### In the Clinic

# Migraine

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**CME Objective:** To review current evidence for the risk and prevention, diagnosis, treatment, and follow-up of migraine.

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ore than 90% of patients who have recurrent headache on presentation to primary care offices or emergency departments have migraine. Migraine affects approximately 13% of adults in the United States and is associated with high socioeconomic and personal impact. In the Global Burden of Disease Survey 2010, it was ranked as the third most prevalent disorder and seventh-highest specific cause of disability worldwide.

## Risk and Prevention

## **Prevention** Who is at risk for migraine headache?

Studies have shown that the tendency to develop migraines can be inherited. If one parent has migraine headaches, there is a 40% chance that their children will also have migraine; if both parents have migraine, the likelihood that their children will have migraine increases to 75%. Migraine usually begins in late childhood or early adolescence and follows various courses: The headache may go into remission after a few years, recur in cycles of variable activity for many years or decades, or evolve into a

chronic and more refractory state (in a minority of patients). Migraine is more common in preadolescent boys than girls but becomes 3 times more common in adult women than men. Prevalence peaks in the fifth decade of life, decreases significantly in the sixth and seventh decades, and is rare in later decades.

## Can migraine in patients at increased risk be prevented?

Although it is not possible to change the natural history of migraine, early diagnosis and early management improve the long-term prognosis.

### **Diagnosis**

## What clinical features are required for diagnosis?

A typical migraine attack consists of a unilateral, throbbing headache accompanied by photophobia, phonophobia, nausea, and disability (see the Box: International Headache Society Criteria for Migraine Diagnosis).

Migraine headache is preceded by focal neurologic symptoms, termed "aura," in up to 30% of patients. Aura is typically characterized by any combination of visual, hemisensory, or language abnormalities, with each symptom developing over at least 5 minutes and lasting a maximum of 60 minutes. The most common aura is visual, consisting of a flashing light or an enlarging blind spot rimmed with a shimmering edge or jagged lines in the peripheral vision. Common nonvisual auras include spreading unilateral numbness or tingling affecting the face and arms and

disturbed thinking or speech. The associated headache usually occurs within 1 hour, but auras do not always progress to head pain.

The 5 criteria most predictive of migraine may be remembered more easily by the mnemonic "POUND," as in "pounding headache": Pulsatile quality (headache described as pounding or throbbing), One-day duration (episode of headache lasts 4 to 72 hours if untreated), Unilateral location, Nausea or vomiting, Disabling intensity (altered usual daily activities during headache episode).

A study of the International Headache Society (IHS) criteria for diagnosis of migraine showed that the criteria had excellent specificity but sensitivity <50%, which could be due to the restrictive nature of the criteria. Use of the 5 criteria most predictive of migraine resulted in 95% sensitivity and 78% specificity. The presence of 3 of these 5 criteria is predictive of migraine and 4 of 5 is highly predictive (1).

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## What clinical features are helpful in distinguishing migraine from tension-type headache?

Tension-type headache is a "featureless" headache, lacking the characteristic symptoms that define migraine. It is typically bilateral, lasting from 30 minutes to 7 days. The nonpulsating pressing or tightening quality is described by patients as a "band-like" constriction around their head. The attacks are mild to moderate in intensity and do not prohibit activity. There is no aggravation of headache by routine physical activity and no association with nausea or vomiting (although anorexia may occur). Photophobia or phonophobia may be present. However, extensive variability in the clinical expressions of migraine

often leads to misdiagnosis of tension headache in the presence of steady bilateral pain or sinus headache, when the discomfort is a frontal or facial pressure.

## What clinical features suggest that the cause of headache may be more serious than migraine?

More serious causes of headache (Table 1) must always be considered because certain conditions that sometimes cause headache, such as aneurysm or giant cell arteritis (temporal arteritis), are so serious that delayed diagnosis or treatment could cause death or permanent impairment (see the Box: Symptoms Suggesting Serious Secondary Causes of Head-ache). Aspects of the history

### Table 1. Differential Diagnosis of Serious Secondary Causes of Headache

Table 1. Differential Diagnosis of Serious Secondary Causes of Headache		
Disease	Characteristics	
Subarachnoid hemorrhage	Sudden, explosive onset of severe headache ("worst headache of my life"); sometimes preceded by "sentinel" headaches (10%)	
Acute or chronic subdural hematoma	History of antecedent trauma; may have subacute onset; may have an altered level of consciousness or neurologic deficit	
Meningitis	Usually associated with fever and meningeal signs	
Encephalitis	Associated with neurologic abnormalities, confusion, altered mental state, or change in level of consciousness	
Intracranial neoplasms	Worse on awakening, generally progressive; headache aggravated by coughing, straining, or changing position	
Benign intracranial hypertension (pseudotumor cerebri)	Often abrupt in onset, associated with nausea, vomiting, dizziness, blurred vision, papilledema; neurologic examination usually normal but may have cranial nerve VI palsy; headache aggravated by coughing, straining, or changing position	
Giant cell arteritis (temporal arteritis)	Patients older than 50 years of age; associated with tenderness of scalp, the temporal artery, and jaw claudication; visual changes	
Acute severe hypertension	Marked blood pressure elevation (systolic ≥210 mm Hg or diastolic ≥120 mm Hg); may have symptoms of encephalopathy (e.g., confusion, irritability)	
Carbon monoxide poisoning	May be insidious or associated with dyspnea, if severe; occurs more commonly in the colder months	
Acute glaucoma	Associated with blurred vision and seeing halos around lights	
Carotid dissection	Cause of stroke; can present with headache, can be spontaneous or follow minor trauma or sudden neck movement; present as unilateral	

### International Headache Society Criteria for Migraine Diagnosis

#### Without aura

- A. At least 5 attacks in a lifetime fulfilling criteria B–D
- B. Headache lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache with at least 2 of the following characteristics:
  - Unilateral location
  - Pulsating quality
  - Moderate or severe pain intensity
- Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
- D. During heacache, occurrence of at least one of following symptoms:
  - Nausea and/or vomiting
  - Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

### With typical aura

- A. At least 2 attacks in a lifetime fulfilling criteria B and C
- B. Aura consisting of visual, sensory, and/or speech/ language symptoms, each fully reversible, but no motor weakness or brainstem symptoms.
- C. At least 2 of the following characteristics:
  - At least 1 aura symptom spreads gradually over 5 or more minutes, and/or 2 or more symptoms occur in succession
  - Each individual aura symptom lasts 5–60 minutes
  - At least 1 aura symptom is unilateral
  - The aura is accompanied, or followed within 60 minutes, by headache
- D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

ICHD-3 = International Classification of Headache Disorders, 3rd ed. Adapted from Headache Classification of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version). Cephalalgia. 2013;33:629-808. [PMID: 23771276] Reprinted with permission.

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headache/face pain, ipsilateral Horner syndrome

### **Symptoms Suggesting Serious** Secondary Causes of Headache

headache (intensity, frequency, pattern)

Daily or continuous headache Effort-related or positional headache

Headache associated with change of personality or mental status

Headache brought on by coughing,

Headache brought on by exercise or

Headaches awakening from sleep Headaches that become refractory to previously effective treatment

Migraine aura that begins or

persists after the headache has dissipated

New onset after age 50 years attacks ("side-locked")

Previous head trauma Rapidly increasing headache

Subjective numbness or tingling inconsistent with sensory aura of migraine

with rapid progression over seconds to minutes

maneuver

Change in previously existing

sneezing, or bending

orgasm

Jaw pain (claudication)

Persistent pain on one side of the head without any contralateral

frequency

Sudden explosive onset of headache

Worsens with the Valsalva

Worst headache of life

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that are atypical for migraine, even in a patient with a history of migraine, should alert the physician to exclude a secondary headache.

Onset of migraine after age 50 years is unusual, and the likelihood of secondary causes is greater. The combination of new-onset headache, jaw claudication, and abnormal (nodular or tender) arteries is highly predictive of giant cell arteritis; patients with these symptoms should have erythrocyte sedimentation rate (ESR) measured and temporal artery biopsy (2).

A cohort study of patients with giant cell arteritis revealed that headache was the predominant symptom in 65%-80% of patients (3).

### What is the role of physical examination in patients who present with migraine?

The main purpose of the examination is to assure both physician and patient that there is no underlying sinister pathology causing the headache, and patients can be reassured if the findings are "normal" (see the Box: Signs Suggesting Serious Secondary Causes of Headache). In patients seen in a specialist clinic, fewer than 1% have headaches secondary to intracranial disease, and all of such patients have signs attributable to the intracranial process.

The examination can be brief but should be thorough. Particular attention should be paid to the cranial nerves, tendon reflexes, and optic discs. Pulse and blood pressure should be measured, and auscultation for cardiac abnormalities and bruits should be done first and are particularly important if vasoconstrictor drugs, such as ergotamine or triptans, are being considered. Examining the jaw can identify temporomandibular joint dysfunction that causes headache. Examination of the neck and cervical spine may reveal muscle contraction, cervical spondylosis, or even meningismus.

### What is the role of diagnostic testing, including imaging studies and electroencephalogram, in patients with suspected migraine?

Neuroimaging is not usually warranted for migraine and is unlikely to reveal an abnormality in patients with a normal neurologic examination.

A meta-analysis of studies of migraine patients and a normal neurologic examination found a rate of significant intracranial lesions of 0.18% (4).

A lower threshold for obtaining neuroimaging should be applied for patients with unexplained abnormal findings on the neurologic examination or who have atypical features, particularly headache worsened by the Valsalva maneuver, headache causing awakening from sleep, new headache in an older person, or progressively worsening headache; these symptoms indicate a higher likelihood of significant intracranial pathology (5). Electroencephalography is not useful for routine evaluation of patients with headache and should be considered only if symptoms suggest a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness (6). ESR should be measured in patients older than 50 years with newonset headache. An elevated ESR (>30 mm/h) is highly sensitive for giant cell arteritis but lacks specificity; a temporal artery biopsy confirms the diagnosis.

### Signs Suggesting Serious Secondary Causes of Headache

Any focal abnormality on neurologic examination

Diastolic blood pressure >120 mm Hg Diminished or absent temporal artery pulsations

Necrotic lesions of scalp or tongue Nuchal rigidity or limitation of anterior neck flexion

Papilledema

Reddened, tender scalp nodules Tender or nodular temporal arteries Decreased visual acuity and elevated intraocular pressure

### When should a neurologist be consulted for diagnosis?

Migraine headaches and medication-overuse headache (MOH) can be managed in primary care. Referral is indicated if the headache is atypical, difficult to classify, or fails to respond to recommended management strategies (see the Box: Reasons for Neurologic Referral).

# Are there special considerations for pregnant women who present with symptoms consistent with migraine headache?

Migraine is a risk factor for hypertensive disorders of pregnancy (7). Hence, it is important to consult with an obstetrician when pregnant women have headaches associated with peripheral edema or hypertension to exclude preeclampsia.

In pregnant women with typical migraine features by history and a

normal neurologic examination, imaging studies should be deferred until after delivery. When neuroimaging is needed for abnormal findings on neurologic examination, progressively worse headache, or an unexplained change in headache pattern, magnetic resonance imaging is the study of choice for most pregnant women.

Head computed tomography is relatively safe during pregnancy (exposure of <0.05 rad to the fetus) and is the study of choice for head trauma and suspected intracranial hemorrhage (8). Reducing voltage and limiting z-axis is more effective than shields at reducing fetal dose. Contrast agents should not be used unless absolutely necessary. Although no ill effects on the fetus have been shown, gadolinium crosses the placental barrier and is excreted by the fetal kidney.

Diagnosis... Migraine without aura is the most likely headache diagnosis in a patient who has had at least 5 episodes of headache lasting 4–72 hours associated with photophobia and phonophobia, nausea, and disability who is otherwise well between attacks. Aura is diagnosed when fully reversible symptoms of visual, sensory, motor, or language abnormalities develop over a minimum of 5 minutes and last a maximum of 60 minutes and resolve before headache onset. Tension headache is a bilateral "featureless" headache lasting 30 minutes to 7 days. Secondary headache must be excluded if focal neurologic signs are present on examination. Neuroimaging is not warranted in patients with a normal neurologic examination and typical headache characteristics.

### **CLINICAL BOTTOM LINE**

## What is the role of diet in management of migraine?

The most important dietary triggers for migraine are delayed or missed meals, so regular meal times are necessary. Specific dietary triggers are associated with migraines in some individuals (9, 10). A few careful studies have shown a causal relationship between food and migraines for some children (11) and adults (12). Patients should be encouraged to identify and avoid dietary factors, which can decrease migraine symp-

toms substantially in some, but not all, individuals. In particular, reduced intake of caffeine, artificial sweeteners, and additives (such as monosodium glutamate) can help prevent migraine. Possible triggers should be avoided for at least 4 weeks. If there has been some improvement in migraine, each food can be slowly reintroduced to determine the relevant triggers, bearing in mind that migraine starts around 24-48 hours before the onset of headache.

1TC5-5

#### Reasons for Neurologic Referral

Diagnostic uncertainty

Suspicion of serious secondary headache Any headache that is new or unexpected in an individual patient, but especially:

- New headache in a prepubertal child
- New headache in a patient older than 50 years
- Thunderclap headache (intense headache with abrupt or "explosive" onset)
- New headache in a patient with a history of cancer

HIV infection or immunodeficiency Unusual migraine aura, especially:

- Duration >1 hour
- Featuring motor weakness

Aura without headache in the absence of a history of migraine with aura

Progressively worsening headache over weeks or longer

Headache associated with postural change indicative of high or low intracranial pressure

Headache associated with unexplained fever

Headache associated with unexplained physical signs

Persistent management failure

### Treatment

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### Indications for Behavioral Therapy for Migraine

Preference for nondrug interventions
Poor tolerance for specific drug
treatments

Medical contraindications for specific drug treatments

Insufficient or no response to drug treatment

Pregnancy, planned pregnancy, or nursing

History of long-term, frequent, or excessive use of analgesic or acute medications (can aggravate headache problems or lead to decreased responsiveness to other drug therapies)

Significant stress or deficient stresscoping skills

## Is behavioral therapy effective in management of migraine?

Behavioral approaches provide relief without risk for adverse effects associated with drug treatment (see the Box: Indications for Behavioral Therapy for Migraine).

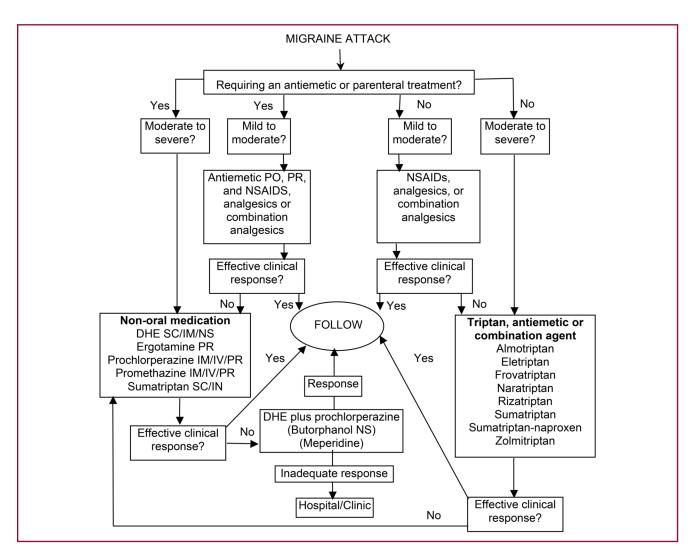
Relaxation training, thermal biofeedback combined with relaxation training, electromyography biofeedback, and cognitive-behavioral therapy have been shown in randomized, controlled trials (RCTs) to reduce migraine frequency by 30%–50% (13).

## Which drugs are indicated for patients with mild-to-moderate migraine?

For patients with mild-to-moderate migraine (able to perform daily

activities but function is impaired), mild analgesics are preferred because they are effective, less costly, and less likely to cause adverse effects than are migraine-specific drugs. Evidence from well-designed placebo-controlled trials supports the use of acetaminophen (14), aspirin (15), or combined analysis (e.g., aspirin plus acetaminophen plus caffeine) (16) in patients with mild-to-moderate migraine and no vomiting or severe nausea. Nonsteroidal anti-inflammatory drugs (NSAIDs) are also effective in adequate doses (Figure and Table 2).

A systematic review showed that ibuprofen provided pain relief in 50% of patients



**Figure 1.** Attack treatment. DHE = dihydroergotamine; IM = intramuscular; IN = intranasal; IV = intravenous; NS = nasal spray; NSAIDs = non-steroidal anti-inflammatory drugs; PR = per rectum; SC = subcutaneous.

Drug	Recommended Dose	Maximum Daily Dose
Nonsteroidal anti-inflammatory drugs		, , , , , , , , , , , , , , , , , , , ,
Aspirin	325-900 mg	4000 mg
Ibuprofen	400-800 mg	1200 mg
Naproxen sodium	250-1000 mg	1000 mg
Combination of acetaminophen 250 mg/aspirin 250 mg/caffeine 65 mg	2 caplets	2 caplets
Migraine-specific oral agents		
Almotriptan*	6.25-12.5 mg	25 mg
Eletriptan+	20-40 mg	80 mg
Frovatriptan+	2.5 mg	7.5 mg
Naratriptan+	1-2.5 mg	5 mg
Rizatriptan†	5-10 mg	20 mg
Sumatriptan*	25-100 mg	300 mg
Sumatriptan 85 mg-naproxen 500 mg	1 tablet	2 tablets
Zolmitriptan*	2.5-5 mg	10 mg
Nonoral therapies		
Dihydroergotamine	1 mg nasally, repeated in 15 min if needed	2 mg
	1 mg subcutaneously, repeated in 30–60 min if needed	3 mg
Prochlorperazine	10 mg intravenously (5 mg/min)	40 mg
	25 mg rectally	50 mg
Promethazine	12.5-25 mg intravenously	100 mg
	25 mg rectally	100 mg
Sumatriptan†	5-20 mg nasally	40 mg
	4-6 mg subcutaneously, repeated in 60 min if needed	12 mg
Zolmitriptan*	5 mg nasally	10 mg

<sup>\*</sup>May repeat dose at least 2 h after the first dose if needed.

but achieved complete relief from pain and associated symptoms only in a minority of patients. A 400-mg dose provided greater efficacy than a 200-mg dose (17).

Antiemetics provide symptomatic relief of nausea, which is prominent in some patients with migraine. An oral or rectal antiemetic drug in patients with mild to moderate nausea can facilitate the use of oral analgesics for migraine pain relief (18).

A dose-ranging study found that metoclopramide, 10 mg, was as effective for acute migraine as the 20-mg and 40-mg doses (19).

### Which drugs are indicated for patients with severe migraine?

Patients with severe migraine are unable to perform daily activities and are often confined to bed. Failure to use an effective treatment promptly may increase pain and disability, so migraine-specific agents (e.g., triptans, dihydroergo-tamine, ergotamine) are indicated.

An RCT showed that for patients with severe migraine, initially selecting a migraine-specific drug led to better outcomes than did a stepped-care approach in which patients used a simple analgesic and then progressed to migraine-specific agents only if initial treatment failed (20).

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<sup>+</sup>May repeat dose if symptoms recur at least 2 h (4 h for naratriptan) after initial response.

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Triptans are a first-line migraine-specific agent because they are more effective than ergots and cause less nausea. Meta-analyses of RCTs show the efficacy of subcutaneous, oral, and nasal sumatriptan (21) and the 6 later oral triptans—naratriptan, zolmitriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan (22, 23).

Oral formulations are appropriate when nausea is mild to moderate and vomiting is absent at the time of treatment. Because comparative studies do not clearly establish superiority of one oral triptan over another, a specific agent may be chosen on the basis of formulary availability and previous therapeutic trials. Among the subcutaneous triptans, sumatriptan is the fastest and most efficacious. It is indicated for migraine accompanied by severe nausea or vomiting, for migraines already established by the time of awakening, or in patients who do not respond consistently to oral or nasal preparations.

Triptans are contraindicated in patients with known or suspected vasospastic or ischemic vascular disorders, uncontrolled hypertension, and the rare migraine subtypes hemiplegic migraine (in which migraine is accompanied by motor weakness) or basilar migraine (in which the aura includes such brainstem symptoms as ataxis, vertigo, tinnitus, or decreased consciousness). Adverse effects include limb heaviness; flushing; paresthesia; and tightness in the chest, neck, or throat. These side effects are almost always benign and can be mitigated by reducing the dose, switching to an alternative triptan, or treating earlier in the attack. Although severe cardiovascular reactions have been reported with use of triptans, the incidence is estimated at <1 in 4 million treatments. Drug interactions are rare, and evidence suggests that combining triptans with

antidepressants does not significantly increase risk for the serotonin syndrome (24).

Nonoral dihydroergotamine with an antiemetic can be an effective alternative to sumatriptan (25, 26), but the effectiveness of ergotamine is less certain (27). Ergots are also contraindicated in the presence of coronary artery disease.

No evidence supports the efficacy of butalbital compounds, despite their widespread use.

A nonoral route of administration for antiemetics and migraine-specific drugs is usually necessary in patients with severe nausea or vomiting.

A 2004 meta-analysis of controlled trials found that metoclopramide is effective for migraine and may be effective when combined with other treatments (28).

A randomized, double-blind study found that intravenous metoclopramide, 20 mg, given up to 4 times over 2 hours, provided similar relief of migraine headache pain as subcutaneous sumatriptan, 6 mg (29).

A 2010 meta-analysis found that phenothiazines were more effective than placebo for treatment of migraine. Phenothiazines were more effective than other antiemetics, including metoclopramide, against which they had been compared (30).

## What is the appropriate treatment strategy when first-line drugs fail?

For refractory headaches that fail to respond to usual treatment, pain relief, as opposed to preserving normal function, becomes the overriding objective. Opiate analgesics in oral (e.g., compounds containing codeine, hydrocodone, or oxycodone) or nasal (butorphanol) formulations should be considered for infrequent use in patients with no relief within 1 hour from the initial, nonopiate treatment. Use of opiates should not exceed 2 doses per week on a regular basis and should not be used in more than half of migraine attacks; more frequent use may lead to MOH, a pattern of increasing headache

frequency that often results in daily headaches.

Developing a written plan encourages proper use of opiates; specific training on how and when to use these drugs improved compliance and effectiveness in 1 RCT (31). Hospitalization for parenteral treatment should be considered if there is no effective clinical response.

### When should clinicians consider preventive therapy for patients with migraine, and which drugs are useful in prevention?

Pharmacologic prophylaxis of migraine is indicated in the following 6 situations: recurrent headaches that interfere with daily routine, contraindication to acute therapy, failure or overuse of acute therapy, adverse effects from acute therapy, patient preference, and uncommon migraine (e.g., basilartype, hemiplegic).

Daily preventive drug treatment should be considered in patients with significant disability related to frequent or severe migraines (usually at least 2/mo) and in patients for whom acute medications do not achieve effective control of attacks, are contraindicated, or are overused. If attacks are frequent enough, then the expected 33%-55% reduction in headache frequency warrants the risks, costs, and inconvenience of taking a daily preventive medication.

The U.S. Headache Consortium guidelines for preventive therapy of migraine identify 3 goals of preventive therapy: reducing the frequency, severity, and duration of attacks; improving the response to treatment of acute attacks; and improving function and reducing disability (32).

Avoiding use of acute headache medications, analgesics, decongestants, and stimulants for more than 10 days per month is critical for ensuring optimal benefit from

the prophylactic drug. In patients who overuse acute medications, such as butalbital and opiate compounds, gradual tapering over several weeks may be necessary, and a full response to preventive therapies may be delayed by several months.

Drug selection should be based first on efficacy, with consideration given to patient preference and patient adherence. Comorbid conditions and the drug's side effect profile should be considered during selection of a preventive drug. All migraine-preventive drugs have primary indications for other conditions, some of which are relatively common in persons with migraine, including stroke, myocardial infarction, the Raynaud phenomenon, epilepsy, affective disorders, and anxiety disorders.

Evidence for episodic migraine prevention is strongest for propranolol (60-240 mg/d), timolol (5-30 mg/d), divalproex sodium (500-2000 mg/d), and topiramate (100–200 mg/d) (33) (see the Box: Preventive Migraine Therapies Available in the United States).

Prophylactic agents are generally titrated upward over a few weeks and then sustained for 4-8 weeks before benefit is realized. Adherence can be enhanced with daily or twice-daily dosing.

Menstrually related migraine can be prevented by perimenstrual (2 days before, continuing for 6 days) frovatriptan, 2.5 mg twice daily (34).

Combining behavioral therapy (e.g., relaxation, biofeedback) with preventive drug therapy should be considered to achieve further clinical improvement in migraine patients.

Several complementary treatments, including Petasites (butterbur), Feverfew, high-dose riboflavin (vitamin B2), and magnesium have

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- 30. Kelly AM, Walcynski T, Gunn B. The relative efficacy of phenothiazines for the treatment of acute migraine: a metaanalysis. Headache 2009;49:1324-32. [PMID: 19496829]
- 31. Holroyd KA, Cordingley GE, Pingel JD, et al. Enhancing the effectiveness of abortive therapy: a controlled evaluation of self-management training. Headache. 1989;29:148-53. [PMID: 2496052]
- 32. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician 2000;62:2359-60, 2363.
- [PMID: 11126860] 33. Silberstein S, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012:78:1337-4 [PMID: 33354521) Correction published in Neurology 2013;80:871
- 34. Silberstein SD. Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. Neurology. 2004;63:261-9. [PMID: 15277618]
- 35. Holland S. Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology [PMID: 3335449]

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#### Preventive Migraine Therapies Available in the United States

Level A: Medications with established efficacy (two or more Class I trials)

Antiepileptic drugs: Divalproex sodium; sodium valproate; topiramate

 $\beta\text{-blockers: Propranolol; metoprolol;}\\timolol$ 

Triptans (menstrually related migraine): Frovatriptan

Level B: Medications are probably effective (one Class I or two Class II studies)

Angiotensin-receptor blocker: Candesartan

Antidepressants: Amitriptyline; venlafaxine

β-blockers: Atenolol; nadolol

Triptans (menstrually related migraine): Naratriptan; zolmitriptan

Level C: Medications are possibly effective (one Class II study)

Angiotensin-converting enzyme inhibitors: Lisinopril α-agonists: Guanfacine

Antiepileptic drugs: Carbamazepine Antihistamines: Cyproheptadine

β-blockers: Nebivolol

Calcium-channel blockers: Nicardipine

shown efficacy in clinical trials and should be considered for migraine prevention (35).

## What is medication-overuse headache and how can it be prevented and treated?

Although correct use of prescribed and over-the-counter medications can alleviate headaches, regular overuse can have a paradoxic effect, causing headaches rather than relieving them and leading to MOH. It is dose frequency rather than the absolute quantity of drug consumed that is important—lower daily doses create a greater risk for MOH than larger episodic doses. MOH should be suspected in patients with headache occurring on 15 or more days per month who have taken ergots, triptans, opioids, or combined analgesic medications 10 or more days per month; or simple analgesics alone or any combination

of ergotamine, triptans, and analgesic opioids on 15 or more days per month for more than 3 months. The type of headache may be tension-type daily headache and/or migraine-like attacks. Associated symptoms can include nausea and gastrointestinal symptoms, irritability, anxiety, depression, and problems with concentration and memory. It usually but not always resolves after overuse is stopped.

Prevention is preferred to management. Prevention includes restricting consumption of commonly responsible medications and avoiding caffeine and codeine. Early prophylaxis, either medical or behavioral, may be appropriate in patients with frequent headaches. Patients with primary headaches should be educated about the risk for medication overuse and be encouraged to keep a diary to monitor headache frequency and drug

Once MOH has developed, management involves education of the patient on the cause as well as drug withdrawal. Overall improvement occurs within 7-10 days when the causative drug is a triptan, after 2-3 weeks when it is a simple analgesic, and after 2–4 weeks when it is an opioid. The patient should be evaluated in 2-3 weeks to ensure withdrawal has been achieved. Recovery continues slowly for weeks to months, and follow-up is necessary. Most patients revert to their original headache type within 2 months. Onabotulinumtoxin A (36) or topiramate (37) may help reduce withdrawal symptoms. Overused medications (if needed) may be reintroduced for symptomatic relief after 2 months, with explicit restrictions to ensure that frequency does not exceed 2 days per week on a regular basis. Patients should be followed regularly to prevent relapse, which is most

36. Dodick DW, Turkel CC, DeGryse RE et al. Onabotulinumtoxin Af for treatment of chronic migraine: pooled results from the double-blind, randomized, place-bo-controlled phases of the PREEMPT clinical program. Headache 2010; 50: 921-936

[PMID: 20487038]
37. Diener HC, Bussone G, Van Oene JC et al. Topiramate reduces headache days in chronic migraine: a randomized, doubleblind, placebo-controlled study. Cephalalgia 2007; 27: 814-823 [PMID: 17441971])

38. Granella F, Sances G, Zanferrari C, et al. Migraine without aura and reproductive life events: a clinical epidemiological study in 1300 women. Headache. 1993;33:385-9. [PMID: 8376100] likely in the first year after withdrawal.

### Are there special considerations for the treatment of migraine in the pregnant patient?

Migraine can develop or worsen during the first trimester of pregnancy, although approximately two thirds of women with migraine experience improvement or remission of attacks during the last 6 months of pregnancy (38). This is believed to be because of the sustained estrogen levels of the second and third trimesters.

For most women, migraine in pregnancy is usually benign and there is no significant impact on the mother or fetus. However, recent population-based studies have documented an association between migraine, pregnancy-induced hypertension, and preeclampsia. This risk is highest in women older than age 30 years or who are obese (39).

Nonpharmacologic therapies, including magnesium supplementation, and simple remedies (such as rest and local application of ice), are strongly preferred for migraine prevention during pregnancy and for attacks persisting throughout pregnancy.

In a prospective study, 30 pregnant women were treated with physical therapy, relaxation training, and biofeedback. Eighty percent of the women had significant relief of headache following treatment. This beneficial effect was maintained for up to a year after delivery (40).

All acute and preventive migraine therapies have U.S. Food and Drug Administration and Teratogen Information System pregnancy ratings. For acute treatment, see the Box: Management of Acute Migraine in Pregnancy. Acetaminophen and metoclopramide, caffeine, certain opiates, and NSAIDs are classified as Pregnancy Category B (no evidence of risk in humans but no controlled human studies). NSAIDs have been linked with premature closure of the

### Management of Acute Migraine in Pregnancy

Use acetaminophen, NSAIDs, and codeine or other narcotics (in that order), with or without metoclopramide

Avoid NSAIDs from week 32 Avoid opioids in the late third trimester Use sumatriptan and other triptans with caution

Do not use ergots

patent ductus arteriosus when used later in pregnancy and should be discontinued before week 32. Opioids should be discontinued in the late third trimester because of risk for neonatal withdrawal.

Prednisone carries a Category B rating and may be useful in truncating stretches of active migraine. Triptans are rated Pregnancy Category C (risk to humans not ruled out) and can be used when the benefits outweigh the risks; a prospective sumatriptan pregnancy registry has produced no evidence of significant teratogenicity to date (41), although an increased rate of low birthweight and preterm delivery was associated with its use during pregnancy in some studies (42).

Ergots are potent vasoconstrictors and may induce abortion and cause birth defects.

Prophylactic medication should be limited to women with particularly frequent or disabling migraine. Beta-blockers are rated Category C but have demonstrated relative safety during pregnancy; they should be tapered during the last weeks of pregnancy to avoid maternal or fetal bradycardia during

Treatment should be started at the lowest effective dose; response and adverse events must be monitored.

The American Academy of Pediatrics provides additional safety

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- DA, Turk DC. Mainte nance of effects in the nonmedical treatment of headaches during pregnancy. Headaché. 1996;36:285-90. [PMID: 8682668]
- 41. Duong S, Bozzo P, Nordeng H, Einarson A. Safety of triptans for migraine headaches during pregnancy and breastfeeding. Can Fam Physician. 2010;56:537-9. [PMID: 20547518]
- 42. Olesen C, Steffensen FH, Sorensen HT, et al. Pregnancy outcome following prescription for sumatriptan. Headache. [PMID: 10759898]

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information for lactating mothers. NSAIDs, with the exception of aspirin, can be used during lactation. If triptans are indicated, sumatriptan is the triptan of choice. Ergots are contraindicated. If prophylaxis is necessary, propranolol and amitriptyline can be used during lactation. Breastfeeding is encouraged for women whose headaches improve during pregnancy because it sustains the benefits of pregnancy.

## When should clinicians consider hospitalization for a patient with migraine?

Hospitalization should be considered for a particularly severe intractable migraine lasting longer than 72 hours (status migrainosus)

or headache associated with excessive use of analgesic medications (MOH).

Parenteral dihydroergotamine is an extremely effective option for patients who have not received triptans or ergots within 24 hours and is the cornerstone of inpatient management of refractory migraine (43). Intravenous dopamine antagonists, often combined with intravenous diphenhydramine (to limit or eliminate possible dystonic reactions) and hydration, may be helpful. Intravenous preparations of ketorolac and sodium valproic acid are also quite useful, and the addition of a single dose of dexamethasone seems to reduce recurrence.

Treatment... Patients should be encouraged to identify and avoid diet-related factors. Behavioral approaches provide headache relief without the risk for adverse drug effects. Simple or compound analysics are suitable for mild-to moderate migraine. Triptans and ergots should be used in patients with severe migraine. Opiate analysics should be reserved for infrequent use as rescue medications. Antiemetics provide symptomatic relief of nausea and can facilitate the use of oral analysics for migraine pain relief. Propranolol, timolol, divalproex sodium, and topiramate have the strongest evidence of effectiveness in preventing episodic migraine.

### **CLINICAL BOTTOM LINE**

### Follow-up

## What are the components of good follow-up care?

Patients should generally be reevaluated after treatment of no fewer than 3 attacks. Patients should keep a record of headache severity, associated disability, and response to treatments. These diaries and the need for preventive therapy should be reviewed at follow-up. Preventive therapy is indicated if there is poor response to treatment or frequent need for rescue medication, which puts the patient at risk for analgesic overuse or "rebound" headache. Increasing dose or changing agents should be considered if headache frequency has not

improved after 3 months of preventive treatment.

## Is it appropriate to taper or discontinue preventive treatment for migraine?

Most clinicians recommend a 6- to 12-month maintenance phase after a response (often defined as a 50% reduction in headache frequency) has been achieved, followed by a tapering phase with the aim to discontinue if there is no relapse. As migraine symptoms change over time and preventive treatment may no longer be needed, this may avoid the risks and costs associated with unnecessary drug therapy.

- 43. Gallagher RM. Emergency treatment of intractable migraine. Headache.1986;26:7
  4-5. [PMID: 3957657]
- 44. Saper JR, Lake AE III, Madden SF, et al. Comprehensive/tertiary care for headache: a 6month outcome study. Headache. 1999;39:249-63. [PMID: 9747046].
- 45. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. Cephalalgia. 2009;29:286-92. [PMID: 19220309]

### When should clinicians consider subspecialty referral for patients with migraine headache?

Consult a neurologist or headache specialist to determine an appropriate further diagnostic workup in patients with possible ophthalmic, basilar, atypical, or complicated migraine (i.e., patients with neurologic deficits during the aura phase or that persist during or after the headache).

Patients with status migrainosus or MOH may also benefit from referral. Alternative or more intensive approaches (e.g., multidisciplinary headache clinics) show good outcomes in uncontrolled case series (44).

Consult a neuro-ophthalmologist or an ophthalmologist when headache is associated with visual changes other than typical aura. A significant change in visual acuity or fields or elevated intraocular pressure, especially with eyecentered pain, may indicate acute glaucoma that must be treated promptly to preserve vision. Newonset visual symptoms in persons older than 50 years may indicate giant cell arteritis. Consult an obstetrician when pregnant women have headaches associated with peripheral edema or hypertension (diastolic blood pressure ≥ 90 mm Hg) because these patients may have preeclampsia (45).

Follow-up... Review symptomatic treatment after treating no fewer than 3 attacks. Review prophylactic treatment after 3 months. Use contemporaneous diaries to assess treatment response. Consider the need for subspecialty referral.

### **CLINICAL BOTTOM LINE**

### What should patients be taught about managing their migraines?

Patient education about the goals, use, and expectations of migraine preventive therapies is crucial in maximizing the chances of therapeutic success. The patient must understand that although these therapies may reduce the frequency or severity of attacks, improve the efficacy of acute medications, and assist in the management of comorbid conditions, they rarely result in complete headache eradication.

Approximately one half of recurrent headache sufferers do not adhere properly to drug treatment regimens, with as many as two thirds of patients neglecting to make optimal use of rescue medications. Treatment can be improved by developing a plan for self-management that all parties acknowledge and accept (e.g.,

patient, primary care physician, neurologist, psychologist). The plan should identify all treatment methods used, including those for coexisting conditions and limits on dosing, rescue medication, and a plan for how and when to contact a health care provider.

In 1 RCT, patients who received an adjunctive educational intervention used abortive medication for a greater percentage of their migraine attacks (70% vs. 40%) and showed a larger reduction in headache activity (40% vs. 26%) (46).

Patients should be encouraged to identify and avoid lifestyle-related factors that may contribute to headaches, including too little or too much sleep, lack of exercise, and stress. Modifications in diet, exercise, and sleep regulation have a significant effect on headache response and affective distress (47).

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### **Practice Improvement**

- 46. Holroyd KA, Cordingley GE, Pingel JD, et al. Enhancing the effectiveness of abortive therapy: a controlled evaluation of self-management training. Headache. 1989;29:148-53. [PMID: 2496052]
- 47. Hoodin F, Brines BJ, Lake AE 3rd, et al. Behavioral self-management in an inpatient headache treatment unit: increasing adherence and relationship to changes in affective distress. Headache. 2000;40:377-83. [PMID: 10849032]

# In the Clinic Tool Kit

### Migraine

#### PIER Module

http://pier.acponline.org/physicians/diseases/d156/d156.html PIER module on migraine from the American College of Physicians (ACP). Also includes information on diagnostic tests and criteria and quality-of-care guidelines.

#### **Patient Information**

http://pier.acponline.org/physicians/diseases/d156/d156-pi .html

Access the Patient Information material that appears on the next page for duplication and distribution to patients.

www.acponline.org/patients\_families/pdfs/health/headache .pdf

www.acponline.org/patients\_families/pdfs/health/ migraine.pdf

Brochures on headache types and on how to prevent and control migraine headaches from ACP.

www.achenet.org/resources/patient\_to\_patient/

Information for patients on common headache topics from the American Headache Society.

www.ninds.nih.gov/disorders/migraine/migraine.htm
Information on migraine from the National Institute of
Neurological Disorders and Stroke of the National
Institute for Health.

#### Clinical Guidelines

www.neurology.org/content/55/6/754.full.pdf
Evidence-based guidelines for migraine headache from the
American Academy of Neurology in 2000.
www.neurology.org/content/78/17/1346.full.pdf+html
www.neurology.org/content/78/17/1337.full.pdf+html

Guideline updates on NSAIDs and other complementary treatments for migraine prevention and on pharmacologic treatment for migraine prevention from the American Academy of Neurology in 2012.

www.guideline.gov/content.aspx?id=38444&search =migraine

Guidelines on the diagnosis and management of headaches in young people and adults from the National Institute for Health and Clinical Excellence in 2012.

www.aafp.org/afp/2005/0315/p1219.html

Guidelines for neuroimaging in patients with nonacute headache from the U.S. Headache Consortium in 2005.

Diagnostic Tests and Criteria

http://pier.acponline.org/physicians/diseases/d156/tables/d156-tlab.html

List of laboratory and other studies for headache.

http://pier.acponline.org/physicians/diseases/d156/tables/d156-thp.html

Elements of patient history for clinical diagnosis of migraine versus tension-type headache.

Quality-of-Care Guidelines

http://pier.acponline.org/physicians/diseases/d156/figures/d156-f1.html

Figure showing treatment for acute migraine attack.

#### Headache Diary

www.achenet.org/resources/headache\_diaries/
Diaries help track headache and related symptoms
between clinic visits. They must be user-friendly and
measure attack frequency, severity, duration, disability,
type of treatment, treatment response, and adverse
effects of medication.



## WHAT YOU SHOULD KNOW ABOUT MIGRAINE

### What is a migraine?

- An intense, throbbing, painful headache that usually occurs on just one side of the head and lasts from 4 to 72 hours.
- Symptoms may include nausea or vomiting and sensitivity to light, sounds, and smells.
- Some people have symptoms called "aura," which include vision disturbances, numbness, and tingling.

### How is migraine diagnosed?

- Your doctor will ask you about your symptoms and about any family history of headaches.
- You may be asked to keep a headache diary to help identify the type of headache.
- Your doctor will perform an examination to rule out any serious illness that could be causing your headaches.
- If you are pregnant, your doctor will consult with your obstetrician.

### How is it treated?

Mild-to-moderate migraine without vomiting or nausea

- Acetaminophen and nonsteroidal anti-inflammatory drugs, such as aspirin.
- Combination pain relievers, such as aspirin plus acetaminophen and caffeine.
- Some drugs are not safe during pregnancy and should be discussed with your doctor.

### Severe migraine

- Prescription migraine medications, such as triptans, dihydroergotamine, or ergotamine.
- Narcotics, such as codeine, meperdine, or oxycodone, may be indicated if the usual treatment is ineffective.



- Hospitalization, if the migraine is severe and longlasting.
- Some drugs are not safe during pregnancy and should be discussed with your doctor.

#### Other treatments

- Behavioral therapy, such as relaxation training or cognitive-behavioral therapy.
- Drugs called antiemetics to stop nausea and vomiting.

### How can migraine be prevented?

- Limit common dietary triggers, such as caffeine and artificial sweeteners.
- Avoid other possible triggers, such as delayed or missed meals and lack of sleep.
- Daily preventive drug treatment may be appropriate if migraine attacks are frequent and severe.

### **For More Information**

www.nlm.nih.gov/medlineplus/tutorials/headacheandmigraine/htm/index.htm

www.nlm.nih.gov/medlineplus/tutorials/headacheandmigraine/htm/index.htm

http://www.nlm.nih.gov/medlineplus/spanish/tutorials/headacheand migrainespanish/htm/index.htm

Information and resourses on migraine from the National Institutes of Health's MedlinePlus, including a tutorial in English and Spanish.

www.headaches.org/content/my-headache

www.headaches.org/educational\_modules/migraine\_module/headache\_diary.pdf

A guide to understanding headache and migraine and a printable migraine diary from the National Headache Foundation.

www.achenet.org/midas/

The MIDAS (Migraine Disability Assessment) questionnaire helps you measure the impact of headaches on your life and communicate this to your doctor.





- 1. A 36-year-old woman is evaluated for worsening headache. She has a 23-year history of migraine with aura that started with menarche. The patient describes recurrent attacks of pulsatile pain on one side of her head that last 1 or 2 days and are often accompanied by nausea, vomiting, and disability. The episodes are occasionally preceded by 20 minutes of bright zig-zags and occasionally complicated by tingling and numbness spreading up one arm lasting 30 minutes. The attacks have become more frequent and now occur once per week. She also has a severe headache for 4 days during menses. The episodes are responsive to oral sumatriptan. Her mother had a stroke at age 50 years. Her only medication is sumatriptan.
  - Physical examination findings, including vital signs, are normal. Magnetic resonance imaging of the brain is normal.

Which of the following is the most appropriate next step in the management of this patient's migraine?

- A. Butalbital with acetaminophen and caffeine
- B. Lumbar puncture
- C. Naproxen sodium daily
- D. Oral contraceptives
- E. Topiramate
- 2. A 28-year-old woman is evaluated for episodic migraine without aura that first presented in high school and has persisted into the third trimester of her current pregnancy. The headaches occur 2 to 4 times monthly; last 12 to 24 hours; and are usually characterized by moderately severe pain, significant nausea, no vomiting, and moderate photophobia. Her only medication is prenatal vitamins.

Physical examination findings, including vital signs, are normal.

Which of the following is the most appropriate treatment?

- A. Acetaminophen
- B. Amitriptyline
- C. Naproxen
- D. Oxygen
- E. Rizatriptan
- 3. A 35-year-old man is evaluated for a 5-year history of recurrent headache that occurs several times per month and lasts 8 to 24 hours. He describes the headache as a bilateral frontal pressure associated with nasal congestion and sensitivity to light, sound, and smell. The pain is generally moderate in intensity but worsens when he bends forward or exercises and has recently caused him to miss 3 days of work. He has no nausea or visual or neurologic symptoms. The patient has a history of nonseasonal allergic rhinitis treated with pseudoephedrine and loratadine and a family history of headaches in his paternal grandmother. His only other medication is naproxen, which he takes as needed for the headache pain, but it has become less effective over time.

Physical examination findings, including vital signs and results of neurologic examination, are normal.

Which of the following is the most appropriate management of this patient's disorder?

- A. Computed tomorgraphy of the sinuses
- B. Magnetic resonance imaging of the brain
- C. Nasal corticosteroids
- D. Oxycodone
- E. Sumatriptan

4. A 40-year-old woman is evaluated for a 3-month history of increasingly frequent headaches and a 6 week history of daily bilateral frontotemporal discomfort. The patient began having headache attacks 8 years ago after the birth of her second child. Episodes originally occurred once or twice monthly and were initially characterized by unilateral severe throbbing pain, nausea with vomiting, and photophobia. Occasionally, a visual aura of "spinning tops" preceded the headache pain by 45 minutes, with the headache extending for 36 to 48 hours, but she has experienced no auras in the past 6 months. Visual blurring now accompanies her headaches intermittently but daily. Although previously helpful, oral triptans have not provided any relief over the past 3 months. Medications are oral zolmitriptan, a monophasic oral contraceptive, and a daily aspirinacetaminophen-caffeine combination.

Physical examination results, including vital signs and findings from a neurologic examination, are unremarkable.

Computed tomography of the head obtained 9 years ago when the headaches began was normal.

Which of the following is the most appropriate next step in management?

- A. Analgesic discontinuation
- B. Erythrocyte sedimentation rate determination
- C. Lumbar puncture
- D. Magnetic resonance imaging of the brain

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products\_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to complete the quiz and earn up to 1.5 CME credits, or to purchase the complete MKSAP program.