in the clinic

Migraine

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Migraine headache affects 18% of women and 6% of men. Three quarters of migraine sufferers have moderate-to-severe symptoms that interfere with work, school, and other normal daily activities. Despite being a significant cause of episodic but disabling symptoms, the condition remains underrecognized, underdiagnosed, and undertreated. Migraine pain was previously believed to be largely vascular in cause, but evidence now shows that it involves genetic control of the activity of some brain cells. It is hypothesized that migraine activity begins in the brainstem and ends with distention and inflammation of meningeal vessels. These events cause an instability in brain cells that triggers surges of abnormal impulses to the periphery and releases inflammatory substances. Although migraines can be highly disruptive to daily life, effective behavioral and drug treatments can prevent attacks or relieve symptoms.

Diagnosis

What clinical features are helpful in distinguishing migraine headache from tension headache? The International Classification of Headache Disorders (ICHD) classifies headache disorders (1), but several simpler diagnostic criteria have been validated against the ICHD. Five important features of migraine are headache that is unilateral, pulsatile, or throbbing; associated with nausea or vomiting; of sufficient intensity to interrupt usual daily activities; and usually lasting 4 to 72 hours if untreated.

Individuals with 3 of the 5 criteria listed above are likely to have migraine; those with 4 of 5 are highly likely to have migraine (2). Other diagnostic criteria perform similarly, including 1 that considers nausea, photophobia, and headache-related disability (any day in the past 3 mo); individuals who have 2 of these 3 symptoms are highly likely to have migraine (3) (Table 1).

The presence of prodrome or aura distinguishes migraine from other types of headache. Prodrome is the occurrence of euphoria, depression, fatigue, hypomania, food cravings, dizziness, cognitive slowing, or asthenia that occurs up to 24 hours before headache. Aura are neurologic symptoms that occur within 1 hour of or during headache and last a few minutes to 1 hour. Aura includes such symptoms as visual changes, loss of vision, hallucinations, numbness, tingling, weakness, or confusion. Approximately 60% to 70% of patients with migraine report prodrome, and 15% to 20% report aura.

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

Other primary causes of headache include tension-type headache, as well as medication-overuse headache and cluster headache. Although they can be disabling, primary headache conditions are generally benign. However, clinicians should exclude secondary causes of headache.

Serious secondary causes of headache include stroke, tumor, arteritis, meningitis, acute glaucoma, and subarachnoid hemorrhage.

"POUND" (as in "a pounding headache") is one way to remember symptoms consistent with migraine headache:

- Pulsatile quality of headache described
- One-day duration (duration < 4 hours suggests tension-type headache)
- Unilateral location
- Nausea or vomiting
- Disabling intensity.

Several historical and physical examination findings are predictive of such secondary causes (See Box). “Red flag” historical findings include changes in the intensity, frequency, or pattern of headaches; blurred vision; dizziness or lack of coordination; sudden, explosive onset of headache with rapid progression; or headache pain aggravated by coughing or movement. Red flag physical findings include fever and scalp nodules or lesions.

Patients may suffer from more than 1 type of headache, have headaches that cannot be easily described or classified, or have had a change in headache pattern over time. The history should include questions about the onset and frequency of the headache disorder; the duration of attacks; pain location, severity, and quality; precipitating and ameliorating factors; and family history. Table 2 presents the differential diagnosis of headache.

What is the role of physical examination in patients who present with migraine? The physical examination should evaluate for features that suggest a secondary headache, such as fever, meningeal or other signs of infection, neurologic abnormalities, changes in visual acuity, increased intraocular pressure, elevated blood pressure, and mental status changes.

What is the role of diagnostic testing, including imaging studies and electroencephalography, in patients with suspected migraine? Neuroimaging, such as magnetic resonance imaging (MRI) or computed tomography, is not usually warranted for patients with migraine symptoms and a normal

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Likelihood Ratio</th>
<th>Negative Likelihood Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea or vomiting</td>
<td>42-60</td>
<td>81-93</td>
<td>6.0</td>
<td>0.62</td>
</tr>
<tr>
<td>Duration 4-72 h</td>
<td>74</td>
<td>53</td>
<td>1.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Pounding or throbbing character</td>
<td>64-87</td>
<td>22-83</td>
<td>3.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Unilateral head pain</td>
<td>65-75</td>
<td>60-85</td>
<td>4.3</td>
<td>0.41</td>
</tr>
<tr>
<td>Disabling for usual activities</td>
<td>59-87</td>
<td>52-76</td>
<td>2.5</td>
<td>0.54</td>
</tr>
<tr>
<td>Presence of ≥4 of the symptoms above</td>
<td>29</td>
<td>100</td>
<td>23.0</td>
<td>0.71</td>
</tr>
<tr>
<td>Presence of ≥3 of the symptoms above</td>
<td>80</td>
<td>94</td>
<td>13.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Presence of ≥2 of the following 3 symptoms:</td>
<td>81</td>
<td>75</td>
<td>3.25</td>
<td>0.25</td>
</tr>
<tr>
<td>nausea, photophobia, and headache-related disability (any day in the previous 3 mo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"Red Flag" or Alarm Features That Suggest Headache Is Due to Nonbenign, Secondary Causes

- Changes in headache pattern, frequency, or intensity
- Daily headache
- Blurred vision
- Dizziness, syncope, discoordination, or focal neurologic abnormality
- Sudden, explosive onset
- Pain worse with coughing or movement
- Change in personality or mental status
- Headache awakens person from sleep
- Onset after 50 years of age
- Fever
- Meningeal signs
- Diastolic blood pressure >120 mm Hg
- Diminished pulse or tenderness of temporal artery
- Papilledema
- Necrotic or tender scalp lesions
- Increased intraocular pressure
A meta-analysis of studies of patients with migraine and a normal neurologic examination found a 0.18% rate of significant intracranial lesions (4). Clinicians should apply a lower threshold for obtaining neuroimaging for patients with atypical headache features, substantial change in headache pattern, or symptoms or signs of neurologic abnormalities (5). For instance, MRI is indicated in patients with a long history of migraine headache who develop substantial changes in headache pattern or in any patient with headache and focal neurologic signs or symptoms.

In patients with new onset headache after 50 years of age, it is important to obtain an erythrocyte sedimentation rate (ESR) to evaluate for secondary causes of headache, particularly temporal arteritis or other vasculitides, even if symptoms are consistent with migraine. An elevated ESR (>30 mm/h) suggests temporal arteritis but lacks specificity, making a temporal artery biopsy necessary in patients in whom temporal arteritis is suspected. Headache is the predominant symptom in 65% to 80% of patients with temporal arteritis (6), and the combination of new-onset headache, jaw claudication, and abnormal (nodular or tender)
arteries is highly predictive of temporal arteritis (7). 

Electroencephalography (EEG) is not routinely used in evaluation of headache, and should be considered only if associated symptoms suggest a seizure disorder, such as atypical migrainous aura or episodic loss of consciousness. A systematic review found no increased prevalence of EEG abnormalities in patients with headache, no useful headache subgroups defined by EEG, and no ability of EEG to identify patients whose headaches have a structural cause (8).

Diagnosis... In patients with normal neurologic examination, evaluation of symptoms distinguishes migraine from tension or other types of headache. Migraines are typically pulsatile, are unilateral, last 4 to 72 hours, are associated with nausea or vomiting, and make it necessary for patients to alter their usual activities. Neuroimaging is not usually warranted for patients with normal neurologic examination, and EEG has not been shown to be useful. Clinicians should ask patients about features that suggest serious secondary causes of headache and conduct appropriate evaluation for these causes.

CLINICAL BOTTOM LINE

What is the role of diet in the management of patients with migraine?
Dietary triggers for migraine are idiosyncratic and can be difficult to identify. However, some foods are known to be associated with migraines (see Box). About 20% of patients with migraine report dietary triggers (9, 10). Clinicians should encourage patients to identify and avoid dietary factors that may contribute to headaches. There is also some controversy over the role of aspartame in triggering migraine.

Researchers at the Montefiore Medical Center Headache Unit questioned 190 consecutive patients about the effect of alcohol, carbohydrates, and aspartame in triggering their headaches. Of the 171 patients who completed the survey, 49.7% reported alcohol as a precipitating factor, 8.2% reported aspartame, and 2.3% reported carbohydrates. Patients with migraine were significantly more likely to report alcohol as a triggering factor and reported aspartame as a precipitant 3 times more often than those having other types of headache (11).

There is some evidence of a causal relationship between food and migraine through elimination diets, reintroduction, and double-blind challenge (12-14). In these studies, elimination diets decreased symptoms substantially in some individuals. The findings suggested that greater efforts are needed to educate patients about the possible benefits of adjusting diet to decrease headache frequency.

An investigation of the awareness and impact of dietary risk factors on patients with chronic headache found that three quarters of the 130 participants were aware of the possible link between certain foods and headache, although most did not

Treatment

Common Dietary Triggers for Migraine
- Caffeine withdrawal
- Nitrates and nitrites in preserved meats
- Phenylethylamines, tyramines, xanthines in aged cheeses, red wine, beer, champagne, chocolate
- Monosodium glutamate in some Asian and prepared foods
- Dairy products
- Fatty foods

report hearing about this from their doctor. Notably, knowledge of the possible link did not prompt changes in food consumption practices (15).

Is behavioral therapy effective in the management of migraine? Behavioral approaches provide headache relief for some patients with migraine. Randomized, controlled trials (RCTs) have shown that relaxation training, thermal biofeedback with relaxation training, electromyogram (EMG) biofeedback, and cognitive behavioral therapy reduce migraine frequency by 30% to 50%. These data suggest that behavioral therapies can be as effective as many pharmacologic treatments.

A meta-analysis that included 25 clinical trials involving propranolol and 35 clinical trials involving relaxation or biofeedback training showed substantial and similar 43% reductions in migraine activity following both propranolol and relaxation or biofeedback training, compared with 14% reduction from placebo and no reduction in untreated patients (16).

Data are lacking to guide selection of a specific type of behavioral therapy for specific patients. A review of randomized and quasi-randomized controlled trials comparing noninvasive physical treatments for chronic or recurrent headaches to a control found that although some noninvasive physical treatments seem to prevent chronic or recurrent headaches with little risk for adverse effects, determining the clinical effectiveness and cost-effectiveness of noninvasive physical treatments requires further research (17).

Behavioral approaches are particularly recommended for patients who prefer nondrug interventions, who tolerate drugs poorly, who have medical contraindications to drug therapy, or who have insufficient response to specific drug treatments. Behavioral therapies are also good options for patients who are pregnant, nursing, or planning to become pregnant. Patients under significant stress or who have deficient stress-coping skills may derive benefit from nonpharmacologic interventions. Restful sleep decreases irritability in the brain and therefore may decrease the frequency and severity of migraine. However, clinicians should be aware that not all nonpharmacologic treatments are clearly beneficial. Acupuncture, spinal manipulation, and hypnosis have not been shown to be effective in relieving migraine (17,18).

When should migraine drug therapy be administered? Treatment of migraine should begin as early as possible during the episode to increase the chances of headache relief and minimize the total amount of medication needed. Regardless of the form of migraine-specific medication used, the headache phase being treated determines the level of efficacy achieved. Treatment during prodrome or aura or within the first hour of headache is significantly more effective than treatment during later stages. Treatment efficacy decreases after headache has been present for more than 2 hours. This time-dependent nature of efficacy may be a result of central (within the brain) sensitization during migraine, which causes hypersensitivity to environmental stimuli, such as light, sound, smells, and touch (19). Once central sensitization begins, migraine treatment becomes less effective and repeated doses may be necessary to relieve symptoms.

Which drugs are indicated for patients with mild-to-moderate migraine? When symptoms are not severe and there is no vomiting, mild over-the-counter analgesics are effective, less expensive, and less likely to cause adverse effects than migraine-specific drugs. Nonspecific therapy with acetaminophen or other nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or combination analgesics (e.g., aspirin plus acetaminophen plus caffeine)
should be used in patients with mild-to-moderate headache without severe nausea or vomiting. Table 3 provides information on drug therapy for acute migraine symptoms.

A randomized, double-blind, placebo-controlled study compared oral acetaminophen 1000 mg with placebo in the treatment of a single acute migraine episode. The headache response rate 2 hours after dosing was 57.8% in the acetaminophen group compared with 38.7% in the placebo group (P = 0.002). Pain-free rates at 2 hours were 22.4% in the acetaminophen group and 11.3% in the placebo group (P = 0.01) (20).

A randomized trial evaluated the efficacy of a single 1000-mg dose of aspirin in 409 persons for the treatment of acute moderate-to-severe migraine, with or without aura. The 2-hour headache response rate was 52% with aspirin versus 34% with placebo (P < 0.001), and significantly more participants were pain-free from the 1-hour evaluation through the 6-hour evaluation (21).

In a study that examined the benefits of acetaminophen, aspirin, and caffeine in the treatment of severe, disabling migraine attacks, there was significant improvement in functional disability, photophobia, and phonophobia with the combined analgesic compared with placebo from 2 to 6 hours after dosing (22).

Which drugs are indicated for patients with severe migraine?

Migraine-specific agents (triptans, dihydroergotamine, and ergotamines) are advised for patients with severe migraine or headaches that respond poorly to acetaminophen, NSAIDs, or over-the-counter combination analgesics (Table 3). Evidence suggests that initial selection of a migraine-specific drug leads to better outcomes than a stepped-care approach for severe symptoms (23).

Triptans

When using migraine-specific therapy, clinicians should consider triptans first because they are more effective and cause less nausea in most patients. However, triptans are contraindicated in persons with a history of coronary disease because they are associated with a low but real risk for cardiac side effects. The high cost of triptans may deter their use as first-line therapy in some patients. Triptans may be administered orally, intranasally, or by injection. Administration by injection or nasal spray may be preferred by patients who desire rapid relief, are nauseated, or develop headache rapidly. However, triptan administration by injection is associated with more side effects, including chest discomfort, nausea, dizziness, somnolence, tingling, numbness, and flushing.

One systematic review evaluated 30 studies on the effects of 6 mg subcutaneous, 100 mg oral, and 20 mg intranasal sumatriptan for treating migraine attacks. The review found that subcutaneous sumatriptan was the most efficacious and the fastest-acting form of administration. However, there were more adverse events with subcutaneous sumatriptan than with oral sumatriptan (data were limited on adverse events for intranasal sumatriptan). Intranasal sumatriptan had the same efficacy as oral sumatriptan and a quicker onset of action, but the difference in therapeutic effect was limited to the first 30 minutes after administration (24).

A systematic review of the data from 53 double-blind RCTs of oral triptans in migraine involving 24,089 patients showed that all oral triptans were effective and well tolerated. The investigators found that 10 mg rizatRIPTAN, 80 mg eleetroPTAN, and 12.5 mg almotriPTAN were most likely to be consistently successful for treating migraine (25).

Another systematic review evaluated the effects of various migraine treatments in 54 trials with 79 placebo comparisons and found that headache relief at 2 hours was best for subcutaneous sumatriptan 6 mg and that sustained relief over 24 hours was best for eleetroPTAN 80 mg. Most migraine interventions were effective in relieving headache pain (26).

Triptans with both long (e.g., frovatriPTAN) and short (e.g., sumatriPTAN) half-lives are available. Those with a short half-life
Table 3. Short-Term Drug Treatment for Migraine*

<table>
<thead>
<tr>
<th>Agent (Route)</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Migraine-specific</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan (subcutaneous)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>6 mg at onset (may repeat after 1 h; maximum 12 mg/d)</td>
<td>Rapid onset of action; little sedation; treatment of choice for moderate-severe attacks; not effective if given during aura; contraindicated in patients with CAD, uncontrolled hypertension, or patients with strictly basilar or hemiplegic migraine; pregnancy category C</td>
</tr>
<tr>
<td>Sumatriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>25–100 mg at onset (may repeat after 2 h; maximum 200 mg/d)</td>
<td>Well tolerated; little sedation; less rapid onset; may be used again for recurrent headache; no evidence of teratogenicity</td>
</tr>
<tr>
<td>Sumatriptan (nasal)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>20 mg at onset (may repeat after 2 h; maximum 40 mg/d)</td>
<td>Well tolerated; little sedation; speed of action and effectiveness similar to oral sumatriptan; useful when non-oral route of administration needed; no evidence of teratogenicity</td>
</tr>
<tr>
<td>Almotriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>6.25–12.5 mg at onset (may repeat after 2 h; maximum 25 mg/d)</td>
<td>Similar efficacy to oral sumatriptan</td>
</tr>
<tr>
<td>Eletriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>20–40 mg at onset (may repeat after 2 h; maximum 80 mg/d)</td>
<td>Highly effective oral triptan; rapid onset of action; slightly higher efficacy compared with oral sumatriptan</td>
</tr>
<tr>
<td>Frovatriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>2.5 mg at onset (may repeat after 2 h; maximum 7.5 mg/d)</td>
<td>Well tolerated; little sedation; effective for prevention of menstrual migraine</td>
</tr>
<tr>
<td>Naratriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>1.0–2.5 mg at onset (may repeat after 4 h; maximum 5 mg/d)</td>
<td>Possibly lower risk for headache recurrence than other oral triptans; relatively lower efficacy and incidence of side effects than other triptans</td>
</tr>
<tr>
<td>Rizatriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>5–10 mg at onset (may repeat after 2 h; maximum 30 mg/d)</td>
<td>Available in a fast-melt preparation, which may be no faster in providing pain relief than the regular tablet; slightly higher efficacy compared with oral sumatriptan</td>
</tr>
<tr>
<td>Zolmitriptan (oral)</td>
<td>Selective serotonin (5-HT1B/1D) agonist</td>
<td>1.25–2.5 mg at onset (may repeat after 2 h; maximum 10 mg/d)</td>
<td>Similar efficacy to oral sumatriptan; also available in a rapidly dispersing tablet formulation</td>
</tr>
<tr>
<td>Dihydroergotamine (nasal)</td>
<td>Nonselective serotonin agonist</td>
<td>1 spray (0.5 mg) into each nostril (may repeat after 15 min; maximum 4 sprays/d, 8/wk)</td>
<td>No sedation; should not be used with a 5-HT1B/1D; pregnancy category X</td>
</tr>
<tr>
<td>Dihydroergotamine (all other routes)</td>
<td>Nonselective serotonin agonist</td>
<td>1 mg SC/IM/IV (may repeat after 1 h; maximum 2 mg/dose, 3 mg/attack, 6 mg/wk)</td>
<td>Useful in status migrainosus; contraindicated in patients with CAD; pregnancy category X</td>
</tr>
<tr>
<td><strong>Nonspecific (good evidence for effectiveness)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen and other NSAIDs (oral)</td>
<td>Inhibits cyclo-oxygenase, decreases prostaglandin synthesis</td>
<td>500 mg at onset (may repeat after 6–8 h)</td>
<td>Well tolerated; treatment of choice for mild-to-moderate attacks; may be given with antiemetic; avoid in pregnancy after 32-wk gestation; pregnancy category B</td>
</tr>
<tr>
<td>Aspirin/metoclopramide (oral)</td>
<td>Blocks dopamine receptors in CTZ; increases response to acetylcholine in upper GI tract</td>
<td>650 mg/10 mg at onset (may repeat after 3–4 h)</td>
<td>Antinausea effect; elderly are more likely to develop dystonic reactions than are younger adults; use lowest recommended doses initially; pregnancy category C (D in third trimester)</td>
</tr>
<tr>
<td>Butorphanol (nasal)</td>
<td>Opiate agonist-antagonist</td>
<td>1 spray in 1 nostril (may repeat after 1 h)</td>
<td>Well-tolerated rescue medication; risk for opiate dependence; pregnancy category C</td>
</tr>
<tr>
<td>Metoclopramide/diphenhydramine (intravenous)</td>
<td>Blocks dopamine receptors in CTZ</td>
<td>20–25 mg over 20 min (may repeat after 1 h)</td>
<td>Antinausea effect; recent RCT showed equal effectiveness to sumatriptan; pregnancy category C</td>
</tr>
<tr>
<td><strong>Nonspecific (moderate evidence for effectiveness)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetaminophen (oral)</td>
<td>Analgesic; mechanism unknown</td>
<td>650–1000 mg at onset (may repeat after 4–6 h; maximum 4 g/d)</td>
<td>Well tolerated; little sedation; no stomach irritation; pregnancy category B</td>
</tr>
<tr>
<td>Codeine combinations: acetaminophen/codeine (oral)</td>
<td>Opiate agonist</td>
<td>Acetaminophen 300 mg/codeine 30 mg; dosage based on codeine 1–2 tablets (30–60 mg codeine) every 4–6 h</td>
<td>High potential for drug-induced or “rebound” headache; risk for opiate dependence; pregnancy category C (D if prolonged or at term)</td>
</tr>
</tbody>
</table>
Table 3. Short-Term Drug Treatment for Migraine (continued)

<table>
<thead>
<tr>
<th>Agent (Route)</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine or other phenothiazine, prochlorperazine</td>
<td>Selective dopamine antagonist (D2)</td>
<td>Chlorpromazine 25 mg IM/IV (may repeat after 30 min); prochlorperazine 10 mg IM/IV or 25 mg rectally (may repeat)</td>
<td>Antinausea effect; rescue therapy in supervised setting; pregnancy category C</td>
</tr>
<tr>
<td>Lidocaine, 4% topical solution</td>
<td>Anesthetic</td>
<td>1–4 drops in nostril ipsilateral to head pain (may repeat after 2 min)</td>
<td>Rapid onset of action; uncertain effectiveness over 2–4 h</td>
</tr>
<tr>
<td>Isometheptene-containing compound (acetaminophen/dichloral-phenazone/isometheptene) (oral)</td>
<td>Weak sedative</td>
<td>2 capsules (2 x 325 mg/100 mg/65 mg) at onset (may repeat 1 capsule after 1 h; maximum 5 capsules every 12 h)</td>
<td>Well tolerated, but limited effectiveness; pregnancy category C</td>
</tr>
</tbody>
</table>

Conflicting or inconsistent evidence of effectiveness

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergotamine/caffeine combination tablet, ergotamine/caffeine combination suppository, ergotamine tartrate tablet</td>
<td>Nonselective serotonin agonist</td>
<td>1–2 tablets (1 mg/100 mg) orally (may repeat after 1 h); 1 suppository (2 mg/100 mg) rectally (may repeat after 1 h); 1 tablet (2 mg) sublingual (may repeat after 30 min); 1 tablet (2 mg) sublingual (may repeat after 30 min); maximum 6 mg/d, 10 mg/wk based on ergotamine</td>
<td>No sedation; contraindicated in patients with CAD or pregnancy; relatively weak evidence for effectiveness; should not be used with 5-HT1B/1D agonists, protease inhibitors, or macrolide antibiotics; a European consensus conference recommended ergotamine as the drug of choice in a limited number of persons with migraine who have infrequent or long-duration headaches; pregnancy category X</td>
</tr>
<tr>
<td>Dexamethasone or other corticosteroids (IV)</td>
<td>Multiple glucocorticoid and mineralocorticoid effects</td>
<td>6 mg</td>
<td>Rescue therapy for status migrainosus; relatively little evidence for effectiveness; pregnancy category C</td>
</tr>
</tbody>
</table>

*5-HT = 5-hydroxytryptamine; CAD = coronary artery disease; CTZ = chemoreceptor trigger zone; GI = gastrointestinal; IM = intramuscular; IV = intravenous; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized, controlled trial; SC = subcutaneous.

Generally have a more rapid action but also have more side effects than long half-life agents, but these findings may not apply in all patients because of idiosyncratic differences among individuals. Triptans with a long half-life also may be beneficial in prophylaxis of migraine when administered during prodrome or before onset of predictable headaches, such as menstrual migraines.

Generally, the following factors should guide selection of triptans: Triptans do not have a class effect, so lack of efficacy or side effects associated with 1 triptan agent is not predictive of a patient’s response to other triptans. Also, once a patient has been successfully treated with a particular triptan, recurrence of headache may indicate the need for a repeated dose, not treatment failure. Patients taking triptans should note the following factors: the stage of migraine at which medication was begun, efficacy, side effects, and whether migraine returns. Treatment with an alternate triptan is indicated in patients who take medication during an early migraine phase but have inconsistent relief or side effects that preclude early use of that medication in the future.

**Dihydroergotamine**

Dihydroergotamine is the alternative to triptans for migraine-specific treatment (27, 28). Dihydroergotamine may be administered via nasal spray or injection. Intravenous dihydroergotamine is the preferred treatment for patients with status migrainosus. With training, patients may self-administer this agent via intramuscular or subcutaneous injection. As with triptans, administration of dihydroergotamine via injection is more effective than other methods but may be associated with more side effects, specifically nausea and

restlessness. Compared with administration via injection, nasal dihydroergotamine has fewer side effects and an efficacy profile similar to many oral triptans (29).

**Ergotamines**

The effectiveness of ergotamine is less certain than for the other migraine-specific drugs (26, 30).

**What therapies should clinicians consider in addition to analgesics and migraine-specific therapies?**

Antiemetic agents, such as metoclopramide, may be helpful in treating the nausea and vomiting associated with migraine. In patients with mild-to-moderate nausea, using an oral or rectal antiemetic drug enables patients to take oral analgesics for migraine pain relief. Patients with severe nausea or vomiting may require a nonoral route of administration for antiemetics and migraine-specific drugs. Intravenous metoclopramide is effective for relief of both pain and nausea and thus may be considered for monotherapy (31).

**What is the appropriate treatment strategy for patients who do not respond to their usual first-line migraine drugs?**

Systematic reviews of controlled clinical trials have found that rescue agents are effective for reducing headache severity when acute therapy is ineffective (32). Patients should have a rescue medication and a plan for use in the event of a debilitating migraine that fails to respond to initial treatment.

Rescue medications are intended for infrequent use when a patient with migraine has no relief within 1 hour from initial acute treatment. Opiate analgesics are typically prescribed for this purpose. These agents should not be used more than a few times per year. Their use for migraine treatment is somewhat controversial because of the potential for dependence, diversion, or abuse.

Frequent use of migraine drug treatments may lead to a medication-overuse headache, a pattern of increasing headache frequency that often results in daily headaches. Some research has suggested that about one half of recurrent headache sufferers do not adhere properly to drug treatment regimens, with as many as two thirds of patients failing to make optimal use of abortive medications. A written plan can help the patient to use rescue medications properly.

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

Taking a daily preventive medication typically reduces headache frequency by one third to one half. Preventive drug treatment may be called for in persons with frequent disabling headaches (usually at least 2/mo) or poor relief from appropriately used short-term treatments, or in those with uncommon migraine, such as basilar or hemiplegic migraine. Other appropriate candidates for preventive medications are those with a contraindication to acute therapy, failure or overuse of acute therapy, adverse effects from acute therapy, or a preference for preventive therapy.

Good symptomatic control of individual attacks, however, may make preventive medication unnecessary. Before starting preventive therapy, clinicians should ask the patient to keep a headache diary for 1 month, and they should also consider the presence of coexisting conditions and the drug’s adverse effect profile. Efficacy may not be immediately clear, so patients should use a particular drug therapy for at least 2 months before declaring it to be ineffective.

Preventive drug therapies for migraine are listed in Table 4. The strength of evidence is greatest for
β-blockers without intrinsic sympathomimetic activity (33, 34), followed by anticonvulsants (35), antidepressants, and calcium antagonists (36). Valproate and topiramate are the only anticonvulsants approved by the U.S. Food and Drug Administration for migraine prevention. Perimenstrual preventive therapy with a triptan may be helpful for patients with migraines associated with menstruation (37). When preventive therapy is appropriate, it should be started at a low dose and slowly increased over 1 to 2 months to minimize adverse effects. Once a therapeutic dose is achieved, the treatment should be continued for at least 2 months to assess benefit. If headaches are

### Table 4. Preventive Drug Treatment for Migraine*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medium-to-High Efficacy, Good Strength of Evidence, and Mild-to-Moderate Side Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Inhibits norepinephrine</td>
<td>Amitriptyline, 30–150 mg PO qd</td>
<td>Anticholinergic effects, dry mouth, drowsiness; weight gain</td>
</tr>
<tr>
<td>Divalproex sodium, other anticonvulsants (e.g., sodium valproate, gabapentin, topiramate)</td>
<td>Unknown</td>
<td>Divalproex sodium, 250–500 mg PO bid</td>
<td>Bone marrow suppression, liver inflammation, alopecia, tremors, weight loss with topiramate</td>
</tr>
<tr>
<td>Propranolol, other non-ISA β-adrenergic antagonists (e.g., timolol, atenolol, metoprolol, nadolol)</td>
<td>β-adrenergic antagonists</td>
<td>Propranolol, 120–240 mg PO qd in divided doses</td>
<td>Fatigue, bradycardia, hypotension (check blood pressure and heart rate before prescribing)</td>
</tr>
<tr>
<td><strong>Lower Efficacy than above or Limited Strength of Evidence and Mild-to-Moderate Side Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>20–40 mg PO qd</td>
<td>Insomnia, anxiety</td>
</tr>
<tr>
<td>Verapamil, other calcium-channel blockers (e.g., nifedipine)</td>
<td>Vasodilator</td>
<td>Verapamil, 80–120 mg PO tid</td>
<td>Constipation, hypotension</td>
</tr>
<tr>
<td>Naproxen, other long-acting NSAIDs (e.g., naproxen sodium, ketoprofen)</td>
<td>Inhibits cyclooxygenase, reduces prostaglandin synthesis</td>
<td>Naproxen, 250–500 mg PO bid</td>
<td>Stomach irritation</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Inhibitory effects on platelet aggregation, release of serotonin, and prostaglandin synthesis</td>
<td>Powdered or granulated feverfew leaves, 50–143 mg PO qd</td>
<td>&quot;Post-feverfew syndrome&quot; (i.e., rebound of migraine symptoms, anxiety, insomnia, and muscle and joint stiffness)</td>
</tr>
<tr>
<td>High-dose riboflavin (vitamin B₂)</td>
<td>Unknown, but presumably related to its necessity for conversion of tryptophan to niacin</td>
<td>400 mg PO qd</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Unknown, but presumably relates to calcium-antagonist properties</td>
<td>Magnesium oxide, 400 mg PO qd; Magnesium gluconate 1500 mg PO tid</td>
<td>Infrequent adverse effects</td>
</tr>
<tr>
<td>ACE inhibitors (e.g., lisinopril) and angiotensin II receptor blockers (e.g., candesartan)</td>
<td>Unknown, but presumably through reduced effect of angiotensin II</td>
<td>Lisinopril, 20 mg PO qd; Candesartan, 16 mg PO qd</td>
<td>Angioedema, hyperkalemia, hypotension, cough (ACE inhibitors only)</td>
</tr>
<tr>
<td><strong>Medium-to-High Efficacy, Good Strength of Evidence, but with Side-Effect Concerns</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>Selective serotonin agonist (5-HT₂); constricts cranial and peripheral blood vessels</td>
<td>4–8 mg PO qd</td>
<td>Retropertioneal fibrosis, pulmonary fibrosis, nausea, vomiting; no longer available in the United States</td>
</tr>
</tbody>
</table>

*5-HT = 5-hydroxytryptamine; ACE = angiotensin-converting enzyme; bid = twice daily; ISA = intrinsic sympathomimetic activity; NSAIDs = nonsteroidal anti-inflammatory drugs; PO = oral; qd = once daily; RCT = randomized, controlled trial; SSRI = selective serotonin reuptake inhibitor; tid = three times daily.

well controlled for 6 to 12 months, tapering and discontinuation can be considered, and the medication can be resumed if headaches recur.

Definitive data are lacking about the usefulness of injections of botulinum toxin into the scalp and face for migraine prophylaxis (38). Ongoing multicenter national trials may determine a standardized method for botulinum toxin administration for migraine.

Any preventive drug therapy may be combined with nondrug preventive treatments, such as relaxation and biofeedback, which work in different and complementary ways and may have additive effects.

A trial that studied the effects of propranolol combined with 1) thermal biofeedback plus relaxation plus cognitive behavioral therapy, 2) thermal biofeedback plus relaxation, and 3) EMG biofeedback found that concomitant propranolol therapy significantly enhanced the effectiveness of relaxation-biofeedback training when either daily headache recordings (79% vs. 54% reduction in migraine activity) or a neurologist’s clinical evaluations (90% vs. 66% reduction) were used to assess treatment outcome (39).

When should clinicians consider hospitalizing patients with migraine?

Patients with prolonged, intractable migraine (status migrainosus) with associated nausea and vomiting may require hospitalization for hydration, parenteral dihydroergotamine, corticosteroids, phenothiazines, or parenteral analgesics after primary and rescue treatments have failed (40, 41). Patients with headache associated with excessive use of analgesic medications—so-called medication-overuse or rebound headache—may also require hospitalization when outpatient weaning fails.

What are the components of good follow-up care for patients with migraine?

Clinicians should monitor headache severity, frequency, and disability to assess treatment response and the need to change treatment. Because attacks vary in severity, treating at least 3 attacks of migraine is necessary before evaluating response to a specific treatment. Response to particular medications is highly individual, so a trial-and-error approach is reasonable.

Clinicians should ask patients about medication adherence and attempt to identify medication overuse, which is defined as the use of more than 10 doses per week of analgesic medications, ergotamine tartrate, or ergotamine tartrate plus caffeine. Additionally, clinicians should also periodically ask patients about lifestyle factors associated with headache symptoms. In evaluating the effectiveness of treatment, it can be helpful for patients to keep a daily record of symptoms between clinic visits. Retrospective recall of headache frequency and severity is unreliable compared with contemporaneously recorded symptoms (42).

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

Migraine symptoms change over time, and preventive therapy may become unnecessary in patients who previously needed it. After a sustained reduction in headache frequency that lasts 6 to 12 months, a trial of medication withdrawal may allow the patient to cease preventive treatment and avoid the associated risks and costs. However, a 1999 systematic review found no published studies to evaluate systematic withdrawal of preventive medications (36), and we continue to be lack evidence
Treatment... Nonpharmacologic management of migraine includes modification of diet to avoid foods that trigger symptoms, sleep hygiene, and behavioral therapy. Over-the-counter analgesics are appropriate first-line therapy for mild-to-moderate symptoms. More severe symptoms require migraine-specific therapy with triptans, dihydroergotamine, or ergotamine. When symptoms are frequent, refractory to therapy, or include neurologic sequelae, preventive drug therapy is indicated. Evidence for effectiveness in prevention is greatest for β-blockers, followed by valproate, antidepressants, and then calcium antagonists. Patients should participate in the selection of therapy and have a clear plan to institute when symptoms occur.

CLINICAL BOTTOM LINE

What do professional organizations recommend about caring for patients with migraine? In 2000, the U.S. Headache Consortium published evidence-based guidelines for migraine (46). In 2002, the American College of Physicians and the American Academy of Family Physicians with the American Headache Society developed a clinical guideline based on systematic reviews that had been part of the evidence base for the 2000 U.S. Headache Consortium guideline (47). The Figure summarizes an evidence-based strategy for the management of acute migraine.
in the clinic
Tool Kit

Migraine

PIER Modules
PIER.acponline.org
Access PIER module on Migraine

Practice Guidelines
www.neurology.org/cgi/reprint/55/6/754.pdf
Access the US Headache Consortium 2000 guideline
www.annals.org/cgi/content/full/137/10/840
Access the American College of Physicians/American Academy of Family Physicians Guideline. Includes a table comparing this guideline with the U.S. Headache Consortium Guideline.

Patient Information
www.annals/intheclinic/tools
Download the patient information that appears on the following page for duplication and distribution to your patients.
Obtain the American College of Physicians patient brochure on headache.

Migraine in a Minute Encounter Kit
www.aan.com/globals/axon/assets/2361.pdf
Obtain the American Academy of Neurology's brief guide for migraine assessment.

Headache Diary
www.achenet.org/your/diary1.php
Download a headache diary for distribution to your patients.

Migraine Disability Assessment (MIDAS)
Questionnaire.
www.zomig.info/pUserFiles/Midasquestionnairev5.pdf
Obtain a free copy of the questionnaire.

Figure. Strategy for the management of acute migraine.
Migraines are headaches related to changes in chemicals and blood vessels in the brain.

"POUND" (as in "a pounding headache") is one way to remember migraine symptoms:

- Pulsatile quality of headache described
- One-day duration (duration < 4 hours suggests tension-type headache)
- Unilateral location
- Nausea or vomiting
- Disabling intensity.

- Good sleep habits, avoidance of foods that trigger migraine symptoms, behavioral therapy (such as biofeedback), and drugs can all help to decrease the frequency and severity of migraine attacks. Migraine sufferers should participate in selecting treatment.
- Over-the-counter drugs, such as acetaminophen, aspirin, and ibuprofen, are usually the first drugs used to treat migraine. When these drugs do not help, prescription drugs may be necessary.
- Talk to your doctor if you think you may have migraine headaches.

**Daily drugs to prevent migraine may help you if you:**

- Get 2 or more migraines per month
- Are unable to use migraine treatments because of side effects
- Get no benefit from migraine treatment
- Have migraine complicated by nerve symptoms, such visual changes, numbness, or weakness

**Web Sites with Good Information about Migraine**

- American Academy of Neurology
  www.aan.com/globals/axon/assets/2346.pdf
- MedlinePLUS
- National Institute of Neurological Disorders and Stroke
  www.ninds.nih.gov/disorders/headache/headache.htm
- National Headache Foundation
  www.headaches.org/consumer/topicsheets/migraine.html
1. A 32-year-old man is evaluated for what he calls a “sinus headache.” The headache occurs 2 or 3 times a month and is accompanied by facial pressure and occasional rhinorrhea; it worsens with movement. Resting in a dark, quiet room results in subjective improvement. The symptoms resolve in 1 or 2 days regardless of treatment. He has tried multiple varieties of decongestants and antihistamines without success. Acetaminophen-aspirin-caffeine preparations offer minimal relief. He is currently asymptomatic. On examination, the patient is pale and moderately distressed. Temperature is 37.1°C (98.8°F), pulse rate 84/min, respiration rate 16/min, and blood pressure 132/75 mm Hg. His face is tender on palpation.

What is the most likely diagnosis?
A. Cluster headache
B. Migraine without aura
C. Sinus headache
D. Tension headache

2. A 23-year-old woman comes to the office for re-evaluation of migraine headaches. She was seen 2 weeks earlier because of recurrent generalized, moderate to severe pulsatile headaches associated with nausea and light and noise sensitivity. The headaches typically last 1 to 2 days, and she was having approximately 10 headache days per month. Amitriptyline was begun at a dose of 10 mg at bedtime, with instructions to increase the dose in 10-mg increments every 1 week toward an initial target dose of 50 mg. The current dose is 30 mg at bedtime. She tolerates the amitriptyline well. Today she has developed a typical attack that is treated with subcutaneous sumatriptan in the office.

What plan should be pursued for prophylactic treatment?
A. Continue amitriptyline at the current dose.
B. Continue increasing amitriptyline as planned.
C. Discontinue all prophylaxis.
D. Discontinue amitriptyline and begin propranolol.
E. Discontinue amitriptyline and begin divalproex sodium.

3. A 32-year-old woman has approximately 2 migraine headaches per week accompanied by nausea and vomiting, each lasting 24 to 48 hours. On onset of these attacks, she has dizziness and scalp sensitivity when brushing her hair or lying on the affected side of her head. The attacks and accompanying systemic symptoms interfere significantly with her work and social activities. She usually waits to take an oral triptan until her headache progresses to be certain that she is having a migraine headache. Physical examination is unremarkable except for obesity (BMI of 30).

In addition to taking an oral triptan at onset of dizziness and scalp hypersensitivity, which of the following is the most appropriate prophylaxis?
A. Amitriptyline
B. Intravenous botulinum toxin type A
C. Oxycodone
D. Topiramate

4. A 36-year-old woman with a 15-year history of headaches comes to the office for a follow-up visit. Initially, she had moderate to severe bilateral pulsatile, frontal headaches accompanied by nausea, light and noise sensitivity, and occasional vomiting. They occurred 1 to 2 times each month and lasted 24 to 36 hours. In the last 2 years, she has developed a daily mild-to-moderate bilateral frontal headache that is present when she awakens and lasts all day. Approximately once per week she has a headache that is similar to her previous episodic headaches but less severe. She takes amitriptyline, 75 mg at bedtime, as a prophylactic agent. She takes acetaminophen/caffeine/butalbital, 4 tablets/d, and rizatriptan, 10 to 20 mg, 1 to 2 days per week for more severe headaches. Physical and neurologic examinations are normal.

What is the most appropriate next step in managing this patient’s headache disorder?
A. Discontinue amitriptyline and initiate treatment with divalproex sodium.
B. Discontinue acetaminophen/caffeine/butalbital.
C. Discontinue rizatriptan.
D. Increase dose of amitriptyline.

5. A 24-year-old woman comes to the office because of severe generalized, throbbing headaches associated with nausea, occasional vomiting, and light and noise sensitivity. The headaches occur 2 to 3 times weekly and last 12 to 24 hours. She misses approximately 1 workday each month. She has been taking zolmitriptan, 5 mg orally, for acute attacks, with good benefit approximately two thirds of the time. She has insomnia and a past history of childhood asthma.

Which of the following medications is most appropriate to prevent the headaches?
A. Amitriptyline
B. Nadolol
C. Naratriptan
D. Propranolol
E. Sertraline

6. A 37-year-old woman comes to the office because of recurrent headaches for 5 years. Initially, the headaches were of moderate intensity and occurred approximately 4 times per year. In the past year, she has had right-sided severe, pulsatile pain associated with light and noise sensitivity and nausea without vomiting; the headaches last 12 to 16 hours and occur once or twice monthly. The headaches cause her to miss work and other activities occasionally. She uses acetaminophen without benefit. Physical and neurologic examinations are normal.

Which of the following is most likely to be effective for acute treatment of this patient’s headaches?
A. Acetaminophen/ASA/caffeine combination
B. Acetaminophen/butalbital/caffeine combination
C. Aspirin
D. Naproxen
E. Zolmitriptan

Questions are largely from the ACP’s Medical Knowledge Self-Assessment Program (MKSAP). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.