

# 1 **Migraine**

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## **Epidemiology and Risk Factors**

1. One year prevalence: 18% women, 6% men. In the United States, 28 million persons have migraine per year.
2. Lifetime prevalence: 25% women, 8% men
3. Migraine begins before the age of 20 in 50% and over the age of 50 in 2%.
4. Prevalence is highest from the ages of 25 years to 50 years.
5. About 70% of migraineurs have a positive family history in a first-degree relative.
  - a. First-degree relatives of those with migraine with aura have a fourfold greater risk of migraine with aura, and those with migraine without aura have a 1.9-fold increased risk of migraine without aura.
  - b. Family histories are often inaccurate because many migraineurs do not know they have migraine.
  - c. Mode of transmission is unclear; genetic heterogeneity is present.
6. In the United States, prevalence is highest among Caucasians, intermediate among African Americans, and lowest among Asian Americans.
7. Prevalence is highest in low-income and low-education groups in the United States.
8. High prevalence among neurologists (lifetime of 47% in males and 63% in females).
9. Frequency can range from once in a lifetime to daily.
  - a. 1–12 per year, 38%
  - b. 1–3 per month, 37%
  - c. 1 per week, 11%
  - d. 2–6 per week, 14%
10. About 50% of migraineurs have medically diagnosed migraine. Many patients and some doctors misdiagnose migraine as “sinus.”
11. Co-morbidity (greater than coincidental association of two disorders in the same individual). Migraineurs have an increased prevalence of many disorders.
  - a. Mitral valve prolapse, patent foramen ovale, and hypertension

- b. Stroke and epilepsy
- c. Atopic allergies, asthma, and irritable bowel syndrome
- d. Depression, bipolar disease, anxiety disorders, and panic attacks

### **Facts About Migraine**

- 28 million persons in the United States suffer migraines each year.
- Prevalence (lifetime): 25% women, 8% men
- Prevalence highest in those between the ages of 25 years to 50 years
- In the United States, prevalence highest among Caucasians, intermediate among African Americans, and lowest among Asian Americans
- Low-income and low-education groups have the highest rate of migraine in the United States.
- High prevalence among neurologists (lifetime of 47% in males and 63% in females)
- Frequency of migraine can range from once in a lifetime to daily.

## **Etiology and Pathophysiology**

1. Incompletely understood. Migraine is a neurovascular headache.
2. Migraine aura is a slow march of visual or other neurologic symptoms associated with changes in neuronal activity that result in spreading depression from the occipital cortex. Excitatory changes produce increased blood flow followed by reduced blood flow from neuronal inhibition.
3. The trigeminovascular system may constitute the anatomic substrate for migraine pain.
  - a. The pain-producing cranial nerves and dura
    - (1) Input passes through the ophthalmic division of the trigeminal ganglion to the trigeminocervical complex (the trigeminal nucleus caudalis and dorsal horns of C<sub>1</sub> and C<sub>2</sub>), which produces pain in the head (especially the ophthalmic division) and upper posterior neck.

- b. The peripheral branches of the trigeminal nerve which are activated during migraine
  - (1) The pain results from neurogenic inflammation produced by the antidromic release of calcitonin gene-related peptide by trigeminal nerve endings and associated with the release of other pain substances from plasma, platelets, and mast cells (e.g., histamine, prostaglandin, serotonin).
  - (2) This release induces the vasodilatation and extravasation of plasma proteins and the sensitization of trigeminal nociceptive nerve endings.
    - (a) Throbbing pain and exacerbation by activities such as bending over, head movement, coughing, and walking may be due to mechanical hypersensitivity of meningeal C-fiber nociceptors.
  - (3) Nitric oxide released from blood vessels, perivascular nerve endings, or brain tissue can trigger migraine pain.
- c. Central processing of pain signals in the trigeminocervical complex
  - (1) Second-order neurons receive input and project rostrally to the contralateral thalamus (ventrobasal complex and medial nuclei) and then activate cortex (anterior cingulate, insular, and frontal), periaqueductal gray matter (dorsal raphe nuclei), and locus coeruleus.
  - (2) Aminergic areas in the periaqueductal gray matter and locus coeruleus influence the incoming pain and cortical blood flow.
  - (3) A continuous discharge in this pain-control system might result from stimulation from the cortex or the hypothalamus owing to stress or to excessive afferent input from the special senses or from cerebral or extracranial vessels.
    - (a) Migraine prodrome may originate in the hypothalamus.
- d. Ergot derivatives and triptans are 5-hydroxytryptamine (5-HT)<sub>1B/1D</sub> agonists.
  - (1) They activate the 5-HT receptors present in cranial vessels and second-order trigeminal neurons, which leads to inhibition of cyclic aminomonophosphate production.
  - (2) Cranial vasoconstriction, peripheral neuronal inhibition, and central trigeminal nucleus inhibition result.

## Clinical Features

### 1. General features

- a. Unilateral in 60%, bilateral in 40%
  - (1) Often more intense in the frontotemporal and ocular regions before spreading to the parietal and occipital area.
  - (2) Any region of the head or face may be affected, including the parietal region, the upper or lower jaw or teeth, the malar eminence, or the upper anterior neck. Unilateral or bilateral posterior neck pain occurs in up to 75% of migraines and can lead to diagnostic confusion with tension-type headaches.
  - (3) 15% report side-locked headaches, migraine always occurring on the same side.
- b. Throbbing pain is reported in 85%, although up to 50% of migraineurs describe nonthrobbing pain during some attacks.
- c. Headache lasts 4 to 72 hours untreated or unsuccessfully treated.
  - (1) Median untreated attack duration is 24 hours
  - (2) Migraine persisting for more than 72 hours is termed “status migrainosus.”
- d. Untreated, 80% have moderate-severe intensity of pain; 20% mild pain.
- e. Pain is usually increased by physical activity or movement.
- f. Nausea occurs in about 80%; vomiting, in about 30%.
- g. Photophobia (light sensitivity) is present in about 90%; phonophobia (noise sensitivity), in about 80%.
- h. Migraine without aura (common) 80% of migraineurs; with aura (classic), in 20%
- i. 45% of migraineurs have at least one autonomic symptom due to parasympathetic activation (lacrimation, eye redness, ptosis, eyelid edema, nasal congestion, and rhinorrhea). Of these, 45% have both nasal and ocular symptoms, 21% have only nasal symptoms, and 34% have only ocular symptoms. These symptoms result in diagnostic confusion with “sinus” and allergies.
- j. Prodromal symptoms (premonitory phenomena) may be present in about 10% and precede the migraine attack by hours or up to 1 or 2 days.
  - (1) Changes in mental state may be reflected by depressed, hyperactive, euphoric, talk-

- ative, irritable, drowsy, or restless behaviors.
- (2) Neurologic symptoms may include photophobia, difficulty concentrating, phonophobia, dysphasia, hyperosmia, and yawning.
  - (3) General symptoms may include stiff neck, food cravings, cold feeling, anorexia, sluggishness, diarrhea or constipation, thirst, and fluid retention.
- k. Triggers or precipitating factors are present in about 85% of migraineurs who report an average of three triggers. There are numerous triggers
- (1) Stress is reported by about 50%. Other persons may report migraines triggered by let down after stress, vacations, or crying.
  - (2) Missing a meal (40%), lack of sleep, oversleeping, and fatigue
  - (3) Environmental triggers: changes in weather, heat, high humidity, high altitude
  - (4) Sensory triggers: bright lights, glare, flickering lights, loud noise, strong smells such as perfume or cigarette smoke
  - (5) Menses is a trigger for about 50% of female migraineurs.
  - (6) Up to 50% report alcohol as a trigger (can be all forms of alcohol or only one type such as red wine or beer).
  - (7) 10% to 45% report food triggers such as chocolate, dairy foods (particularly cheese), citrus fruit, fried fatty foods, and nitrates and nitrites in cured meats or fish (e.g., frankfurters, bacon, and lox).
  - (8) Other triggers include head trauma, exertion, and nitroglycerin.
- Food (10%–45%) such as chocolate, dairy foods (particularly cheese), citrus fruit, fried fatty foods, and nitrates and nitrites in cured meats or fish (e.g., frankfurters, bacon, and lox)
  - Head trauma, exertion, and nitroglycerin
- l. Resolution phase or postdrome
    - (1) Frequent symptoms include changes in mood, weakness, tiredness, and reduced appetite.
    - (2) May report feeling tired and washed out, irritable, or experiencing poor concentration (“mashed potato brain”). Less often, unusually refreshed or euphoric.
  - m. Sleep
    - (1) Sleep may relieve migraine, especially in children.
    - (2) Migraine can also begin during sleep and cause awakening or can be present upon awakening at the usual time.
2. Migraine without aura: about 80%
- a. International Headache Society (IHS) criteria
    - (1) At least five attacks fulfilling criteria (2)–(4)
    - (2) Headache lasting 4 to 72 hours (untreated or unsuccessfully treated)
    - (3) Headache has at least two of the following characteristics:
      - (a) Unilateral location
      - (b) Pulsating quality
      - (c) Moderate or severe intensity (inhibits or prohibits daily activities)
      - (d) Aggravation by walking stairs or similar routine physical activity
    - (4) During headache at least one of the following
      - (a) Nausea and/or vomiting
      - (b) Photophobia and phonophobia
    - (5) History, physical, and neurologic examinations do not suggest another disorder.
  3. Migraine with aura: 20%
    - a. IHS criteria
      - (1) At least two attacks fulfilling criterion (2)
      - (2) At least three of the following four characteristics:
        - (a) One or more fully reversible aura symptoms indicating brain dysfunction.
        - (b) At least one aura symptom develops gradually over more than 4 minutes or 2 or more symptoms occur in succession.



### Key Precipitating Factors or Triggers

Triggers or precipitating factors present in about 85% of those affected; an average of three triggers are usually reported:

- Stress (approximately 50%)
- Missing a meal (40%), lack of sleep, oversleeping, fatigue
- Environmental: changes in weather, heat, high humidity, high altitude
- Sensory: bright lights, glare, flickering lights, loud noise, strong smells such as perfume or cigarette smoke
- Menses (about 50% of female patients)
- Alcohol (up to 50%)

- (c) No single aura symptom lasts more than 60 minutes.
  - (d) Headache follows aura with a free interval of less than 60 minutes (it may also begin before or with the aura).
- (3) History, physical examination and, when appropriate, diagnostic tests exclude a secondary cause.
- b. Most migraineurs with aura also have migraine without aura.
- c. Total duration of the aura is usually less than 1 hour. If the aura lasts more than 1 hour but less than 1 week, then it is “migraine with prolonged aura” (also termed “complicated migraine”).
- d. Aura symptoms
- (1) Visual aura: the most common aura; present in 99% of cases
    - (a) Two types: positive visual phenomena with hallucinations and negative visual phenomena or scotomas with either incomplete or complete loss of vision in a portion or the whole of the visual field
    - (b) Most visual auras have a hemianoptic distribution.
    - (c) Photopsias consist of small spots, dots, stars, unformed flashes or streaks of light, or simple geometric forms and patterns that typically flicker or sparkle.
    - (d) Scintillating scotomas
      - (i) Also called “fortification spectra” (looks like a medieval fortified town as viewed from above) or *teichopsia* (“seeing fortifications”). Fortification spectra present in about 10%.
      - (ii) A scotomatous arc or band with a shimmering or glittering, bright, zigzag border.
      - (iii) The visual alteration usually commences in the center of the visual field and slowly extends laterally.
      - (iv) The scotoma frequently is semicircular or horseshoe-shaped.
    - (e) Occasionally, objects may appear to change in size and shape (metamorphopsia). Includes macropsia, micropsia, telescopic vision (objects larger than normal), teleopsia (objects too far away), mosaic vision, and Alice in Wonderland syndrome (episodes of distorted body image). Multiple images can also be present.
  - (f) Most consist of flickering, colored or uncolored, unilateral or bilateral zigzag lines or patterns, semicircular or arcuate patterns, wavy lines, or irregular patterns.
  - (g) Headaches are usually contralateral but can occasionally be unilateral, on the side of the visual symptoms.
- (2) Sensory aura: present in about 30% of migraine with aura.
- (a) Numbness, tingling, or pins and needles sensations which are usually unilateral.
  - (b) Cheiro-oral (hand-mouth) distribution is common.
  - (c) Sensory symptoms often slowly spread in distribution, e.g., from hand to mouth.
  - (d) The hand and then the face, alone or in combination, are the parts of the body most commonly affected. Paresthesia of one side of the tongue is typical. Less often, the leg and trunk may be involved.
- (3) Motor aura is rare: Often sensory ataxia or a heavy feeling is misinterpreted as “weakness.”
- (4) Speech and language disturbances may occur in up to 20% of cases.
- (a) Patients often report speech disturbance occurring as the spreading paresthesias reach the face or tongue.
  - (b) Slurred speech and, with involvement of the dominant hemisphere, paraphasic errors and other types of impaired language production, and impaired comprehension may occur.
  - (c) Duration is usually less than 30 minutes.
- (5) Other aura symptoms: Rarely, other symptoms include déjà vu and olfactory and gustatory hallucinations
- (6) Combinations of aura symptoms
- (a) Visual symptoms frequently occur alone.
  - (b) Sensory, speech, and motor symptoms are usually associated with visual symptoms or with one or more of the other symptoms.
  - (c) When two or more aura symptoms are present, they almost always occur in succession and not simultaneously.

4. Migraine aura without headache (acephalgic migraine).
  - a. Migraine aura can occur without headache, often in those with migraine with or without aura. Visual aura is the most common.
  - b. Episodic vertigo without headache or auditory or other neurologic symptoms lasting minutes to days can also be an aura.
  - c. In older persons, can be confused with transient ischemic attacks and are termed “late-life migraine accompaniments” (see Part XI, Chapter 8, Headaches in Patients Over the Age of 50).
  - d. Rarely, migraineurs have persistent visual aura.
    - (1) Usually simple, unformed hallucinations in the entire visual field of both eyes may be described as a million dots, television static, clouds, dots, heat waves, flashing or flickering lights, lines of ants, rainlike pattern, snow, squiggles, bubbles, and grainy vision.
    - (2) Occasionally, palinopsia (the persistence of visual images), micropsia, or formed hallucinations.
    - (3) Might respond to preventive treatment with divalproex sodium.
5. Pediatric migraine and variants including familial hemiplegic, basilar, ophthalmoplegic, benign paroxysmal vertigo of childhood, abdominal, confusional, and “footballer’s” are discussed in Part XI, Chapter 6, Headaches during Childhood and Adolescence. Posttraumatic migraine is also discussed in Part XIII, Chapter 1, Mild Head Injury and the Postconcussion Syndrome.
6. Part XI, Chapter 7, Headaches in Women, reviews other migraine topics including menstrual, menopause, oral contraceptive use, and headaches during pregnancy and postpartum.
7. Benign episodic mydriasis
  - a. Transient isolated mydriasis with normal vision and pupillary reactivity to light may occasionally accompany migraine headaches, typically in young adults or children.
    - (1) Duration of episodes 15 minutes to 24 hours often associated with blurred vision.
    - (2) Episodes average 2 to 3 per month
  - b. Eyelid or motility abnormalities are absent
  - c. Dilation of the pupil is from either parasympathetic insufficiency of the iris sphincter or sympathetic hyperactivity of the iris dilator.
  - d. Angle-closure glaucoma should be excluded



### Key Clinical Features

- Unilateral headache, 60%; bilateral headache, 40%
- Thobbing pain 80%, nausea 80%, vomiting 30%
- Photophobia 90%, phonophobia 80%
- At least one autonomic symptom in 45%
- Without aura, 80%; with aura, 20%

### Differential Diagnosis

1. Although most migraines can be diagnosed on the basis of clinical criteria, some may have features of tension and migraine (“migrainous” especially when occurring in persons with definite migraine) or cluster and migraine (“cluster-migraine”).
2. First severe migraine attacks, the worst migraine attacks, or migraine with a thunderclap onset (“crash” migraine) may raise concerns about possible other causes such as subarachnoid hemorrhage or meningitis (see Part XI, Chapter 5, First or Worst Headaches).
3. With the first attack, 7% of patients with multiple sclerosis present with significant headaches that may be confused with migraine. In addition, migraine may be as much as twice as common in those with multiple sclerosis as in controls.

### Laboratory Testing

1. Electroencephalograms are not indicated except when there is a question of a seizure disorder or in the case of migraine with altered consciousness—e.g., confusional or basilar migraine.
2. Blood tests are generally not helpful except as a baseline when monitoring for side effects of medications.
3. Lumbar puncture is not indicated except in some special cases (e.g., first or worst migraine, crash migraine, persistent or unusual auras, or to rule out pseudomigraine (see Part II, Chapter 1, Lumbar Puncture and Cerebrospinal Fluid Evaluation).

### Radiologic Features

1. The routine use of neuroimaging for migraine is not indicated when there is no recent change in headache pattern, no history of seizures, and no other focal neurologic signs or symptoms.
2. Indications for neuroimaging (usually magnetic resonance imaging—MRI) in migraineurs include

the following: unusual, prolonged, or persistent aura; increasing frequency, severity, or change in clinical features; migraine status; first or worst migraine; migraine with a sudden onset and severe intensity (“crash” migraine); new onset over the age of 50 years; variants including basilar confusional, hemiplegic, and aura without headache; late-life migraine accompaniments; and posttraumatic migraine.

3. White matter abnormalities (WMA) are present on MRI scans more often in migraineurs (variably reported in 12% to 46%) than in controls (2% to 14%).
  - a. WMA, foci of hyperintensity on both proton-density and T<sub>2</sub>-weighted images in the deep and periventricular white matter, are due to either interstitial edema or periventricular demyelination.
  - b. Although the cause is not certain, various hypotheses have been proposed, including increased platelet aggregation with microemboli, abnormal cerebrovascular regulation, and repeated attacks of hypoperfusion during the aura.
  - c. Although antiphospholipid antibody syndrome can cause WMAs, this disorder is no more common in people with migraine than in controls.
  - d. In some cases, nonspecific WMA present on MRI scans of migraineurs can be incorrectly diagnosed as signifying multiple sclerosis.
    - (1) There are several features of WMA that are more typical of multiple sclerosis than migraine as visualized on T<sub>2</sub>-weighted and FLAIR scans, including primarily periventricular rather than peripheral location, oval rather than round or punctate shape, irregular or fuzzy margins rather than sharply defined edges, and oriented perpendicular to the ventricles.
    - (2) Corpus callosum or infratentorial lesions are more likely due to multiple sclerosis, as are lesions greater than 6 mm in diameter.
  - e. WMA may also be present in systemic lupus erythematosus (SLE) but are not specific for central nervous system (CNS) involvement. Migraine is more common in patients with SLE than in controls.

#### Indications for Considering Neuroimaging

- Unusual, prolonged, or persistent aura
- Increasing frequency, severity, or change in clinical features
- Migraine status
- First or worst headache
- Crash migraine
- Onset over the age of 50 years
- Posttraumatic migraine

## Treatment

1. Acute (symptomatic)
  - a. General principles
    - (1) Early treatment when the headache is mild is much more effective than later treatment when the migraine is moderate-severe in intensity.
    - (2) Frequent use of acute medications can lead to rebound (recurring headache induced by repetitive and chronic overuse of acute headache medications.)
      - (a) Generally, the use of acute therapy should be restricted to a maximum of 2 to 3 days per week.
    - (3) Different patients may respond to different medications at different times.
    - (4) There are numerous options which are briefly summarized here. Refer to standard pharmacology textbooks and references for more information.
    - (5) Patients benefit from stratified care.
      - (a) Treatment based on attack characteristics including peak intensity, time to peak intensity, associated symptoms, and disability
      - (b) Individually tailored to specific patient needs
      - (c) Use nasal, parenteral, or rectal forms of medication in patients with significant nausea or vomiting or gastroparesis. Antinausea medications such as promethazine or prochlorperazine may help.

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- Early treatment—when the headache is mild—is much more effective than when the migraine is moderate–severe in intensity.
- Medications for acute headaches should be used only 2 to 3 days per week; their frequent use may lead to rebound.
- Treatment should be based on attack characteristics such as peak intensity, time to peak intensity, associated symptoms, and disability.

- Over-the-counter medications including aspirin, acetaminophen, aspirin plus caffeine, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Opioid combinations and butalbital combinations and butorphanol nasal spray; use should be restricted because of the potential for rebound headaches and habituation.
- Prescription NSAIDs (oral such as naproxen and intramuscular ketorolac) and isometheptene combinations.
- Ergotamine ± caffeine. Used extensively before triptans became available but much less now. Overuse can result in rebound and dependence. Contraindications are the same as for dihydroergotamine (see below).
- Dihydroergotamine (DHE). Can be administered as nasal spray (NS) or by subcutaneous (SC), intramuscular (IM), or intravenous (IV) injection.
  - Does not result in dependence.
  - NS provides relief in 65%; parenteral administration, in about 90%
  - May cause nausea. Can be administered with metoclopramide, promethazine, or prochlorperazine.
  - Contraindications
    - Concurrent use of a triptan. Use of the two drugs should be separated by at least 24 hours because of the potential for additive vasoconstriction.
    - Coronary artery disease, cerebral, and peripheral vascular disease, and uncontrolled hypertension. In patients with risk factors including older age, consider the possibility of undiagnosed

coronary artery or peripheral vascular disease. (CAD or PVD).

- Pregnancy and breast-feeding
- For acute migraine, can administer NS or as IM or SC dose of 1 mg.
  - For an attack that has climaxed, can administer prochlorperazine 5 mg IV or metoclopramide 5–10 mg IV followed immediately by 0.5–0.75 mg DHE given slowly over 2 to 3 minutes. If the patient is not improving in 30 to 60 minutes, another 0.5 mg DHE can be given IV without prochlorperazine or metoclopramide.
- Triptans (5-HT<sub>1B/1D</sub> agonists)
    - 2-hour efficacy (reduction of moderate to severe pain to mild or no pain) 80% with sumatriptan SC; 65% to 70% with sumatriptan, rizatriptan, and zolmitriptan, and almotriptan PO, and less with naratriptan and frovatriptan succinate.
    - Triptans are more effective and more likely to result in pain freedom with treatment of migraine when pain is mild.
    - Options
      - Sumatriptan tablet (25 mg, 50 mg, 100 mg), nasal spray (5 and 20 mg), and subcutaneous injectable (6 mg)
      - Zolmitriptan tablet (2.5 mg and 5 mg) and orally disintegrating tablet (2.5 and 5 mg)
      - Naratriptan tablet (1 mg and 2.5 mg)
      - Rizatriptan tablet (5 and 10 mg) and orally dissolvable wafer (10 mg)
      - Almotriptan 12.5 mg tablet
      - Frovatriptan succinate 2.5 mg tablet
    - Contraindications include
      - Coronary artery disease, cerebral and peripheral vascular disease, and uncontrolled hypertension
      - In those with risk factors including older age, consider the possibility of undiagnosed CAD and PVD.
    - Side effects are usually mild and transient and include chest pressure/heaviness, jaw tightness, dizziness, somnolence, asthenia/fatigue, nausea, and paresthesias. Recurrence (return of episodic headache during the same attack after acute treatment) is common with triptans, occurring in 20% to 40% of patients, depending on the triptan, about 11 hours later. A second dose will usually relieve the recurrent headache.



### Key Treatment

#### Acute Headaches

- Over-the-counter medications such as aspirin, acetaminophen, aspirin plus caffeine, and NSAIDs
- Opioid and butalbital combinations and butorphanol nasal spray
- Prescription NSAIDs and isometheptene combinations
- Ergotamine ± caffeine
- Dihydroergotamine
- Triptans

- h. Intractable migraine and migraine status: options
  - (1) Intravenous fluids and electrolyte replacement as indicated
  - (2) Sumatriptan 6 mg SC
  - (3) Intractable migraine may respond to metoclopramide 10 mg IV and DHE 0.5 to 1.0 mg (depending upon response) IV every 8 hours for 2 to 3 days as indicated. DHE and triptans should not be used within 24 hours of each other.
  - (4) Prochlorperazine 5 to 10 mg IV
  - (5) Ketorolac 30 to 60 mg IM
  - (6) Corticosteroids (single or rapidly tapering dose of prednisone starting at 80 mg a day or dexamethasone 6 mg PO or IV)
  - (7) Parenteral narcotics such as meperidine with promethazine
  - (8) Valproate sodium 500 mg diluted in 50 ml of saline administered IV over 5 to 10 minutes: can be repeated every 8 hours for 2 days
  - (9) Droperidol (2.5 mg IM or IV)
  - (10) Magnesium sulfate 1 g IV over 15 minutes.
2. Preventive (prophylactic)
  - a. Guidelines for use of prophylactic treatment
    - (1) Migraine significantly interferes with patient's daily routine despite acute treatment
    - (2) Acute medications contraindicated, ineffective, have intolerable side effects, or are overused
    - (3) Frequent headache (2 or more attacks per week)
    - (4) Uncommon migraine type (hemiplegic, basilar, prolonged aura, or migrainous infarction)
    - (5) Cost of both acute and preventive treatments
    - (6) Patient preference
  - b. General principles for administering prophylactic treatment
    - (1) Start low and increase dose slowly
    - (2) Perform an adequate trial of 2 to 3 months at an adequate dose
    - (3) Discontinue or taper off (depending on the drug) overused medications that may be causing rebound and that may decrease the efficacy of preventive treatment
    - (4) Monitor with a headache diary
    - (5) Educate the patient about the rationale for treatment and possible side effects; address the patient's expectations for treatment.
    - (6) Consider co-existent or co-morbid disease
      - (a) Some medications may treat two disorders such as migraine and epilepsy, hypertension, depression, bipolar disorder, and insomnia.
      - (b) Co-existent diseases (e.g., depression or asthma) may be relative contraindications in the use of beta-blockers
      - (c) In women who are pregnant or might become pregnant, the potential for teratogenicity should be considered (see Section XI, Chapter 8, Headaches in Women)
    - (7) Withdraw some medications especially at moderate-high doses slowly (e.g. tricyclic antidepressants and beta-blockers)
    - (8) Those with mild responses to one preventative may benefit from the addition of a second.
    - (9) First line preventatives reduce the frequency more than 50% in about 50–60% of migraineurs.
  - c. Antidepressants
    - (1) Tricyclic antidepressants such as amitriptyline and nortriptyline starting at 10 to 25 mg at bedtime slowly increasing the dose as appropriate. Efficacy typically at a dose range up to 150 mg. Protriptyline, which is nonsedating, may also be effective.
      - (a) Side effects include drowsiness, weight gain, dry mouth, and constipation. May lower the seizure threshold in those with frequent seizures (amitriptyline more so than nortriptyline).
      - (b) Amitriptyline and nortriptyline may treat more than one disorder for patients with sleep disturbance and/or depression.

- (2) Fluoxetine, a second-line drug; Has questionable efficacy in migraine. Venlafaxine might be effective.
- d. Beta-blockers (starting dose and upper range)
- (1) Propranolol (40-240 mg in divided doses), propranolol long-acting (60-160 mg once daily)
  - (2) Atenolol (50-100 mg)
  - (3) Metoprolol (50-200 mg)
  - (4) Nadolol (40-160 mg)
  - (5) Timolol (10-30 mg in divided doses)
  - (6) Contraindications
    - (a) Asthma, congestive heart failure, sinus bradycardia, second- and third-degree heart block
    - (b) May exacerbate depression
    - (c) In diabetics, may block the symptoms and signs of hypoglycemia
    - (d) Some authorities urge caution in the use of beta-blockers in migraine with prolonged aura and basilar migraine because of the potential for limiting compensatory vasodilator capacitance.
  - (7) Side effects include tiredness, fatigue, dizziness. Need to monitor for symptomatic bradycardia and hypotension.
  - (8) The failure to respond to one beta-blocker does not generally predict the failure to respond to another.
  - (9) May treat more than one disorder if the patient also has hypertension, essential tremor, or anxiety/panic attacks.
- e. Anticonvulsants
- (1) Divalproex sodium
    - (a) Starting dose of 500 mg day (administered twice daily or, with extended-release tablet, once a day). May dose up to 1500 mg/day for migraine (for epilepsy, need to monitor serum levels; in migraine, serum levels may be helpful for monitoring toxicity but not predicting efficacy)
    - (b) Contraindicated in patients with hepatic disease or significant hepatic dysfunction
    - (c) Side effects include nausea, asthenia, somnolence, weight gain, hair loss, tremor, dizziness, and teratogenic potential (neural tube defects in 1% to 2%). Can also cause thrombocytopenia and abnormal coagulation. Very rare side effects, which can be fatal: liver failure (usually during the first 6 months of treatment) and pancreatitis
    - (d) Obtain baseline hematologic and liver function studies and then at periodic intervals. Platelet counts and coagulation profile prior to planned surgery
    - (e) Consider for migraineurs with prolonged or atypical migraine aura.
    - (f) May be useful as monotherapy in those with migraine and epilepsy or bipolar disease
  - (2) Topiramate
    - (a) Start at 25 mg daily (bedtime dosing may be preferable) and increase by 25 mg weekly. Can be given in a single daily dose if not on a hepatic enzyme inducer. If bothersome side effects, wait before increasing dose or decrease dose. Effective dose for migraine may be up to 300 mg; efficacy often at 100 mg daily.
    - (b) Side effects include somnolence, fatigue, decreased appetite, weight loss, dizziness, paresthesias of hands and feet (persistent paresthesias may improve by taking potassium chloride 20 to 40 mEq per day or vitamin C), psychomotor slowing, and difficulty with speech, language, concentration, and memory (cognitive side effects less at lower doses used for migraine than for epilepsy). Kidney stones, which usually pass without surgery in 1.5% or less. Very rare reports of secondary angle-closure glaucoma occurring during the first month of treatment.
    - (c) No need for baseline or periodic blood work.
    - (d) May be useful for patients with migraine who are overweight or who also have epilepsy, bipolar disease, or essential tremor.
  - (3) Gabapentin
    - (a) Start at 300 mg given three times daily. May increase up to 2400 mg daily in three divided doses.
    - (b) Side effects include somnolence, dizziness, asthenia, and ataxia.
    - (c) No need for baseline or periodic blood work.
    - (d) May be useful for those with migraine and essential tremor or epilepsy.
- f. Other preventatives
- (1) Verapamil
    - (a) Start at 120 to 240 mg per day in three divided doses or once daily with the

- extended-release preparation, going up to 240 mg daily.
- (b) Contraindications: severe left ventricular dysfunction, hypotension, sick sinus syndrome, or second- or third-degree atrioventricular block, atrial flutter or fibrillation with an accessory bypass tract. Combination use with beta-blockers may produce excessive bradycardia and atrioventricular block.
  - (c) Side effects include constipation, hypotension, atrioventricular block, edema, headache, and nausea.
  - (d) Efficacy for migraine prevention is poorly established. Flunarizine, a calcium channel blocker not available in the United States, has well-demonstrated efficacy. Consider use as a second-line treatment or in migraineurs with coexistent stroke, prolonged or atypical migraine aura, or basilar migraine.
- (2) NSAIDs such as naproxen 500 mg per day and ketoprofen 150 mg per day may be modestly effective.
  - (3) Methysergide
    - (a) Highly effective but use restricted to refractory severe migraine due to side effects
    - (b) Start at 1 mg daily and increase, as indicated by 1 mg every third day to a daily dose of 3 to 6 mg in three divided doses.
    - (c) Contraindications include cardiovascular diseases, severe hypertension, history of thrombophlebitis, peptic ulcers, pregnancy, familial fibrotic disorders, lung diseases, collagenoses, and liver and kidney diseases.
    - (d) Side effects include nausea and vomiting, diarrhea, leg pain, edema, dizziness, sedation, and lassitude. Use triptans and ergotamine with caution because of additional vasoconstrictor effect of methysergide.
    - (e) Long-term use may rarely lead to retroperitoneal, heart valve, and pleural fibrosis (1/2500).
      - (i) Manufacturer's labeling recommends use for 6 months followed by 3 to 4 weeks off the drug before starting again.
      - (ii) With long-term use, period laboratory testing for fibrotic reactions is recommended.
  - (4) Magnesium
 

Daily oral magnesium (e.g., trimagnesium dicitrate 300 mg twice daily) has been reported both as effective and as ineffective.
  - (5) Riboflavin
 

400 mg daily may be effective based upon one randomized controlled trial.
  - (6) Feverfew (the herb *Tanacetum parthenium*)
 

50 to 82 mg per day may be modestly effective.
  - (7) Coenzyme Q10 150 mg a day may be effective.
  - (8) Botulinum toxin injections may be effective.



#### Key Preventive Treatments

- Antidepressants
- Beta-blockers
- Anticonvulsants

#### g. Behavioral and physical treatments

- (1) Relaxation training (including progressive muscle relaxation, autogenic training, and meditation or passive relaxation), thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy are all somewhat effective in preventing migraine.
- (2) Acupuncture might be effective but further study is needed.



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