Pharmacologic Management of Acute Attacks of Migraine and Prevention of Migraine Headache

Vincenza Snow, MD; Kevin Weiss, MD; Eric M. Wall, MD, MPH; and Christel Mottur-Pilson, PhD, for the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine*

Migraine headache is a common disorder seen in primary care. It affects 18% of women and 6.5% of men in the United States, almost half of whom are undiagnosed or undertreated (1, 2). These guidelines, developed by the American Academy of Family Physicians and the American College of Physicians–American Society of Internal Medicine, with assistance from the American Headache Society, are based on two previously published papers (3, 4). The papers, titled "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management of Acute Attacks," by Matchar and colleagues (3), and "Evidence-Based Guidelines for Migraine Headache in the Primary Care Setting: Pharmacological Management for Prevention of Migraine," by Ramadan and coworkers (4), can be found at www.aan-.com/professionals/practice/guidelines.cfm.[1]

The target audience for this guideline is primary care physicians. The guideline applies to patients with acute migraine attacks, with or without aura, and patients with migraine who are candidates for preventive drug therapy. Although these guidelines are all based on the articles by Matchar and Ramadan and colleagues, the recommendations may differ because different thresholds of evidence were needed for making a positive recommendation. **Table 1** compares the AAFP/ACP–ASIM guideline and the U.S. Headache Consortium Guideline.

Throughout the text, asterisks indicate drugs that are currently not available in the United States.

Diagnosis

Headache has many potential causes. Most headaches are caused by the primary headache disorders, which include migraine, cluster, and tension-type headaches. Secondary headaches, which are those with underlying pathologic causes, are far less common. Migraine is a chronic condition with recurrent acute attacks whose characteristics vary among patients and often among attacks within a single patient. Migraine is a syndrome with a wide variety of neurologic and non-neurologic manifestations. The International Headache Society (6) has developed diagnostic criteria for migraine with and without aura (**Appendix Table 1**). This classification system serves to diagnose headache syndromes, not patients. Thus, one patient could have more than one type of headache disorder. For example, it is not uncommon for migraine patients to also have episodic tension-type headaches.

Management of Acute Attacks

Effective long-term management of patients with migraine is challenging because of the complexity of the condition. Experts suggest several goals for successful treatment of acute attacks of migraine. These include treating attacks rapidly and consistently to avoid headache recurrence, to restore the patient's ability to function, and to minimize the use of backup and rescue medications.

Clinicians need to educate people with migraine about their condition and its treatment and encourage them to participate in their own management. The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms. Patient input can provide the best guide to treatment selection and helps the physician to better understand and accommodate patient treatment goals. Developing an effective acute migraine management strategy can be complex, and an engaged patient is more likely to negotiate this process successfully. Encouraging patients to identify and avoid triggers (**Table 2**) and to be actively involved in their own management by tracking their own progress may be especially useful.

Once a diagnosis of migraine is established, patients

For author affiliations, see end of text.

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[1] In an effort to educate clinicians and patients about headache's impact, diagnosis, management, and prognosis, the U.S. Headache Consortium was founded in 1996. The Consortium was made up of seven member organizations representing primary care, emergency medicine, neurology, and headache specialists. The objective of the U.S. Headache Consortium was to develop scientifically sound, clinically relevant practice guidelines on chronic headache, particularly migraine, in the primary care setting. Five documents on headache and migraine were produced. These documents can be found on the American Academy of Neurology Web site (www.aan.com).

and their health care providers should decide together how to treat acute attacks and whether the patient is a candidate for preventive medications. A wide range of acute treatments with varying efficacies is currently in use (**Appendix Table 2,** available at www.annals.org). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy in the management of acute migraine headache. It also provides a clear understanding of the adverse events associated with various agents.

The Headache Consortium's review of the evidence on antiemetics, barbiturate hypnotics, ergot alkaloids and derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), combination analgesics and nonopiate analgesics, opiate analgesics, triptans, and other agents found good evidence of the efficacy of only a few agents in the treatment of acute migraine (3).

Available Agents

NSAIDs

Their demonstrated efficacy and favorable tolerability make NSAIDs a first-line treatment choice for all migraine attacks, including severe attacks that have responded to NSAIDs in the past. Among the NSAIDs, the most consistent evidence exists for aspirin (8–10), ibuprofen (11, 12), naproxen sodium (13, 14), tolfenamic acid* (8, 15), and the combination agent acetaminophen plus aspirin plus caffeine for the acute treatment of migraine (16). The evidence shows that acetaminophen alone is ineffective (17).

Serotonin$_{1B/1D}$ Agonists (Triptans)

There is good evidence for the effectiveness of the oral triptans naratriptan (18, 19), rizatriptan (20–23), sumatriptan (24–31), and zolmitriptan (32–34). In addition, there is good evidence for the effectiveness of subcutaneous (35–38) and intranasal (39–41) sumatriptan, making it an option for patients with nausea and vomiting. Adverse effects of the triptans include chest symptoms, but postmarketing data indicate that true ischemic events are rare. Triptans are contraindicated in patients with risk for heart disease, basilar or hemiplegic migraine, or uncontrolled hypertension. Subcutaneous sumatriptan is associated with a very rapid onset of action, and oral naratriptan is associated with a slower onset of action.

Ergotamines

There is good evidence for the efficacy and safety of intranasal dihydroergotamine (DHE) as monotherapy for acute migraine attacks (42–46). Placebo-controlled studies of intravenous DHE did not clearly establish its efficacy in the acute treatment of migraine (47, 48). The evidence was inconsistent to support efficacy of ergotamine or ergotamine–caffeine, and the studies documented frequent adverse events.

Opioids

It is well recognized that opiates are good analgesics, but there is good evidence only for the efficacy of butorphanol nasal spray (49, 50). Although opioids are commonly used, surprisingly few studies of opioid use in headache pain document whether overuse and the development of dependence are as frequent as clinically perceived. Until further data are available, these drugs may be better reserved for use when other medications cannot be used, when sedation effects are not a concern, or the risk for abuse has been addressed.

Other Agents

Fair evidence suggests that the antiemetic metoclopramide, given intravenously, may be an appropriate choice as monotherapy for acute attacks (51–53), particularly in patients with nausea and vomiting when the sedating side effect may also be useful. Isometheptene and isometheptene combinations obtained only borderline significance in relieving headache pain (17, 54, 55). Other agents used in practice, such as intravenous corticosteroids and intranasal lidocaine, are not effective.

Choice of Treatment

Since patient responses to these therapies are not always predictable, individualized management is important. The choice of treatment should be based on, among other characteristics, the frequency and severity of attacks; the presence and degree of temporary disability; and the profile of associated symptoms, such as nausea and vomiting. The patient's history of, response to, and tolerance for specific medications must also be considered. Coexisting conditions (such as heart disease, pregnancy, and uncontrolled hypertension) may limit treatment choices.

No studies document the effectiveness of specific treatment schedules, but experts suggest that acute therapy should be limited to no more than two times per week to guard against medication-overuse headache (or drug-induced headache). Medication-overuse headache is thought to result from frequent use of acute medication and has a pattern of increasing headache frequency, often resulting in daily headaches. In patients with suspected medication overuse or patients at risk for medication overuse, preventive migraine therapy should be considered.

Although some use the term *rebound headache* interchangeably with the term *medication-overuse headache*, rebound headache is a distinct entity. Rebound headache is associated with withdrawal of analgesics or abortive migraine medication. There is no uniform agreement about which agents can cause rebound headache, although ergotamine (not DHE); opiates; triptans; and simple and mixed analgesics containing butalbital, caffeine, or isometheptene

Table 1. **Summary of U.S. Headache Consortium Recommendations Compared with AAFP/ACP–ASIM Recommendations***

Treatment Type	U.S. Headache Consortium Recommendations	AAFP/ACP–ASIM Recommendations
Acute	Use migraine-specific agents (triptans, DHE, ergotamine) in patients with severe migraine and in patients whose migraines respond poorly to NSAIDs or combination analgesics such as aspirin + acetaminophen + caffeine. Recommended medications based on at least two double-blind, placebo-controlled trials and clinical impression of effect: Oral acetaminophen + aspirin + caffeine Oral aspirin IN Butorphanol SC, IM, IV, IN DHE IV DHE + antiemetic Oral ibuprofen Oral naproxen sodium Oral naratriptan IV prochlorperazine Oral rizatriptan SC, IN, oral sumatriptan Oral zolmitriptan	Use NSAIDs as first-line therapy. Recommended agents: Aspirin Ibuprofen Naproxen sodium Tolfenamic acid† Acetaminophen + aspirin + caffeine In patients whose migraines fail to respond to NSAIDs, use migraine-specific agents. Recommended agents: DHE nasal spray Oral naratriptan SC, oral sumatriptan Oral rizatriptan Oral zolmitriptan
	Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex.	Select a non-oral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea and vomiting with an antiemetic.
	Consider a self-administered rescue medication for patients with severe migraine that does not respond well to or fails other treatments‡.	
	Guard against medication-overuse headache.	
	Educate patients with migraine about their condition and its treatment, and encourage them to participate in their own management	Educate patients with migraine about their condition and its treatment, and encourage them to participate in their own management
Preventive	Medication use Initiate treatment with lowest effective dose Give each treatment an adequate trial Avoid interfering medications Use a long-acting formulation to improve adherence	Patients with migraine should be evaluated for use of preventive therapy. Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability that lasts 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) use of abortive medication more than twice per week; or 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.
	Recommended agents found to have medium to high efficacy and mild or infrequent side effects: Amitriptyline Divalproex sodium Lisuride† Propranolol Timolol	Recommended first-line agents, currently available in the United States, for the prevention of migraine headache: Propranolol (80–240 mg/d) Timolol (20–30 mg/d) Amitriptyline (30–150 mg/d) Divalproex sodium (500–1500 mg/d) Sodium valproate (800–1500 mg/d)
	Recommended agents found to have medium to high efficacy but with side effect concerns: Methysergide Flunarizine† Pizotifen† Time-released DHE*	Other medications with proven efficacy but limited published data on adverse events, or frequent or severe adverse events: Flunarizine† Lisuride† Pizotifen† Time-released DHE† Methysergide
	Recommended agents based on consensus and clinical experience: Cyprohetadine Buproprion Diltiazem Doxepin Fluvoxamine Ibuprofen Imipramine Mirtazepine Nortriptyline Paroxetine Protriptyline	

Continued on following page

Table 1—**Continued**

Treatment Type	U.S. Headache Consortium Recommendations	AAFP/ACP–ASIM Recommendations
Preventive *(continued)*	Sertraline Tiagabine Topiramate Trazadone Venlafaxine	
	Patient education Maximize adherence Address patient expectations Create a formal management plan	Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan. Therapy should be reevaluated on a regular basis.
	Evaluation Monitor patients' headaches by having them keep headache diaries Reevaluate therapy	Encourage patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example. Diaries should measure attack frequency, severity, duration, disability, response to type of treatment, and adverse effects of medication.
	Comorbid conditions Once a coexisting condition is identified, select a pharmacologic agent that will treat both disorders Establish that the coexisting condition is not a contraindication to the selected migraine therapies and that the therapy will not exacerbate the migraine	

* Consortium recommendations are based on references 3 and 4. The ACP–ASIM historically has not used a grading system for guideline recommendations because its development process mandates the use of only high-quality evidence (that is, randomized, controlled trials or "A"-level evidence) as a basis for recommendations. AAFP = American Academy of Family Physicians; ACP–ASIM = American College of Physicians–American Society of Internal Medicine; DHE = dihydroergotamine; IM = intramuscular; IN = intranasal; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; SC = subcutaneous.
† Currently not available in the United States.
‡ Rescue medication is an agent (e.g., an opioid) that the patient can use at home when other treatments have failed.

are generally thought to do so. There is less uniform opinion about other antimigraine agents.

Another clinical consideration is the use of a self-administered rescue medication for patients with severe migraine attack that is not responding to (or failing) other treatments. A rescue medication is an agent such as an opioid or a butalbital-containing compound that the patient can use at home when other treatments have failed. Although rescue medications often do not completely eliminate pain and allow patients to return to normal activities, they permit the patient to achieve relief without the discomfort and expense of a visit to the physician's office or emergency department. A cooperative arrangement between provider and patient may extend to the use of rescue medication in appropriate situations.

Summary of Treatment of Acute Migraine

A body of evidence now points to effective first- and second-line agents for acute treatment of migraine. Beyond the choice of agent lies the choice of management strategy. Recently, interest and research in step care versus stratified care have increased. Step care refers to the initial use of safe, effective, and inexpensive medications as first-line agents in acute attacks of any severity. If the initial agent fails, a second-line, more expensive, migraine-specific medication is then used. The stratified care model initially stratifies migraine attacks by severity, advocating migraine-specific agents for moderate to severe attacks, regardless of previous response to or an unknown response to other agents. Which approach is more effective is still an open question (56).

MANAGEMENT OF MIGRAINE WITH PREVENTIVE THERAPY

Once patients and their health care providers decide how to treat acute attacks, use of preventive medications should be considered. Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) the use of abortive medication more than twice per week; and 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction. Other factors to consider are adverse events with acute therapies, patient preference, and the cost of both acute and preventive therapies. (The U.S. Headache Consortium also produced a document on behavioral and other nonpharmacologic therapies for headache prevention, which can be found at www.aan.com/professionals/practice/guidelines.cfm.)

A wide range of preventive treatments with varying efficacies is currently in use (**Appendix Table 3**, available at www.annals.org). A comprehensive review of the scientific literature, especially the data from randomized, controlled trials, provides a list of treatments that have demonstrated efficacy in the prevention of migraine headache. It also provides a clear understanding of the adverse events associated with various agents. The Headache Consortium's review of the evidence on α_2-agonists, anticonvulsants, antidepressants, β-blockers, calcium-channel blockers, NSAIDs, serotonergic agents (ergot derivatives, methysergide, and others), hormone therapy, feverfew, magnesium,

Table 2. **Some Commonly Reported Triggers of Migraine Headache***

Food triggers
Alcohol
Caffeine
Chocolate
Monosodium glutamate
Tyramine-containing foods
Nitrate-containing foods
Behavioral–physiologic triggers
Too much or too little sleep
Skipped meals
Stress or post-stress
Menstruation
Fatigue
Physical activity
Environmental triggers
Loud noises
Weather changes
Perfumes or fumes
High altitude
Exposure to glare or flickering lights

* Adapted from reference 7.

and riboflavin found that there was good evidence of the efficacy of only a few agents in migraine prevention. A summary of these results follows.

Available Agents

β-Blockers

Evidence consistently showed the efficacy of propranolol, 80 to 240 mg/d (57–63), and timolol, 20 to 30 mg/d (63–65), for the prevention of migraine. One trial comparing propranolol and amitriptyline suggested that propranolol is more efficacious in patients with migraine alone; amitriptyline was superior for patients with mixed migraine and tension-type headache (66). There is limited evidence of a moderate effect for atenolol (67, 68), metoprolol (69–71), and nadolol (72–74). β-Blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol, pindolol) seem to be ineffective for the prevention of migraine. Adverse effects reported most commonly with β-blockers were fatigue, depression, nausea, dizziness, and insomnia. These symptoms appear to be fairly well tolerated and seldom caused premature withdrawal from trials.

Antidepressants

Amitriptyline has been more frequently studied than the other antidepressants and is the only one with consistent support for efficacy in migraine prevention (75–77). The dosages that were most efficacious in the clinical trials ranged from 30 to 150 mg/d. Drowsiness, weight gain, and anticholinergic symptoms were frequently reported with the tricyclic antidepressants studied, including amitriptyline. There is no evidence for the use of nortriptyline, protriptyline, doxepin, clomipramine, or imipramine. There is limited evidence of a modest effect for fluoxetine at dosages ranging from 20 mg every other day to 40 mg per day (78, 79). There is no evidence from controlled trials for the use of fluvoxamine, paroxetine, sertraline, phenelzine, bupropion, mirtazapine, trazodone, or venlafaxine.

Anticonvulsants

For the anticonvulsants, there is good evidence for the efficacy of divalproex sodium (80–82) and sodium valproate (83, 84). Adverse events with these therapies are not uncommon and include weight gain, hair loss, tremor, and teratogenic potential, such as neural tube defects. These agents may be especially useful in patients with prolonged or atypical migraine aura. Carbamazepine and vigabatrin* have been shown to be ineffective, and there is limited evidence for moderate efficacy of gabapentin (85).

NSAIDs

A meta-analysis (4) of five of seven placebo-controlled trials of naproxen or naproxen sodium showed a modest effect on headache prevention (62, 86–92). Similar trends were observed in single placebo-controlled trials of flurbiprofen, indobufen*, ketoprofen, lornoxicam*, and mefenamic acid and in two trials of tolfenamic acid*. Placebo-controlled trials of aspirin, aspirin plus dipyridamole, fenoprofen, and indomethacin were inconclusive. There is no evidence for the use of ibuprofen or nabumetone in the prevention of migraine.

Side effect rates for naproxen were not significantly higher than those seen with placebo. The most commonly reported adverse events with all NSAIDs were gastrointestinal symptoms, including nausea, vomiting, gastritis, and blood in the stool. In the trials reviewed, such symptoms were reported by 3% to 45% of participants (86).

Serotonergic Agents

Of these agents, time-released DHE* had the strongest support, with consistently positive findings in four placebo-controlled trials (93–96). Evidence is insufficient for the efficacy of ergotamine or ergotamine plus caffeine plus butalbital plus belladonna alkaloids or methylergonovine for migraine prevention. Limited information was reported on adverse events associated with these agents. The most commonly reported events for all the ergot alkaloids were gastrointestinal symptoms.

There is strong evidence for the efficacy of methysergide (97–100), a semisynthetic ergot alkaloid. However, there are reports of retroperitoneal and retropleural fibrosis associated with long-term, mostly uninterrupted administration. The manufacturer suggests that methysergide therapy be discontinued for 3 to 4 weeks after each 6-month course of treatment. Other adverse events most commonly reported included gastrointestinal symptoms and leg symptoms (restlessness or pain).

Other serotonergic agents that have been evaluated for the prevention of migraine include pizotifen*, lisuride*, oxitriptan*, iprazochrome*, and tropisetron*. Only

lisuride (101–104) and pizotifen (87, 99, 105–110) have consistent evidence that supports their efficacy in the prevention of migraine. Published data on adverse events associated with lisuride are limited, and pizotifen is often associated with weight gain and drowsiness.

Calcium-Channel Blockers

The evidence for nifedipine, nimodipine, cyclandelate*, and verapamil is poor quality and difficult to interpret, suggesting only a modest effect (see reference 4 for study references). There is no evidence for the use of diltiazem in the prevention of migraine. Symptoms reported with these agents included dizziness, edema, flushing, and constipation.

Flunarizine*, 10 mg/d, has proven efficacy in the prevention of migraine and is commonly used in countries where it is available (111–115). Adverse events reported with flunarizine include sedation, weight gain, and abdominal pain. Depression and extrapyramidal symptoms can be observed, particularly in elderly persons.

α_2-Agonists

There is good evidence for the lack of efficacy of the α_2-agonist clonidine in the prevention of migraine (116–120). Limited evidence shows moderate efficacy of guanfacine (121).

Hormone Therapy, Feverfew, Magnesium, and Riboflavin

There is fair evidence for modest efficacy of these agents in certain circumstances, but more trials need to be done. Most of the existing trials had small sample sizes, had self-referred or special patient samples, or had other methodologic flaws (see reference 4 for more details and references).

Summary of Preventive Therapy

To alleviate the suffering of many patients with migraine, clinicians need to be aware of the commonly accepted indications for preventive therapy and initiate effective therapy in those patients. Although many agents are available for the preventive treatment of migraine, only a few have proven efficacy. Once an agent has been chosen, clinicians should initiate therapy with a low dose and titrate the dose slowly up until clinical benefits are achieved in the absence of adverse events or until limited by adverse events. Because a clinical benefit may take as long as 2 to 3 months to manifest, each treatment should be given an adequate trial. Once preventive treatment is under way, interfering medications, such as overused acute medications such as ergotamine, should be avoided. After a period of stability, clinicians should consider tapering or discontinuing treatment. Patient and clinician need to engage in an ongoing dialogue in which patient expectations and goals for therapy are taken into account when agents are chosen, titrated, or discontinued.

RECOMMENDATIONS

Recommendation 1: For most migraine sufferers, nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy.

To date, the most consistent evidence exists for aspirin, ibuprofen, naproxen sodium, tolfenamic acid*, and the combination agent acetaminophen plus aspirin plus caffeine. There is no evidence for the use of acetaminophen alone.

Recommendation 2: In patients whose migraine attack has not responded to NSAIDs, use migraine-specific agents (triptans, DHE).

There is good evidence for the following triptans: oral naratriptan, rizatriptan, and zolmitriptan; oral and subcu-

Appendix Table 1. **International Headache Society Classification***

- Migraine without aura
  - A. At least five attacks fulfilling criteria B, C, and D
  - B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
  - C. Headache with at least two of the following characteristics
    - Unilateral location
    - Pulsating quality
    - Moderate or severe intensity (inhibits or prohibits daily activities)
    - Aggravation by walking stairs or performing similar routine physical activity
  - D. During headache, at least one of the following events
    - Nausea and/or vomiting
    - Photophobia and phonophobia
  - E. At least one of the following scenarios
    - History and physical and neurologic examination do not suggest one of the disorders causing secondary headaches.
    - History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations.
    - One of such disorders is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.
- Migraine with aura
  - A. At least two attacks fulfilling criterion B
  - B. At least three of the following four characteristics
    - One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
    - At least one aura symptom developing gradually over more than 4 minutes, or two or more symptoms occurring in succession
    - No aura symptom lasting more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased.
    - Headache following aura with a free interval of less than 60 minutes (It may also begin before or simultaneously with the aura.)
  - C. At least one of the following:
    - History and physical and neurologic examinations do not suggest one of the following disorders:
      - Headache associated with head trauma
      - Headache associated with vascular disorders
      - Headache associated with nonvascular intracranial disorder
      - Headache associated with substances or their withdrawal
      - Headache associated with noncephalic disorder
      - Headache associated with metabolic disorder
      - Headache or facial pain associated with disorders of the cranium; neck; or ear, nose, and throat
      - Cranial neuralgias
    - History and/or physical and/or neurologic examinations suggest such a disorder, but it is ruled out by appropriate investigations.
    - Such a disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.

* For migraine without aura, headaches must meet criterion A; those five attacks must fulfill criteria B through D *and* must fulfill at least one of the criteria under E. For migraine with aura, headaches must meet criterion A; those two attacks must fulfill criteria B *and* at least one of those listed under C. Adapted from reference 6.

taneous sumatriptan; and DHE nasal spray. Few data in the literature demonstrate which triptans are more effective. Oral opiate combinations and butorphanol may be considered in acute migraine when sedation side effects are not a concern and the risk for abuse has been addressed.

Recommendation 3: Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex. Treat nausea and vomiting with an antiemetic.

Evidence is limited, but in some patients, concomitant treatment with an antiemetic and an oral migraine medication may be appropriate. Antiemetics should not be restricted to patients who are vomiting or likely to vomit. Nausea itself is one of the most aversive and disabling symptoms of a migraine attack and should be treated appropriately.

Recommendation 4: Migraine sufferers should be evaluated for use of preventive therapy.

Generally accepted indications for migraine prevention include 1) two or more attacks per month that produce disability lasting 3 or more days per month; 2) contraindication to, or failure of, acute treatments; 3) use of abortive medication more than twice per week; or 4) the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.

Recommendation 5: Recommended first-line agents for the prevention of migraine headache are propranolol (80 to 240 mg/d), timolol (20 to 30 mg/d), amitriptyline (30 to 150 mg/d), divalproex sodium (500 to 1500 mg/d), and sodium valproate (800 to 1500 mg/d).

Medications with proven efficacy but limited published data on adverse events or frequent or severe adverse events include flunarizine*, lisuride*, pizotifen*, time-released DHE*, and methysergide.

Recommendation 6: Educate migraine sufferers about the control of acute attacks and preventive therapy and engage them in the formulation of a management plan. Therapy should be reevaluated on a regular basis.

There is strong consensus about the need for educating people with migraine. The physician must help the patient establish realistic expectations by discussing therapeutic options and their benefits and harms, such as medication-overuse headache. Encouraging patients to be actively involved in their own management by tracking their own progress through daily flow sheets, for example, may be especially useful. Diaries should measure attack frequency, severity, and duration; resulting disability; response to type of treatment; and adverse effects of medication. Patient input can provide the best guide to treatment selection.

From American Academy of Family Physicians, Leawood, Kansas; Hines Veterans Affairs Medical Center and Northwestern University Feinberg School of Medicine, Chicago, Illinois; and American College of Physicians–American Society of Internal Medicine, Philadelphia, Pennsylvania.

Note: Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment. All ACP–ASIM clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication or once an update has been issued.

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Requests for Single Reprints: Vincenza Snow, MD, American College of Physicians–American Society of Internal Medicine, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, vincenza@mail.acponline.org.

Current author addresses are available at www.annals.org.

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Current Author Addresse: Drs. Snow and Mottur-Pilson: American College of Physicians–American Society of Internal Medicine, 190 N. Independence Mall West, Philadelphia, PA 19106.
Dr. Weiss: 676 North St. Clair Street, Suite 200, Chicago, IL 60611.
Dr. Wall: LifeWise, 2020 SW 4th, Suite 1000, Portland, OR 97201.

Appendix Table 2. **Summary of the Evidence Available for Acute Treatment***

Drug Class	Evidence	Conclusions
Antiemetics	16 controlled trials 5 of metoclopramide 3 of prochlorperazine 2 of domperidone† 1 of chlorpromazine 1 of granisetron 1 of zatosetron† 1 of methotrimeprazine† 2 comparisons	Two of three placebo-controlled trials of IV metoclopramide showed effectiveness. The three placebo-controlled trials of prochlorperazine also showed effectiveness, but there was only one study for each form (IV, IM, PR). None of the other agents were shown to be effective.
Barbiturate hypnotics	1 controlled trial of IN butorphanol vs. butalbital + aspirin + caffeine + codeine	The literature for butalbital-containing drugs focuses on treatment of tension-type headache; there is only one trial, with no placebo arm, in patients with migraine.
Ergot alkaloids and derivatives	23 controlled trials 9 of DHE nasal spray and 2 comparisons 2 of IV DHE plus antiemetics 5 of ergotamine 3 of ergotamine + caffeine 1 of ergostine + caffeine 1 of ergotamine + caffeine + pentobarbital + Bellafoline (Abiquif, Rio de Janeiro, Brazil)†	The nine placebo-controlled trials of DHE nasal spray were generally consistent in showing its efficacy. The findings of trials of IV DHE, ergotamine, and ergotamine + caffeine were inconsistent. Only one trial supports efficacy of ergostine + caffeine and the Bellafoline combination.
NSAIDs	33 controlled trials 3 of aspirin 2 of ibuprofen 2 of tolfenamic acid† 2 of naproxen sodium 3 of acetaminophen + aspirin + caffeine (Excedrin, Bristol-Myers Squibb, New York, NY) 1 of diclofenac-K 1 of flurbiprofen 1 of naproxen 1 of SL piroxicam 1 of pirprofen† 1 of proquazone† 1 of IM diclofenac sodium† 1 of acetaminophen 3 of NSAID vs. NSAID 10 of NSAIDs vs. other classes	Comparisons with placebo consistently demonstrated the efficacy of this class. The agents with the most evidence are aspirin, ibuprofen, naproxen sodium, acetaminophen + aspirin + caffeine, and tolfenamic acid. The trial of acetaminophen alone showed no benefit over placebo. Comparisons with other classes demonstrated few important differences.
Opiate analgesics	6 controlled trials 2 of IN butorphanol 1 of acetaminophen + codeine 1 of acetaminophen + codeine + doxylamine 1 of acetaminophen + codeine + buclizine 1 of IM methadone	In general, these trials showed evidence of effective pain relief but only IN butorphanol had consistent evidence for migraine relief. Side effects are a major concern in this class of drugs.
Subcutaneous triptans	17 controlled trials 14 placebo-controlled trials of SC sumatriptan 1 of SC almotriptan† 2 of SC sumatriptan vs. oral sumatriptan	The 14 trials of sumatriptan were consistent in showing SC sumatriptan to be efficacious. Almotriptan has only one supporting trial in abstract form. Comparisons of SC vs. oral sumatriptan favored the SC route. Significantly higher rates of side effects were reported.
Oral triptans	26 controlled trials 11 of sumatriptan 4 of rizatriptan 3 of zolmitriptan 2 of naratriptan 2 of eletriptan† 3 for frovatriptan† 1 of almotriptan	The 11 placebo-controlled trials provide consistent evidence that oral sumatriptan is significantly more effective than placebo. All other agents were also found to be effective. Relief rates were lower with naratriptan, and high doses of rizatriptan (40 mg) provided better relief vs. sumatriptan (100 mg). Adverse events were frequent and were dose dependent with rizatriptan and zolmitriptan.
Nasal triptans	6 controlled trials of sumatriptan nasal spray	This agent was not consistently effective at doses of 5 and 10 mg but was effective at higher doses. Side effects were frequent, particularly taste disturbance.
Isometheptene-containing agents	5 controlled trials 2 of isometheptene 3 of isometheptene mucate + acetaminophen + dichloralphenazone	Isometheptene obtained only borderline significance in two trials, and its combination was modestly efficacious in two of three trials. Adverse events were frequent and even more frequent than comparator medications.

* Adapted from reference 3. DHE = dihydroergotamine; IM = intramuscular; IN = intranasal; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; NY = New York; PR = per rectum; SC = subcutaneous; SL = sublingual.
† Currently not available in the United States.

Appendix Table 3. **Summary of the Evidence Available for Preventive Treatment***

Drug Class	Evidence	Conclusions
α_2-Agonists	17 controlled trials 16 of clonidine 1 of guanfacine	Eight of 11 placebo-controlled trials showed no efficacy of clonidine over placebo. There is only one trial with positive results for guanfacine.
Anticonvulsants	11 controlled trials 3 of divalproex sodium 2 of sodium valproate 1 carbamazepine 1 of clonazepam 2 of gabapentin 1 of lamotrigine 1 of vigabatrin†	Five studies provided strong and consistent support for the efficacy of divalproex sodium and the related compound sodium valproate. Evidence for the other anticonvulsants was weak and did not indicate efficacy.
Antidepressants	16 controlled trials 3 of amitriptyline 3 comparisons of amitriptyline 2 of clomipramine 1 of opipramol† 2 of femoxetine† 1 of fluvoxamine 1 of mianserin 3 of fluoxetine	Amitriptyline is the most frequently studied agent and the only one with fairly consistent support for efficacy.
β-Blockers	74 controlled trials 46 of propranolol 14 of metoprolol 3 of timolol 3 of atenolol 3 of nadolol 2 for pindolol 1 of acebutolol 1 of alprenolol† 1 of oxprenolol†	Trials consistently showed efficacy of propranolol. Results of trials of timolol were consistently positive, while trials of metoprolol yielded mixed results and were weaker for atenolol and nadolol.
Calcium-channel blockers	45 controlled trials 25 of flunarizine† 10 of nimodipine 5 of nifedipine 3 of verapamil 1 of cyclandelate† 1 of nicardipine	A meta-analysis of the flunarizine studies showed it to be effective, but side effects were a concern. The evidence for nimodipine and verapamil showed low efficacy. Results of trials for nifedipine were ambiguous.
NSAIDs	23 controlled trials 7 of naproxen and naproxen sodium 4 of aspirin 2 of aspirin + dipyridamole 2 of fenoprofen 1 of flurbiprofen 1 of indobufen† 1 of indomethacin 1 of ketoprofen 1 of lornoxicam† 1 of mefenamic acid 1 of nabumetone 1 of tolfenamic acid†	A meta-analysis of five of seven trials of naproxen or naproxen sodium suggested a statistically significant effect on headache frequency. Trials of aspirin, aspirin plus dipyridamole, fenoprofen and indomethacin were inconclusive. Trials of flurbiprofen, indobufen, ketoprofen, lornoxicam, mefenamic acid, and tolfenamic acid supported efficacy but were too few in number.
Ergot derivatives	13 controlled trials 4 of time-released DHE† and 2 comparisons 2 of dihydroergotkryptine† and 3 comparisons 1 of ergotamine 1 of ergotamine + caffeine + belladonna alkaloids	Time-released DHE has the strongest support with consistently positive findings in four placebo-controlled studies. Evidence is insufficient for the efficacy of the other agents.
Methysergide	17 controlled trials 4 placebo controlled 13 comparisons	Placebo-controlled trials show that methysergide is efficacious, but its usefulness is now limited by reports of severe side effects with uninterrupted use.
Other serotonergic agents	40 controlled trials 26 of pizotofen† 6 of lisuride† 4 of oxitriptan† 2 of iprazochrome† 2 of tropisetron†	Analysis of 11 placebo-controlled trials of pizotofen suggested a large clinical effect that was statistically significant; however, withdrawal rate was high because of adverse events. Lisuride has consistent support from four placebo-controlled trials and had a lower rate of withdrawal due to adverse events. None of the other agents were shown to be effective.

* Adapted from reference 4. DHE = dihydroergotamine; NSAID = nonsteroidal anti-inflammatory drug.
† Currently not available in the United States.