none developed SAH<sup>2</sup>, leading to more confusion.

If the CT scan and LP are performed late after symptom onset, so that negative results are unreliable, and if clinical features such as family history or past medical history, classic SAH-like symptoms, or the presence of neurological signs (in particular a third cranial nerve palsy affecting the pupil) suggest that the patient is at risk, such patients probably should undergo angiography if an experienced angiographer is available. In patients with unrevealing studies in whom the diagnosis of aneurysmal SAH is possible but very unlikely, MRI and magnetic resonance angiography (MRA) are screening tests, and close follow-up is appropriate if the findings of these tests are negative.

- Another concern is the possibility of a space-occupying lesion mimicking migraine. In a series of 111 patients with primary (34%) or metastatic (66%) brain tumor, headache was reported in 48%; the headache had characteristics similar to migraine in 9% and to tension-type headache in 77%, while the so-called classic brain tumor headache occurred in only 17%. Headache was intermittent in 62%, usually lasting a few hours, and was constant in 36%. It was bilateral in 72% and was moderate to severe in intensity in most patients. All patients with headaches similar to migraine had other neurological symptoms or abnormal signs. Of note is that 32% had history of headache; in 36% of those, the headache was of identical character to prior headaches but was more severe or frequent and was associated with other symptoms such as seizures, confusion, prolonged nausea, and hemiparesis.<sup>3</sup> These data indicate that patients with a history of headache should have further diagnostic workup if the headache is accompanied by new symptoms or abnormal signs or differs in any way from their usual headache. With new-onset headache, imaging should be obtained if headache is severe or occurs with nausea, vomiting, or abnormal signs.

- Other space-occupying lesions must be considered in the appropriate clinical setting. Large intraparenchymal hemorrhage presents dramatically with headache and neurological symptoms or signs shortly after onset. Of patients with chronic, subacute, or acute subdural hematoma, 81%, 53%, and 11%, respectively, have headaches. In brain abscesses, a progressive, severe, intractable headache is common, and headache is reported in 70-90% of patients.
- Cerebral venous thrombosis involves the sagittal sinus in about 70% of cases; these patients present with signs and symptoms of increased intracranial pressure (ICP), such as headache and papilledema. Should the thrombus extend to the superficial cortical veins, then focal findings may be noted. In the appropriate setting with known risk factors, cerebral venous thrombosis must be considered and evaluated with MRI, MRA, or magnetic resonance venography (MRV).
- Spontaneous internal carotid artery dissection is an uncommon cause of headache and acute neurological deficit, but it must be considered in the younger individuals who have unilateral, severe, persistent head pain of sudden onset preceding neurological signs, most commonly Horner syndrome, differentiating it from traumatic causes, in which cerebral ischemic symptoms are more common.
- Other secondary causes of alarming headaches should be sought in the presence of the "red flags" mentioned above and must be sought in the appropriate clinical setting. Other features needing further diagnostic workup include positional headaches, which may occur in colloid cysts or other ventricular tumors such as ependymomas, Chiari malformations, and low CSF pressure headache. Headaches after age 50 years must be investigated to consider temporal or giant cell arteritis. Headaches associated with systemic disease require consideration of infectious and non-infectious inflammatory processes.
- Bear in mind that sumatriptan and related compounds, by virtue of being able to block expression of c-fos by their action on 5-HT<sub>1</sub> receptors, decrease headaches with diverse pathogenesis. These agents may be effective in decreasing headache pain associated with meningovascular irritation, such as viral and bacterial infections and subarachnoid hemorrhage. Hence, response to 5-HT<sub>1</sub> agonists is not diagnostic of a migraine headache.

## Physical

- Most patients with headache have a normal neurological examination.
- Some abnormal findings suggest a secondary cause, which would necessitate a different diagnostic and treatment approach.
- The presence of papilledema suggests increased ICP and warrants a diagnostic imaging study to rule out a mass lesion.
- Nuchal rigidity due to meningeal irritation is seen with meningitis and subarachnoid or intraparenchymal hemorrhage.

## Treatment

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### Medical Care

Approach to migraine treatment involves acute (abortive) and preventive (prophylactic) therapy; patients with frequent attacks usually require both. Acute treatment aims to stop or prevent the progression of a headache or reverse a headache that has started. Preventive treatment, which is given even in the absence of a headache, aims to reduce the frequency and severity of the migraine attack, make acute attacks more responsive to abortive therapy, and perhaps also improve the patient's quality of life.

### Abortive Therapy

Numerous abortive medications are used for migraine, and the choice for each patient depends upon the severity of the attacks, associated symptoms such as nausea and vomiting, comorbid problems, and the patient's treatment response. A stratified approach based on the patient's therapeutic needs has been advanced (see Table 1 below), as has a step-care approach. Simple analgesics alone or in combination with other compounds have provided relief for mild to moderately severe and even at times severe headaches. 5-HT<sub>1</sub> agonists and/or opioid analgesics alone or in combination with dopamine antagonists are used for more severe pain. The use of abortive medications must be limited to 2-3 days a week to prevent development of a rebound headache phenomenon.

Table 1. Abortive Medication Stratification by Headache Severity

<b>Moderate</b>	<b>Severe</b>	<b>Extremely Severe</b>
NSAIDs	Naratriptan	DHE (IV)
Isometheptene	Rizatriptan	Opioids
Ergotamine	Sumatriptan (SC,NS)	Dopamine antagonists
Naratriptan	Zolmitriptan	
Rizatriptan	Almotriptan	
Sumatriptan	Frovatriptan	
Zolmitriptan	Eletriptan	
Almotriptan	DHE (NS/IM)	
Frovatriptan	Ergotamine	
Eletriptan	Dopamine antagonists	
Dopamine antagonists		
<b>Moderate</b>	<b>Severe</b>	<b>Extremely Severe</b>
NSAIDs	Naratriptan	DHE (IV)
Isometheptene	Rizatriptan	Opioids
Ergotamine	Sumatriptan (SC,NS)	Dopamine antagonists
Naratriptan	Zolmitriptan	
Rizatriptan	Almotriptan	
Sumatriptan	Frovatriptan	
Zolmitriptan	Eletriptan	
Almotriptan	DHE (NS/IM)	
Frovatriptan	Ergotamine	
Eletriptan	Dopamine antagonists	
Dopamine antagonists		

Rebound headache has been defined as perpetuation of head pain in chronic headache sufferers secondary to frequent and excessive use of symptomatic medication. Analgesic overuse may be responsible in part for the transformation of episodic migraine or tension-type headache into daily headache and for the perpetuation of the syndrome; however, it is not the absolute cause of transformed migraine or chronic tension-type headache. Although the actual doses and duration of analgesic overuse needed to develop rebound headache have not been defined clearly, the use of abortive medications more than 2 days a week often is cited. Also, no major difference is known among various types of analgesics used in the treatment of headache in producing analgesic rebound headache.

In some US headache centers, 50-80% of patients with chronic daily headaches reported analgesic overuse. In a survey, 40% of responders reported that 20% of headache patients experience analgesic rebound. The following are clinical features of analgesic rebound:

- Headache occurs daily or near daily
- Occurs in a patient with primary headache disorder who uses immediate relief medications very frequently, often in excessive quantities
- Headache varies in intensity, type, severity, and location from time to time
- Slight physical or intellectual effort bring on headaches; threshold for pain low
- Headache accompanied by asthenia, nausea and other GI symptoms, restlessness, anxiety, irritability, memory problems, difficulty in intellectual concentration, and depression
- Drug-dependent rhythmicity of headaches
- Evidence of tolerance to analgesics over a period of time
- Withdrawal symptoms when taken off the medications abruptly

- Spontaneous improvement of headache on discontinuing the medications
- Concomitant prophylactic medications are relatively ineffective while the patient is consuming excessive amounts of immediate relief medications. Its pathogenesis is not understood clearly, but it may be partly due to a defective mechanism of 5-HT uptake caused by analgesic overuse.

To facilitate understanding of the mechanisms of action of the various medications, the relationship between serotonin and migraine is reviewed here briefly, as some of these studies partly define the current understanding of migraine.

Stimulation of the trigeminal nerve releases SP, CGRP, and NKA from the sensory C-fibers, resulting in neurogenic inflammation that then interacts with the blood vessel wall, producing dilatation, plasma extravasation, and sterile inflammation. Plasma extravasation has been shown to be blocked by ergots, sumatriptan, and the newer 5-HT<sub>1B/D</sub> agonists, indomethacin, acetylsalicylic acid, GABA agonists such as valproic acid and benzodiazepines, neurosteroids, substance P antagonists, and the endothelin antagonist bosentan.

Immunohistochemical studies have detected 5-HT<sub>1D</sub> receptors in trigeminal sensory neurons, including peripheral projections to the dura and within the trigeminal nucleus caudalis (TNC) and solitary tract, while 5-HT<sub>1B</sub> receptors are present on smooth muscle cells in meningeal vessels; however, both can be found in both tissues to some extent and even in coronary vessels. These findings suggest that sumatriptan and other selective 5-HT<sub>1</sub> agonists decrease headache by abolishing neuropeptide release in the periphery and blocking neurotransmission by acting on second-order neurons in the trigeminocervical complex.

All the currently available triptans are selective 5-HT<sub>1B/D</sub> full agonists. The major differences among these agents lie in their pharmacokinetic properties, which may affect onset of action (eg, rizatriptan with lesser  $t_{max}$  leading to faster onset), duration of action (eg, naratriptan with longer half-life leading to lower recurrence rate), bioavailability (eg, naratriptan with higher oral bioavailability leading to more consistent response), and CNS penetration (eg, sumatriptan not shown to cross the intact blood-brain barrier).

GABA-A receptor is suggested to reside on the parasympathetic fibers emanating from the sphenopalatine ganglia, as the effects of valproic acid, benzodiazepines, and steroids are abolished when these projections are sectioned. The possible relationship of dopamine and migraine has been shown by a direct relationship between dopamine concentration and migraine symptomatology and the demonstrated efficacy of dopamine antagonists in the acute treatment of migraine.

## Prophylactic Therapy

Prophylactic therapy can be considered under the following conditions:

- Two or more attacks each month with significant disability that lasts 3 or more days
- Contraindication to or ineffectiveness of symptomatic medications
- Use of abortive medications more than twice a week
- Migraine variants such as hemiplegic migraine or rare headache attacks producing profound disruption or risk of permanent neurological injury

Currently, the major prophylactic medications for migraine work via one of the following mechanisms:

- 5-HT<sub>2</sub> antagonism - Methysergide
- Regulation of voltage-gated ion channels - Calcium channel blockers
- Modulation of central neurotransmitters - Beta-blockers, tricyclic antidepressants
- Enhancing GABAergic inhibition - Valproic acid, gabapentin
- Another notable mechanism is through alteration of neuronal oxidative metabolism by riboflavin and reducing neuronal hyperexcitability by magnesium replacement.

Like that of abortive medications, the selection of a preventive medication must take into consideration comorbid conditions and side effect profile (see Table 2 and Table 3). Most preventive medications have modest efficacies and have therapeutic gains less than 50% when compared to placebo. The latency between initiation of therapy and onset of positive treatment response can be quite prolonged. Furthermore, the scientific basis for using most of these medications

are wanting. Propranolol, timolol, methysergide, and valproic acid have been approved by the US Food and Drug Administration (FDA) in the past, and recently topiramate has also been approved for migraine prophylaxis. Refer to Medication for further information on prophylaxis.

Table 2. Preventive Drugs

<b>First line</b>	High efficacy	Beta-blockers Tricyclic antidepressants Divalproex Topiramate
	Low efficacy	Verapamil NSAIDs SSRIs
<b>Second line</b>	High efficacy	Methysergide Flunarizine MAOIs
	Unproven efficacy	Cyproheptadine Gabapentin Lamotrigine
<b>First line</b>	High efficacy	Beta-blockers Tricyclic antidepressants Divalproex Topiramate
	Low efficacy	Verapamil NSAIDs SSRIs
<b>Second line</b>	High efficacy	Methysergide Flunarizine MAOIs
	Unproven efficacy	Cyproheptadine Gabapentin Lamotrigine

Table 3. Preventive Medication for Comorbid Conditions

<b>Comorbid Condition</b>	<b>Medication</b>
Hypertension	Beta-blockers
Angina	Beta-blockers
Stress	Beta-blockers
Depression	Tricyclic antidepressants, SSRIs
Underweight	Tricyclic antidepressants
Epilepsy	Valproic acid, Topiramate
Mania	Valproic acid
<b>Comorbid Condition</b>	<b>Medication</b>
Hypertension	Beta-blockers
Angina	Beta-blockers
Stress	Beta-blockers
Depression	Tricyclic antidepressants, SSRIs
Underweight	Tricyclic antidepressants
Epilepsy	Valproic acid, Topiramate
Mania	Valproic acid

## Surgical Care

Besides the medical management, surgical treatments have also been tried for the prevention of migraines. Guyuron and colleagues have shown that surgical deactivation of migraine headache trigger sites can help eliminate or significantly reduce the symptoms of migraine.<sup>5</sup>

Corrugator muscle resection has a much better chance for improvement with the mild form of migraine headache compared with worse forms as shown by Dirnberger and Becker.<sup>6</sup>

- Botulinum toxin-A (BOTOX®) has been used in multiple trials for the prophylaxis of migraine headaches. Some mixed results have occurred on the use of botulinum toxin-A for the migraine headaches.<sup>7</sup>
  - Pericranial injection of 50-U botulinum toxin-A has shown good efficacy and tolerability as a prophylactic agent. Botulinum toxin-A therapy has been tried for refractory chronic migraine in those who previously have failed to respond to at least 3 prophylactic medications.
  - A recent report from Schulte-Mattler and Martinez-Castrillo has shown no evidence for a beneficial effect of botulinum toxin and thus, they have not supported the widespread use of botulinum toxin therapy in headaches.<sup>8</sup>

## Diet

- A fraction of persons who experience migraines have dietary triggers. Common triggers include chocolate, aged cheeses and meats, wine and beer (ie, sulfites), and citrus fruits.
- Obviously, the avoidance of dietary triggers plays an important role in the treatment of these patients.

## Medication

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Pharmacologic agents used for the treatment of migraine can be classified as abortive (ie, symptomatic) drugs and prophylactic (ie, preventive) agents.

### Abortive medications/ Selective serotonin receptor (5-HT<sub>1</sub>) agonists

The following serotonin receptor (5-HT<sub>1</sub>) agonists/triptans are used as abortive medications for moderately severe to severe migraine headaches.

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#### **Sumatriptan (Imitrex); naratriptan (Amerge, Naramig); zolmitriptan (Zomig, Zomig-ZMT); rizatriptan (Maxalt, Maxalt-MLT); almotriptan (Axert); frovatriptan (Frova)**

Efficacy of SC sumatriptan is 82% at 20 min, that of inhaled is 62% at 2 h, and that of PO is 60-70% at 4 h. Zolmitriptan at initial dose of 2.5 mg PO has efficacy of 62% at 2 h and 75-78% within 4 h. Naratriptan at 2.5 mg PO has higher bioavailability and longer half-life than sumatriptan, which may contribute to lower rate of headache recurrences. Pain relief experienced by 60-68% of patients within 4 h of treatment and maintained up to 24 h in 49-67% of patients. Rizatriptan 10 mg PO has reported early onset of action (30 min) and efficacy of 71% at 2 h. Almotriptan induces cranial vessel constriction, inhibition of neuropeptide release, and reduces pain transmission in trigeminal pathways. Frovatriptan possesses long half-life (ie, 26-30 h), thus, decreases recurrence of migraine within 24 h after treatment. Eletriptan's onset is within 1 h, and the half-life is 18 h.

#### **Adult**

##### **Sumatriptan:**

25-100 mg PO; second dose up to 100 mg may be taken after 2 h; additional doses may be taken at 2-h intervals; not to exceed 300 mg/d

5-20 mg NS inhaled into 1 nostril; second dose may be given after 2 h if headache returns or if response is partial; not to exceed 40 mg in 24 h

6 mg SC; not to exceed 2 6-mg injections separated by minimum interval of 1 h

##### **Zolmitriptan:**

2.5-5 mg PO; if headache returns after initial dose, second dose may be given any time after 2 h of first dose; not to exceed 10 mg/d

**Naratriptan:**

2.5 mg PO; may be repeated after 4 h if headache recurs or if only partial relief with initial dose

**Rizatriptan:**

5-10 mg PO disintegrating tab initially; may be repeated every 2 h; not to exceed 30 mg within 24 h

**Almotriptan:**

6.25-12.5 mg PO at onset of migraine; may repeat once, not to exceed 25 mg/d

**Frovatriptan:**

2.5 mg PO once at onset of migraine attack

**Eletriptan:**

20-40 mg PO at onset of migraine; if initial dose ineffective, may repeat dose once after 2 h; not to exceed 80 mg/d

**Pediatric****Sumatriptan:**

Tab: 12.5-25 mg PO prn; not to exceed 100 mg qd

Nasal spray: 5 mg NS prn

Injection: 0.02 mg/kg SC prn

**Zolmitriptan:** 2.5 mg PO prn; not to exceed 10 mg qd

**Naratriptan:** 1 mg PO prn; not to exceed 5 mg qd

**Rizatriptan:** 5 mg PO prn; not to exceed 30 mg qd

**Almotriptan:** Not established

**Frovatriptan:** <18 years: Not established

>18 years: Administer as in adults

**Eletriptan:** <18 years: Not established

>18 years: Administer as in adults

**Abortive medications/Ergot alkaloids**

These are nonselective 5-HT<sub>1</sub> agonists that have a wider spectrum of receptor affinities outside of the 5-HT<sub>1</sub> system, including dopamine receptors. They can be used for the abortive treatment of moderately severe to severe migraine headache.

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**Ergotamine tartrate (Cafatine, Cafergot, Cafetrate), Dihydroergotamine (DHE-45)**

Counteract episodic dilation of extracranial arteries and arterioles.

DHE differs from ergotamine tartrate in that it is weaker arterial constrictor, has less emetic and less uterine effects, and is less likely to produce drug-rebound headache. DHE 1 mg IM yielded 72% improvement of symptoms (ie, mild pain or no pain) after 1 h.

**Adult****Ergotamine tartrate**

1 mg PO initially; q30min prn; not to exceed 6 mg per attack

1-2 mg SL initially; q30min prn; not to exceed 6 mg per attack

1-2 mg PR initially; q30min prn; not to exceed 4 mg per attack

**DHE**

1 spray (0.5 mg) NS inhaled in each nostril, repeated after 15 min; not to exceed 2 mg

0.5-1 mg IM/SC, repeat dose at 1-h intervals; not to exceed 3 mg

IV route used when more rapid results desired: 1 mg IV q8h with or without metoclopramide is safe and effective for treatment of status migrainosus

**Pediatric**

Not established

## **Abortive medications/analgesics**

These agents are used as initial abortive therapy for patients with infrequent migraines.

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### **Acetaminophen (Tylenol), propoxyphene (Darvon), oxycodone (OxyContin), morphine (Duramorph, MS Contin), meperidine (Demerol), hydromorphone (Dilaudid), butorphanol (Stadol)**

Used as 'rescue' medications if migraine headache not controlled with standard treatment, or if 5-HT<sub>1</sub> agonists contraindicated.

Acetaminophen (with or without metoclopramide) in particular is the first choice for treatment of migraine attacks during pregnancy and breastfeeding.

#### **Adult**

##### **Acetaminophen**

650-1000 mg PO initially, may be repeated after 1-2 h prn

##### **Propoxyphene**

Propoxyphene HCl: 65 mg PO q4h prn; not to exceed 390 mg/d

Propoxyphene napsylate: 100 mg PO q4h prn; not to exceed 600 mg/d

(Propoxyphene napsylate 100 mg = propoxyphene HCl 65 mg)

##### **Oxycodone**

5 mg PO q6h prn

##### **Morphine**

10-30 mg PO q4h prn

5-20 mg/70 kg IM/SC q4h prn

##### **Meperidine**

50-150 mg PO/IM/SC q3-4h prn

##### **Hydromorphone**

2-4 mg PO q4-6h prn

1-4 mg IM/SC q4-6h prn

##### **Butorphanol**

1 mg NS inhaled into 1 nostril; if sufficient relief not obtained in 60-90 min, give additional 1 mg; repeat initial 2-dose sequence in 3-4 h prn

#### **Pediatric**

Acetaminophen: 10 mg/kg/dose PO; not to exceed 720 mg/d (children aged 3-6 y) or 2.6 g/d (children aged 6-12 y)

Meperidine: 1-1.8 mg/kg PO/IM/SC q3-4h; not to exceed recommended adult dosage

Other drugs: Not established

## **Abortive medications/Nonsteroidal anti-inflammatory drugs (NSAIDs)**

Generally used as abortive therapy in mild to moderately severe type of migraine headaches; however, they also may be effective for severe headaches, especially ketorolac.

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### **Aspirin (Bayer Aspirin, Anacin), ibuprofen (Motrin, Ibuprin), naproxen (Naprosyn, Naprelan), ketorolac (Toradol)**

Mild analgesics that can be used to treat infrequent migraine episodes.

#### **Adult**

##### **Aspirin**

900-1000 mg PO initially; repeat same dose after 1-2 h prn

##### **Ibuprofen**

400-1200 mg/attack PO; may be repeated at dose of 400-800 mg in 1-2 h; not to exceed 3200 mg/d

##### **Naproxen sodium**

Up to 825 mg PO initially; may give 550 mg after 1-2 h prn

**Ketorolac**

10 mg PO q4h prn; not to exceed 40 mg/d; limit use to 5 consecutive days

30-60 mg IM initially; repeat q6h prn; not to exceed 120 mg/d; limit use to 3 consecutive days

IV administration similar to IM but dose used is 30 mg

**Pediatric**

Not recommended

**Abortive medications/Combination analgesics**

The first combination product of a 5HT receptor agonist and an NSAID, Treximet, was approved by the US Food and Drug Administration in April 2008. Efficacy was demonstrated in 2 randomized, double-blind, multicenter, parallel-group trials comparing the combination product to placebo and each individual active component (ie, sumatriptan and naproxen sodium). The percentage of patients remaining pain free without use of other medications through 24 hours postdose was significantly greater ( $p < 0.01$ ) among patients receiving a single dose of Treximet (25% and 23%) compared with placebo (8% and 7%) or either sumatriptan (16% and 14%) or naproxen sodium (10%) alone.<sup>9</sup>

Other combination products that contain ergots, sedatives, and analgesics may be used when simple analgesics are not effective and the patient is not a candidate for treatment with 5-HT<sub>1</sub> agonists or when the patient needs an alternative drug.

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**Sumatriptan and naproxen (Treximet)**

Combination product containing sumatriptan, a selective 5-hydroxytryptamine (5-HT<sub>1</sub>) receptor agonist, and naproxen sodium, an arylacetic acid nonsteroidal anti-inflammatory drug (NSAID). Fixed combination contains sumatriptan 85 mg and naproxen sodium 500 mg. Indicated for acute migraine. Sumatriptan mediates vasoconstriction of the basilar artery and vasculature of dura mater, which correlates with migraine relief. Naproxen provides analgesic, anti-inflammatory, and antipyretic properties. Decreases activity of cyclooxygenase, thereby interrupting prostaglandin synthesis.

**Adult**

1 tab PO at onset of migraine; do not exceed 2 tab/24 h; if second dose administered, do not administer until at least 2 h after first dose

**Pediatric**

Not established

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**Butalbital (Fiorinal), Isometheptene and dichloralphenazone (Midrin)**

Combination drugs effective for mild to moderately severe migraine headache.

**Adult**

Butalbital: 1-2 tab PO q4h prn; not to exceed 6 tabs/d

Isometheptene and dichloralphenazone: 2 caps PO initially then 1 capsule q1h until symptoms relieved; not to exceed 5 capsules in 12-h period

**Pediatric**

Butalbital: Not established in patients <12 years

Isometheptene and dichloralphenazone: Not established

**Abortive medications/Antiemetics**

As dopamine antagonists, these agents are effective if nausea and vomiting are prominent features and also may act as prokinetics to increase gastric motility and enhance absorption.

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### **Droperidol (Inapsine), chlorpromazine (Thorazine), metoclopramide (Reglan)**

Used alone or in combination with other analgesics as adjuncts, especially if migraine attack associated with significant nausea and vomiting. Its role in migraine based on findings that increased dopamine concentration is associated with prominent migraine symptomatology.

#### **Adult**

Droperidol: 2.5-10 mg (alone or with an antihistamine) given IM or slow IV

Chlorpromazine: 10-25 mg PO q4-6h prn; 50-100 mg PR q6-8h prn; 25-50 mg IM q3-4h; 5-50 mg IV

Metoclopramide: 10-20 mg PO/IM

#### **Pediatric**

Droperidol: 1-1.5 mg/9-11 kg IM for children aged 2-12 y

Chlorpromazine: 0.55 mg/kg PO/IM q6-8h; not to exceed 75 mg/d for children aged 5-12 y

Metoclopramide: Not established

### **Prophylactic therapy/Antiepileptics**

These drugs are effective in prophylaxis of migraine headache.

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### **Divalproex sodium/valproate (Depakote, Depacon, Depakene), topiramate (Topamax)**

Valproic acid: Now considered first-line preventive medication for migraine. Believed to enhance GABA neurotransmission, which may suppress events related to migraine that occur in cortex, perivascular sympathetics, or trigeminal nucleus caudalis. Has been shown to reduce migraine frequency by 50%.

Topiramate: Indicated for migraine headache prophylaxis. Precise mechanism unknown, but the following properties may contribute to its efficacy: (1) electrophysiological and biochemical evidence showing blockage of voltage-dependent sodium channels, (2) augments activity of the neurotransmitter GABA at some GABA-A receptor subtypes, (3) antagonizes AMPA/kainate subtype of the glutamate receptor, and (4) inhibits the carbonic anhydrase enzyme, particularly isozymes II and IV.

#### **Adult**

Valproic acid: 125-250 mg/d PO initially; titrate dose prn; not to exceed 1500 mg/d; doses higher than 250 mg/d should be divided bid

Topiramate: Slowly titrate upward at a minimum of 1-wk intervals as follows:

Week 1: 25 mg PO qhs

Week 2: 25 mg PO bid

Week 3: 25 mg PO qam

and 50 mg PO qhs

Week 4: 50 mg PO bid

#### **Pediatric**

Valproic acid: Limit use in children <10 y because of increased risk of fatal hepatotoxicity

Topiramate: Not established

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### **Gabapentin (Neurontin)**

Initial open study showed efficacy in migraine and transformed migraine. Randomized, double-blind, placebo-controlled trial showed lower migraine headache rate in gabapentin group than in placebo group; more patients in gabapentin group had >50% reduction in frequency.

#### **Adult**

300 mg PO tid; titrate gradually prn; not to exceed 2400 mg/d

## **Pediatric**

<12 years: Not established

>12 years: Administer as in adults

## **Prophylactic therapy/Beta-blockers**

Propranolol and timolol are both FDA-approved prophylactic agents, but propranolol has more scientific evidence of efficacy than timolol. Atenolol, metoprolol, and nadolol are not FDA-approved preventive agents. Significant to their activity as migraine prophylactic agents is the lack of partial agonistic activity. Latency from initial treatment to therapeutic results may be as long as 2 months.

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### **Propranolol (Inderal), timolol (Blocadren), nadolol (Corgard), atenolol (Tenormin)**

Are effective in prophylactic therapy possibly by blocking vasodilators, decreasing platelet adhesiveness and aggregation, stabilizing the membrane, and increasing the release of oxygen to tissues.

#### **Adult**

Propranolol: Start with low dose, 60 mg PO qd (sustained release) or 40 mg in divided doses; titrate prn; not to exceed 320 mg/d

Timolol: 10 mg/d PO initially; titrate prn; not to exceed 30 mg/d

Nadolol: 20 mg/d PO qd initially; titrate prn; not to exceed 240 mg/d

Atenolol: 50 mg/d PO qd initially; titrate prn; not to exceed 200 mg/d

Metoprolol: 50 mg PO qd or bid initially; titrate prn; not to exceed 200 mg/d

#### **Pediatric**

Only propranolol has been used for children

0.5 mg/kg PO bid initially; may be increased every 3-5 d; not to exceed 1 mg/kg bid

## **Prophylactic therapy/Tricyclic antidepressants**

Amitriptyline, nortriptyline, doxepin, and protriptyline have been used for migraine prophylaxis, but only amitriptyline has proven efficacy and appears to exert its antimigraine effect independent of its effect on depression.

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### **Amitriptyline (Elavil), doxepin (Adapin), nortriptyline (Aventyl), protriptyline (Vivactil)**

Migraine prophylaxis that is effective (independent of antidepressant effect). Mechanism of action is unknown. Inhibits activity of such diverse agents as histamine, 5-HT, and acetylcholine.

#### **Adult**

Amitriptyline, doxepin, nortriptyline: 10-25 mg PO qhs initially; increase by 10-25 mg q1-2wk based on efficacy and tolerance; not to exceed 150-175 mg/d

Protriptyline: 15 mg/d PO initially; titrate prn; not to exceed 40 mg/d given tid or qid

#### **Pediatric**

<12 years: Not recommended

>12 years: Administer as in adults

## **Prophylactic therapy/Calcium channel blockers**

This group is commonly used as prophylactic medication, although studies of their effectiveness have shown mixed results. Flunarizine has the best-documented efficacy but is not available in the United States. The efficacy of verapamil is supported by studies.

This group is particularly useful in patients with comorbid hypertension and in those with contraindications to beta-blockers such as asthma and Raynaud disease. This group may have particular advantage in patients with prolonged aura, vertebrobasilar migraine, or hemiplegic migraine.

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### **Verapamil (Calan, Covera)**

During depolarization, inhibits calcium ion from entering slow channels or voltage-sensitive areas of vascular smooth muscle.

#### **Adult**

120 mg/d PO qd (sustained release) initially or 40 mg tid; increase gradually; not to exceed 480 mg/d

#### **Pediatric**

Not established

### **Prophylactic therapy/Selective serotonin reuptake inhibitors**

These may be considered first-line drugs, but they have low efficacy.

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### **Fluoxetine (Prozac), Sertraline (Zoloft), Paroxetine (Paxil)**

Fluoxetine has been shown by anecdotal reports and small, double-blind, placebo-controlled study to be of benefit in migraine prophylaxis. Atypical, nontricyclic antidepressant with potent specific 5-HT-uptake inhibition with fewer anticholinergic and cardiovascular side effects than TCAs.

#### **Adult**

Fluoxetine: 10 mg/d PO on waking initially; can be increased every 2 wk; not to exceed 60 mg/d

Sertraline: 50 mg/d PO initially; increase at weekly interval over several wk; not to exceed 200 mg/d

Paroxetine: 10 mg/d PO initially; titrate prn; not to exceed 50 mg/d

#### **Pediatric**

Not established

### **Prophylactic therapy/NSAIDs**

These are used as prophylactic agents, but they are associated with a higher risk of adverse effects, particularly gastropathy or nephropathy, than when used as abortive medications. In controlled clinical trials, naproxen sodium demonstrated better efficacy than placebo and efficacy similar to propranolol. Tolfenamic acid has also been tried for migraine prophylaxis, but the clinical efficacy is not as good as that of beta-blockers, valproate, or methysergide.

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### **Naproxen sodium (Anaprox, Naprelan, Naprosyn)**

Inhibits inflammatory reactions and pain by decreasing activity of cyclooxygenase, enzyme responsible for prostaglandin synthesis.

#### **Adult**

275 mg PO tid or 550 mg bid

#### **Pediatric**

<12 years: Not recommended

>12 years: Administer as in adults

### **Prophylactic therapy/Serotonin antagonists**

Reported to provide effective migraine prophylaxis.

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## **Methysergide (Sansert)**

5-HT<sub>2</sub> antagonist with effective 5-HT<sub>1A</sub> agonist activity providing effective migraine prophylaxis in 60% or more of patients, which may be greater in persons who experience migraines with aura. Adverse effects may be severe; should be used only in patients who have not responded to other preventive agents.

### **Adult**

2 mg/d PO initially; increase dose gradually; not to exceed 8 mg/d

### **Pediatric**

Not recommended

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## **Cyproheptadine (Periactin)**

Acts primarily as antagonist of cerebral vascular 5-HT<sub>2</sub> receptors and has been used traditionally for pediatric migraine prevention despite minimal objective evidence of its efficacy.

Pizotifen has been shown to be effective for migraine, especially when used in combination with sumatriptan, but is not available in US.

### **Adult**

2 mg PO initial dose; increase every third day until beneficial effect demonstrated or until adverse effects occur  
Usual maintenance dose: 8-32 mg in 3-4 divided doses

### **Pediatric**

<2 years: Not established

2-6 years: 2 mg PO q8-12h; not to exceed 12 mg/d

6-14 years: 2-4 mg q8-12h; not to exceed 16 mg/d

>14 years: Administer as in adults

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## **Follow-up**

### **Further Inpatient Care**

Inpatient care for migraine may be indicated for the following:

- Treatment of severe nausea, vomiting, and subsequent dehydration
- Treatment of severe refractory migraine pain (ie, status migrainosus)
- Detoxification from overuse of combination analgesics, ergots, or opioids

### **Further Outpatient Care**

Many age related factors influence the clinical expression of headache and these should be taken into account in the diagnosis as well as treatment of patients with juvenile headaches.

### **Inpatient & Outpatient Medications**

For recommended medications in comorbid conditions, see Table 3.

### **Deterrence/Prevention**

See Treatment for information on migraine prophylaxis.

### **Complications**

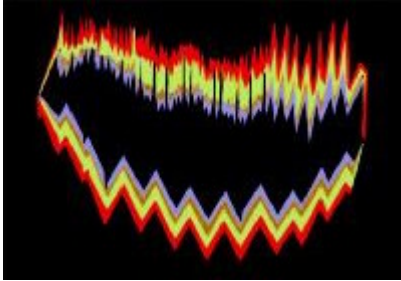
Ischemic stroke may occur as a rare but serious complication of migraine. Risk factors for stroke include migraine with aura, female sex, cigarette smoking, and estrogen use.

## Patient Education

For excellent patient education resources, see eMedicine's Headache Center. Also, visit eMedicine's patient education articles Causes and Treatments of Migraine and Related Headaches, Migraine Headache, Alternative and Complementary Approaches to Migraine and Cluster Headaches, Migraine Headache FAQs, and Understanding Migraine and Cluster Headache Medications.

## Multimedia

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Media file 1:

Migraine headache. Example of a visual migraine aura as described by a person who experiences migraines.

This patient reported that these visual auras preceded her headache by 20-30 minutes.



Media file 2:

Migraine headache. Example of a central scotoma as described by a person who experiences migraines.

Note the visual loss in the center of vision.



Media file 3:

Migraine headache. Example of a central scotoma as described by a person who experiences migraine headaches.

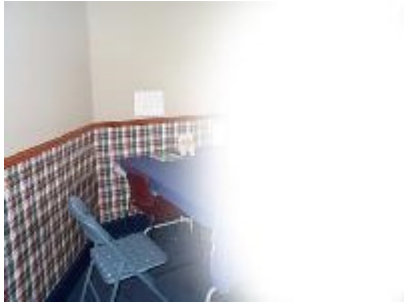
Again note the visual loss in the center of vision.



Media file 4:

Migraine headache. Example of visual changes during migraine.

Multiple spotty scotomata are described by a person who experiences migraines.



#### Media file 5:

Migraine headache. Frank visual field loss can also occur associated with migraine.

This example shows loss of the entire right visual field as described by a person who experiences migraines.

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