

Diagnosis and Management of Migraine Headaches

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Abstract: Migraine headaches afflict approximately 6% of men and 18% of women in the United States, and cost billions of dollars each year in lost productivity, absenteeism, and direct medical expenditures. Despite its prevalence and the availability of therapeutic options, many patients do not seek treatment, and among those who do, a significant portion are misdiagnosed. Correct diagnosis can be made by identifying the historic and physical examination findings that distinguish primary headache disorders from secondary headache disorders, as well as the key clinical features that distinguish migraine headaches from other types. Once diagnosis is made, improper or inadequate management of headache pain, related symptoms such as nausea, and the possible aggravating side-effects of pharmacologic therapies represent further obstacles to effective therapy. Dissatisfaction with migraine therapy on the basis of these factors is common. Among abortive therapy options there are delivery methods available which may avoid aggravating symptoms such as nausea. Recommended pharmacologic agents include nonsteroidal anti-inflammatory drugs, intranasal butorphanol, ergotamine and its derivatives, and the triptans. Indications for prophylactic in addition to abortive therapy include the occurrence of headaches that require abortive therapy more than twice a week, that do not respond well to abortive therapy, and which are particularly severe. Research is ongoing in the pathophysiology of migraines, evaluation of nonpharmacologic treatment modalities, assessment of new drug therapies, and validation of headache guidelines.

Key Words: migraine headaches, diagnosis, therapy

Case Presentation

Ms. P is a 27-year-old woman who presents to you with a chief complaint of headaches. She has had head-

aches for about 10 years, but the headaches are more frequent and more disabling now than in the past, occurring at least 4 to 5 times each month. Ms. P is otherwise healthy and has no significant medical history, including no prior pregnancies. She drinks a few glasses of wine each week. She does not use tobacco or illicit drugs. Her current medications are ibuprofen, naproxen, aspirin, and acetaminophen. Her physical examination is completely within normal limits.

Scope of the Problem

Headaches account for approximately 10 million physician visits each year.¹ A provider's first priority when seeing a headache patient is to determine whether the patient is presenting with a primary headache disorder or a secondary headache disorder. Primary headache disorders include migraine headaches, tension-type headaches, and cluster headaches. Secondary headaches are those that are attributed to an underlying condition such as infection, trauma, vascular disorders, or structural lesions.

Migraine headaches alone afflict approximately 6% of

Key Points

- Migraine headaches are responsible for millions of physician visits each year.
- Primary headache disorders can often be distinguished from secondary headache disorders by historic and physical examination findings.
- Migraine headaches can sometimes be distinguished from tension-type and cluster headaches by duration, frequency, severity, and quality of pain.
- Nonsteroidal anti-inflammatory drugs, intranasal butorphanol, ergotamine and its derivatives, and the triptans are the recommended agents for abortive treatment of acute migraines.
- Patients who require more than two abortive migraine treatments each week, do not respond well to abortive therapy, and who have particularly severe headaches, should be considered for prophylactic migraine therapy.

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men and 18% of women in the United States.^{2,3} The annual cost of absenteeism and lost productivity from migraine headaches is \$13 billion dollars in the United States, and the annual direct medical cost of caring for people with migraines in the United States has been estimated at \$1 billion.³ A recent epidemiologic study in the Netherlands concluded that migraineurs had compromised physical, mental, and social functioning when compared with nonmigraineurs.⁴ The World Health Organization considers migraines to be one of the top 20 most disabling diseases worldwide.⁵

Despite the high prevalence, the large economic burden, and the significant disability caused by migraines, many patients do not seek regular medical care for their recurrent headaches. In fact, fewer than 50% of migraineurs in the United States have consulted a physician in the past year.⁶ When patients do seek medical consultation for their migraine headaches, fewer than 75% are correctly diagnosed.² Other studies have found that the correct diagnosis has been made less than 40% of the time.² Only four in 10 migraineurs use prescription medication for the treatment of their migraines,⁷ and fewer than half of migraineurs are satisfied with their current treatment.⁸

A systematic approach to a patient presenting with headache, and familiarity with treatment options will enable the primary care provider to accurately diagnose and manage migraine headaches.

Discussion

What are the historic and physical examination findings that distinguish primary headache disorders from secondary headache disorders?

Although more than 90% of patients who present with headaches will have a primary headache disorder,⁹ the physician must always be on the alert for a possible underlying disease process. The distinction between primary and secondary headaches can often be made on the basis of a focused history and physical examination. Some of the historic features that suggest a possible secondary cause of headache include the “first” or “worst” headache; the new onset of headaches over the age of 40 years; focal neurologic findings; a history of head trauma; and signs of infection. The physical examination should include a thorough neurologic examination and should also focus on areas of the body that are relevant to headache provocation, such as the head and neck examination. Table 1 provides a more complete list of characteristics that can be used to distinguish primary and secondary causes of headache.

The International Headache Society classification system for headaches, developed in 1988 and revised in 2003, allows clinicians to diagnose patients as having both primary and secondary headache diagnoses when “a pre-existing primary headache is made worse in close temporal relation to another

History and examination findings suggestive of secondary headache disorder

- | | |
|--|-------------------------------------|
| ● First or worst headache ever | ● Immunocompromised host |
| ● Maximum pain at onset | ● Presence of underlying malignancy |
| ● Increase in frequency and severity of usual headaches | ● History of head trauma |
| ● Age greater than 40 yr old | ● Signs of infection |
| ● Increase in head pain with coughing, sneezing, straining | ● Papilledema |
| ● Increase in head pain with exercise | ● Changes in mental status |
| ● Wakes patient from sleep or otherwise disturbs sleep | ● Ataxia |
| | ● Uncoordinated or weak limbs |

References 9, 13, 14.

disorder that is a known cause of headache.”⁵ The presence of signs and symptoms of secondary headaches in whatever context, however, is an indication for further patient evaluation, and providers should obtain appropriate blood work and imaging studies.

From the history and physical examination findings given to us so far, Ms. P appears to have one of the primary headache disorders. Her history of increasing frequency and severity of headache pain, however, needs to be further explored.

Ms. P describes her headaches as a nonthrobbing pain on the left side of her head. The pain can last anywhere from about 8 hours to 2 days, can start at any time of day, and does not wake her up from sleep. She never has a warning of a pending headache such as floaters or odd smells. The headaches are accompanied by nausea and by sensitivity to light and noise but only rarely by vomiting and even more rarely by some blurry vision. Sometimes when Ms. P has a headache, she is able to maintain some or all of her activities, but a few times each month she must lie very still in a quiet, dark room. During these severe attacks, even the slightest movement can cause her headache pain to worsen.

Ms. P has been having similar headaches for about 10 years. Several years ago, Ms. P saw a doctor and was diagnosed as having “vascular headaches.” She usually gets her very painful headaches 2 to 3 times each month, but over the years she has noted that she has times when the headaches occur at about twice that frequency. She is in such an accelerated period now.

What are the clinical features that distinguish migraine headaches from other primary headache disorders?

Migraine headaches, tension-type headaches, cluster headaches, and “other primary headaches” are the four broad categories of primary headache disorders named in the revised International Headache Society guidelines.⁵ Table 2

Table 2. International Headache Society 2003 Revised Diagnostic Criteria for Migraines

Migraine without aura*	Migraine with aura
A. At least five attacks fulfilling criteria B–D B. Headache lasts 4–72 h C. Headache has at least two of the following characteristics a. Unilateral site b. Pulsating quality c. Moderate or severe intensity d. Aggravation by or causing avoidance of routine physical activity D. During headache, at least one of the following a. Nausea and/or vomiting b. Photophobia or phonophobia *Code chronic migraine without aura when attacks occur for ≥ 5 d/mo for ≥ 3 mo	A. At least two attacks fulfilling criteria B–D B. Aura consisting of at least one of the following, but no motor weakness a. Fully reversible visual symptoms b. Fully reversible sensory symptoms c. Fully reversible dysphasic speech disturbance C. At least two of the following: a. Homonymous visual symptoms and/or lateral sensory symptoms b. At least one aura symptom develops gradually over at least 5 min and/or different aura symptoms occur in succession for at least 5 min D. Headache fulfilling migraine criteria begins during the aura or follows aura within 60 min E. Not attributed to another disorder

Reference 5.

lists the diagnostic criteria for migraine without aura (previously known as common migraine) and for migraine with aura (previously known as classic migraines). The primary cause of migraine headaches is currently thought to be a central nervous system event and not a vascular event.⁶ Thus, the term “vascular headache” should no longer be used in classifying headaches.

“Aura” refers to the transient neurologic symptoms that may precede or even accompany a migraine headache. More than 60% of patients with migraine have migraine headaches without aura.¹⁰ There is, however, a great deal of clinical variation, not only between individuals who have migraines, but also between attacks had by one individual. More than 10% of migraineurs have migraines both with and without aura.¹⁰ Hemisensory loss and hemiparesis may occur with migraines, as can diplopia, blurry vision, scotomas, vertigo, ataxia, and other neurologic events.⁹ In some patients, the associated symptoms of nausea, vomiting, photophobia, and phonophobia may be more disabling than the headache pain.¹¹ Twenty-five percent of migraineurs have fewer than 5 headaches each month, whereas 25% have more than 24 headaches each year.¹⁰

Despite this variability, migraines can sometimes be distinguished from tension-type and cluster headaches by the duration, frequency, location, severity, and quality of pain. Tension headaches, for example, typically last from 30 minutes to 7 days, whereas cluster headaches typically resolve within 3 hours. The duration of migraine pain is typically 4 to 72 hours.⁵ The associated migraine features such as photophobia, phonophobia, nausea, and vomiting are the most important way of distinguishing migraines from tension-type headaches.^{5,12}

There can, of course, be overlap in the clinical presentations of the different headache types, particularly between migraines and tension-type headaches. Some experts argue that tension-type headaches and migraines are variations on one type of headache.¹² Other authors suggest that any recurrent, severe headache should be considered a migraine and will likely

respond to antimigraine therapy.⁶ Table 3 outlines some of the distinguishing features of each type of primary headache.

When Ms. P last saw a physician for her headaches, she was encouraged to use acetaminophen, ibuprofen, and caffeine for her symptoms. She was also given a prescription for oxycodone to use whenever her head pain was severe. Ms. P reports that she did not like the increased lethargy and nausea associated with the use of the oxycodone. She has been using over-the-counter remedies about 2 to 4 times each week with varying success, responding more to naproxen and ibuprofen than to acetaminophen. These medications, however, take too long to provide relief of headache pain and seem to aggravate her nausea. In addition, Ms. P’s headaches cause her to miss 4 to 5 days of work as a teacher each month, and she and her school principal are becoming increasingly frustrated with her absenteeism.

Patients with migraine are often reluctant to seek medical care.⁶ Patients may avoid medical consultation for a multitude of reasons, including satisfaction with current remedies, the perception that symptoms are not severe enough to warrant a consultation, prior misdiagnosis, side effects of previously prescribed treatments, and a belief that there are no available treatment options.^{2,7,8,13–16}

Understanding the impact that migraine headaches and migraine therapies have on a patient’s life is necessary to successfully treat migraineurs. Many migraine severity indexes have been developed to allow the hurried provider to gain an understanding of the functional and emotional impact of the headaches on the patient’s daily life.^{5,13,17} Having the patient keep a headache diary (sample available at www.headaches.org) can also help to better inform both the patient and the physician about the duration and frequency of symptoms, possible headache triggers, and responses to any therapeutic interventions.

Table 3. Clinical features of primary headache disorders

Headache disorder	Typical patient	Pain and associated symptoms	Duration	Severity	Frequency
Migraine	Incidence peaks in early to mid-adolescence but can occur in all ages. Rarely starts after age 40. Prevalence in males and females is the same in children, but there is a female preponderance after adolescence; two-thirds have a family history of migraines.	Unilateral, pulsating. Accompanied by nausea, vomiting, photophobia, phonophobia, and/or transient neurological symptoms.	4–72 h	Moderate to severe (prohibits usual activity)	Intermittent, episodic, or chronic
Tension type	All ages. Female preponderance.	Nondescript, bilateral tightening or band-like sensation. No associated symptoms.	30 mins to 7 d	Mild to moderate	Intermittent, episodic, or chronic
Cluster	Highest prevalence in age 30–50 yr but present in all ages above 10 yr; 90% of patients are male.	Unilateral, in orbital or temporal areas. Described as “burning” or “stabbing.” Associated with ipsilateral lacrimation, nasal drainage, lid drooping, and pupillary changes.	15 min to 3 h	Severe	Cyclical. Occurs up to 8 times daily for weeks or months and sometimes for years.

References 5, 9, 12

Ms. P was dissatisfied with her original prescription for oxycodone because of intolerable side effects. She is not getting adequate relief with her current pain medication regimen. The provider needs to address the patient’s dissatisfaction with her previous therapy and her goals for therapy before prescribing further interventions. As noted earlier, dissatisfaction with migraine therapy is common. Less than 50% of migraineurs are pain free at 2 hours after they take their medication, and fewer than 30% are pain free at 24 hours.¹⁸ Patients rate the degree of headache relief, how quickly that relief starts, and concerns about medication side effects as the most important factors in their choice of migraine therapy.¹⁵

You and Ms. P talk about her new diagnosis of migraines, the impact her headaches are having on her life, and her goals for treatment. She cannot identify provoking factors such as the start of her menses, alcohol intake, caffeine intake, or consumption of particular foods. Despite her absences from work, Ms. P would rather not take “too many” pills. She wants to know if there are any migraine treatments that do not involve medications.

What are the effective nonpharmacologic interventions for migraine treatment?

Migraine therapy can be divided into nonpharmacologic interventions, acute therapy for individual attacks (abortive therapy), and preventive (prophylactic) treatment. Many non-

pharmacologic interventions have been tried for both acute and preventive treatment of migraine headaches, including biofeedback, acupuncture, transcutaneous electrical nerve stimulation (TENS), cognitive behavioral therapy, and relaxation training. One simple intervention is for the patient to identify and avoid potential headache triggers, but this behavior does not always yield satisfactory results, as the brain responds variably to exposures over time. Patients should also try to adhere to a consistent schedule because irregular meals and sleep, variation in exercise routines, and stress are thought to be common migraine triggers.^{6,19}

In 2000, the US Headache Consortium, a multidisciplinary group made up of seven member organizations,¹ published evidence-based guidelines for the diagnosis and management of migraine headaches. In this review, the group concluded that relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive behavioral therapy are effective treatment options for migraine prevention. Some of these therapies may also be used as adjunctive treatment with prophylactic medication. There is not yet enough evidence available to make conclusions on the efficacy of hypnosis, acupuncture, transcutaneous electrical nerve stimulation, cervical manipulation, occlusal adjustment, and hyperbaric oxygen as preventive or acute therapies for migraine.¹

What are the effective medications for treating acute migraine attacks?

The US Headache Consortium, based on expert opinion, recommends that the clinician who is prescribing acute migraine therapy¹

(1) Educate patients about migraines so as to empower them to take an active role in the management of this disease;

(2) Individualize therapy for each patient, based on severity and frequency of headaches as well as prior responses to medications for a migraine attack;

(3) Use migraine-specific agents for the treatment of patients with more severe migraine, and in patients whose migraine headaches respond poorly to nonsteroidal anti-inflammatory drugs (NSAIDs) and combination analgesics. Give medications promptly at the start of a migraine attack;

(4) Prescribe medications with a nonoral route of administration for patients who have nausea and vomiting early in their migraine attacks;

(5) Supply a medication the patient can use at home when other medications are not working well (a "rescue medication"); and

(6) Limit acute therapy for headaches so as to avoid medication-overuse headaches.

Acute pharmacologic interventions that have been used to treat migraines most commonly include antiemetics, barbiturate hypnotics, ergot alkaloids and derivatives, NSAIDs, combination analgesics, nonopiate analgesics, opiates, and the 5HT_{1B/D} serotonin receptor agonists (the triptans). The US Headache Consortium guidelines and more recent guidelines published by the American Academy of Family Physicians (AAFP) and the American College of Physicians–American Society of Internal Medicine (ACP-ASIM) both recommend NSAIDs as first-line agents for the treatment of migraine headaches because of their proven efficacy and safety.^{1,19} Aspirin, ibuprofen, and naproxen are the three NSAIDs available in the United States that have the most consistent evidence to support their use as abortive therapy. Acetaminophen alone has not been shown to provide adequate pain relief for migraineurs but was efficacious when used in combination with aspirin and caffeine.^{1,19,20}

Neither of the above guidelines endorses the use of opiates in routine headache management because of the possible side effects and addictive potential of these nonspecific analgesics. The US Headache Consortium, however, does make an exception for butorphanol nasal spray and recommends this agent when other abortive therapies fail.^{1,19} Both guidelines also suggest the use of opiates or butalbital-containing compounds for use as "rescue agents." Having such a medication at home that the patient can self-administer when his usual medications fail to relieve his pain can obviate the need for a trip to the emergency room or to a physician's office.^{1,19}

The ergotamines and the triptans, unlike NSAIDs and opiates, are considered to be migraine-specific medications. They are not analgesics but are thought instead to block the underlying mechanism of migraine headaches. As stated above, the primary cause of migraine headaches is currently thought to be a central nervous system event.^{6,18} A primary disorder in the brain is believed to cause a neural event, such

as changes in neurotransmitter levels, which in turn causes dilation of cerebral blood vessels. The change in vascular tone causes headache pain. The pain stimulates more neural events, and the cycle perpetuates itself.⁶

Both ergotamines and triptans act as 5HT_{1B/D} serotonin receptor agonists, thereby affecting the neural events leading to neurotransmitter release, to cerebral vasodilatation, and to head pain.^{6,13} Ergotamines are inexpensive medications and have been used as migraine therapy for many years. This class of drugs can be given to the patient intravenously, intramuscularly, subcutaneously, orally, rectally, or nasally. Ergotamines are less specific than the triptans because they also act on other 5HT receptors, adrenergic receptors, and dopaminergic receptors.¹³ They have erratic pharmacokinetics.⁶ All of the ergot derivatives cause nausea and vomiting, and the nasal spray can cause mild-to-moderate rhinitis.¹⁹ These medications can cause prolonged vasoconstriction and are thus contraindicated in patients with uncontrolled hypertension, coronary artery disease, cerebrovascular disease, or peripheral vascular disease.¹²

Perhaps the greatest concern regarding the ergot derivatives is that the evidence-based literature reviewed by the US Headache Consortium did not consistently show that these medications were efficacious.¹ Nasal dihydroergotamine (DHE) was the only ergot derivative with enough relevant, well-designed studies to support its use.¹ Various other forms of ergot derivatives did not have enough relevant or consistent evidence to support their use as first-line agents in the therapy of migraines.¹ The AAFP/ACP-ASIM guidelines do not recommend any ergot derivatives as first line agents, and only recommend the DHE nasal spray as a second choice agent after NSAIDs.¹⁹

The triptans, like the ergotamines, can cause vasoconstriction²⁰ and are contraindicated in patients with ischemic heart disease, uncontrolled hypertension, or stroke.²¹ Common triptan side effects also include tingling, paresthesias, dizziness, flushing, and chest symptoms.⁴ The medications in this class are all more expensive than the ergot derivatives. The triptans, nonetheless, have several advantages, including their selective pharmacology, their simple and reliable pharmacokinetics, their proven efficacy, and their tolerability.⁶ The seven available triptans are made in a wide range of formulations, including subcutaneous injections, oral tablets, orally dissolving tablets, nasal sprays, and rectal suppositories.

The differences between the triptans are subtle, and more clinical experience with their use is needed before one can be recommended over another.^{22–24} Nonetheless, a rational choice of a particular triptan takes into account the route of administration, the speed of onset of the symptoms, the typical length of symptoms, and the way in which each drug is metabolized. Table 4 lists all the recommended abortive migraine therapies, and Table 5 compares many of the salient features of the triptans.

Although both the US Headache Consortium guidelines

Table 4. Recommended acute therapies for migraine attacks available in the United States

NSAIDs

- Aspirin
- Ibuprofen
- Naproxen sodium
- Acetaminophen + aspirin + caffeine

Opiates/barbiturate hypnotics

- Intranasal butorphanol
- Other opiates and butalbital-containing compounds may be considered for use as “rescue medications”

Ergotamine and derivatives

- DHE nasal spray
- SC/IM/IV DHE
- IV DHE and antiemetic

Triptans

- Almotriptan (tablets)
- Eletriptan (tablets)
- Frovatriptan (tablets)
- Naratriptan (tablets)
- Rizatriptan (tablets, orally disintegrating tablets)
- Sumatriptan (tablets, nasal spray, subcutaneous injections, suppositories)
- Zolmitriptan (tablets, nasal spray, orally disintegrating tablets)

NSAIDs, nonsteroidal anti-inflammatory drugs; DHE, dihydroergotamine.

References 1 and 19.

and the AAFP/ACP-ASIM guidelines recommend NSAIDs, ergotamine derivatives, and the triptans for treating acute migraines, there is controversy in the literature about how to actually use these drugs. In the absence of good evidence to guide practitioners, some experts advocate the “striated care” model, whereas others advocate the “step care” model.^{1,13,19} In the striated care model, patients assess the severity of their attack and choose an appropriate agent for that particular attack. They may stratify one headache as mild and start with NSAIDs; they may stratify another headache as severe and begin initially with a triptan or other migraine-specific agents.^{13,19} The striated care model is recommended in the US Consortium guidelines.¹ The AAFP/ACP-ASIM advocates the step care model, in which all patients initially try NSAIDs as first-line therapy to abort an attack of any severity.¹⁹ If this therapy fails, a second, more specific migraine medication is used. Comparison studies of these two strategies are underway.¹⁹

Ms. P has already failed NSAIDs and has come to you looking for more effective medications. After a thorough discussion with the patient, you decide to prescribe an injectable sumatriptan for her.

The patient returns to see you 3 months later. She is using her medication 2 to 4 times each week and gets

quick relief of her head pain, but she is growing tired of giving herself so many injections. She complains that her headache pain returns about 4 or 5 hours after she takes her medication. She is also having mild daily headaches that do not interfere with her activities but which are irritating to her.

What are recurrent and rebound headaches?

Ms. P gets quick relief of her headache pain at 2 hours after taking medication, but her pain often returns several hours later. Recurrent headaches are defined as moderate to severe headaches that occur within 24 hours of initial headache relief.²³ Recurrent headaches have been noted with all short-acting migraine medications but have received more attention since the introduction of the triptans.²³ The longer the half-life of a triptan, and perhaps the greater its potency at 5HT_{1B} receptors, the lower the incidence of recurrent headaches.²³ Frovatriptan has the longest half-life of the triptans and may be the best triptan to use to avoid recurrent headaches.^{22,23}

Ms. P’s case also introduces us to the concept of medication-overuse headaches. Medication-overuse headaches are refractory, daily, or near-daily headaches that occur when fast-acting analgesics are used regularly to manage headache pain. Some sources¹ use this term interchangeably with the term “rebound HA,” whereas other sources define rebound headaches as a result of analgesic withdrawal.¹⁹ Despite the dispute in the literature about the use of the terms rebound and medication-overuse HA, it is clear that the use of many of the short-acting analgesics more than 2 to 3 times each week can worsen primary headaches. Ergotamines, triptans, NSAIDs, opiates, aspirin, and acetaminophen are all capable of causing these difficult-to-diagnose and difficult-to-manage headaches.^{1,25,26} All recommended acute headache treatments should be prescribed with the risk of rebound headaches in mind, and preventive therapy should be considered when headaches are requiring more than 2 days of treatment each week.¹ Although Ms. P does not clearly suffer from medication overuse or rebound headaches, her use of sumatriptan several times each week may be the cause of her new daily headaches.

What are the indications for migraine prophylactic therapy?

As noted above, when patients require more than two abortive migraine treatments each week, the provider should consider offering therapy to prevent the migraines from occurring. This recommendation is made to avoid possible medication-overuse headaches, to reduce the frequency and severity of migraine attacks, and to help make the patient as functional as possible. Other indications for prophylactic migraine therapy include recurring migraines that interfere with a patient’s daily activities, two or more headaches each month

Table 5. Comparison of triptans

Triptan	Time to maximal concentration (h)	Half-life (h)	Metabolism and excretion	Characteristics
Almotriptan	1.5–2	3	MAO and CYP450	Better side effect profile
Eletriptan	1–1.5	4	CYP3A4	Clear dose-response curve
Frovatriptan	2–3	25	50% Renal	Longest half-life
Naratriptan	2–3	6	70% Renal and CYP450	Slower onset of action; lower recurrence rate
Rizatriptan	1–1.5	2	MAO	Fastest time to headache response of oral tablets; highest 2-h pain free rates
Sumatriptan	2–3	2	MAO	Greatest number of formulations available; longest experience with its use
Zolmitriptan	1.5–2	3	CYP450 and MAO	Only triptan proved effective when repeated for headache recurrence

MAO, monoamine oxidase; CYP450, cytochrome 450; CYP3A4, the 3A4 isoform of cytochrome P450.

References 7, 13, 22–24.

not responding to abortive therapy, and contraindications to, or adverse effects from, acute therapy. Patient preference and the cost of acute and chronic therapies should also be considered.¹ Finally, the presence of uncommon migraine conditions such as hemiplegic or basilar migraines is an indication for prophylaxis to reduce the risk of neurologic damage from these conditions.¹ Indications for preventive therapy are listed in Table 6.

What are the effective medications for preventing migraine headaches?

The US Headache Consortium evaluated nine classes of medications used for migraine prophylaxis: α -2 agonists, anticonvulsants, antidepressants, β -blockers, calcium channel blockers, NSAIDs, serotonergic agents, hormonal therapy, and “other” (feverfew, minerals, vitamins). After reviewing the evidence-based literature, the Consortium divided more than 60 individual medications into 5 groups. Group 1 consists of the currently available agents that were found to have medium to high efficacy with mild or infrequent side effects: amitriptyline, divalproex sodium, propranolol, timolol, and lisuride (not available in the United States).¹ The AAFP/

Table 6. Indications for prophylactic therapy

- Recurring migraines interfering with patient’s daily activities
- Two headaches each week requiring medication
- Two or more headaches each month not responding to abortive therapy
- Patient preference
- Contraindications to or adverse effects from acute therapy
- Cost of acute and chronic therapies
- Presence of uncommon migraine conditions such as hemiplegic or basilar migraines (expert consensus—to reduce risk of neurological damage)

Reference 1.

ACP-ASIM adds sodium valproate to this list of efficacious and well-tolerated prophylactic medications.¹⁹ Table 7 lists these group 1 agents.^{1,19}

The Consortium divided the other prophylactic medications into four groups. These medications are those with less efficacy, with more potential side effects, and/or with less evidence to support their use. A complete list of these four groups of medications is available on the American Academy of Neurology website.¹ Neither the US Headache Consortium nor the ACP-ASIM specifies how to treat a patient already taking one of the medications listed in groups 2, 3, 4, or 5.^{1,19} If a migraineur has had a good response to one of these agents and is not having adverse reactions, my opinion is that the agent should be continued until the clinical situation changes. Migraineurs who meet indications for prophylactic therapy and who have yet to be started on preventive agents should be started on one of the medications in group 1.

Since the US Headache Consortium review was conducted, several newer medications have shown promising results in the prevention of migraine attacks. Large, placebo-controlled trials are now being done with topiramate, a structurally unique antiepileptic medication found to be useful in preventing migraines in small, short-term studies.²⁷

Table 7. Prophylactic migraine therapy: Recommended medications, currently available in the United States, with medium to high efficacy and mild or infrequent side effects

- Amitriptyline (30–150 mg/d)
- Divalproex sodium (500–1500 mg/d)
- Sodium valproate (800–1500 mg/d)
- Propranolol (80–240 mg/d)
- Timolol (20–30 mg/d)

References 1 and 19.

Pericranial injections of botulinum toxin type A have been evaluated in the prevention of moderate-to-severe migraine headaches and again show promising results.^{27,28} The optimal dose and injection site are unknown, and further trials are underway to assess these issues as well as the side effect profile and the efficacy of botulinum toxin type A in migraine prevention.^{27,28} Candesartan was shown to be a well-tolerated and efficacious preventive medication in a 12-week, double-blinded, placebo-controlled, crossover trial involving 60 randomly assigned patients.²⁹ Again, further studies are in progress, and no recommendations can be made currently for the use of angiotensin II receptor blockers as migraine prophylaxis.

The provider should start the prophylactic medication at the lowest effective dose and titrate it until there is symptomatic relief or the development of adverse effects. No matter which agent is selected, the patient must be prepared to give that medication an adequate trial as clinical benefit may not be apparent for 2 to 3 months. Patients should also have reasonable expectations. Most clinical trials showing efficacy of prophylactic medications used 50% reduction in migraine frequency as their end point; patients probably will still need to use abortive therapy for their ongoing headaches.¹

Conclusion

In conclusion, migraine headache disorder is a debilitating chronic disease that significantly impairs individuals, and that affects society. Migraines, however, are often misdiagnosed and inadequately treated. Research is ongoing in the pathophysiology of migraines, evaluation of nonpharmacologic treatment modalities, assessment of new drug therapies, and validation of headache guidelines. Currently, a primary care physician can use the strategy reviewed above to accurately diagnose patients, to educate patients, and to provide effective abortive and prophylactic migraine therapy.

References

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3. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States. *Arch Intern Med*. 1999;159:813–818. An often-quoted study that helped to identify the huge economic burden of migraines.
4. Terwindt GM, Ferrari MD, Tijhuis M, et al. The impact of migraine on quality of life in the general population: the GEM study. *Neurology* 2000;55:624–629. A cross-sectional study designed to assess the impact of headaches on migraineurs was done in the context of a population-based study in the Netherlands.
5. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders, 2nd edition. *Cephalgia* 2004;24(Suppl 1). In 1988, the International Headache Society (IHS) introduced its original classification system. This system has greatly influenced the headache research community and, to a lesser extent, practicing clinicians. The guidelines have been criticized for their failure to recognize the possibility of the coexistence of multiple headache diagnoses, to fully classify medication-overuse headaches, and to adequately discuss chronic daily headaches. Revised guidelines were released in September 2003 and attempt to address these and other concerns. These guidelines are currently available only on-line at www.ihs.org; they can be read and downloaded, but not printed.
6. Wood AJJ. Migraine: current understanding and therapy. *N Engl J Med* 2002;346:257–270. This article is a very useful review of migraine diagnosis and treatment, and is particularly useful for its brief summary of migraine pathophysiology.
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8. MacGregor EA, Brandes J, Eikermann A. Migraine prevalence and treatment patterns: the global migraine and zolmitriptan evaluation survey. *Headache* 2003;43:19–26. This pharmaceutical company-sponsored survey looked at the epidemiology of migraines and patterns of health care use in migraineurs in France, Germany, Italy, the United Kingdom, and the United States.
9. Saper JR. Headache disorders. *Med Clin North Am* 1999;83:663–689. This review is a very useful summary of the different primary headache disorders and the pathogenesis of migraines, and is written by one of the experts in migraine headaches.
10. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. *Neurology* 1999;53:537–542. This article looks at the epidemiology of migraines in the Dutch population. This is same study as noted above in Reference 4.
11. Cutrer FM. Migraine: does one size fit all? *Curr Opin Neurol* 2003;16:315–317. This editorial review provides a useful summary of the clinical variation seen in migraine attacks and in the responses of migraines to therapy.
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13. Cady RC, Dodick DW. Diagnosis and treatment of migraine. *Mayo Clin Proc* 2002;77:255–261. This paper is another useful review article, and is particularly helpful in clarifying different models of care for migraines.
14. Lipton RB, Silberstein SD, Saper JR, et al. Why headache treatment fails. *Neurology* 2003;60:1064–1070. Three experts in migraine headaches summarize and clarify the five main reasons why primary care physicians do not always successfully treat headache disorders.
15. Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. *Headache* 2003;43:36–43. This study, supported by the International Headache Foundation and a pharmaceutical company, surveyed 1,160 migraineurs (from a larger sample of 4,000 adults) about their use of prescription migraine medications.
16. Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. *Neurology* 2003;60:

- 441–448. A computer-assisted telephone survey, the same one used in the study cited in Reference 2, examined patterns of migraine diagnosis and treatment in two countries.
17. Maizels M, Burchette R. Rapid and sensitive paradigm for screening patients with headache in primary care settings. *Headache* 2003;43:441–450. This paper is an attempt to clarify the sensitivity and specificity of a primary care screening tool developed by the author.
 18. Ashkenazi A, Silberstein S. The evolving management of migraine. *Curr Opin Neurol* 2003;16:341–355. This article is a current review of selected medications for both acute migraine attacks and migraine prophylaxis.
 19. Snow V, Weiss K, Wall EM, et al. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med* 2002;137:840–849. This paper is a very user-friendly guide to both acute and prophylactic pharmacologic management of migraines. This practice guideline clearly indicates when its recommendations conflict with those of the US Headache Consortium. It provides a useful summary of the US Headache Consortium's evidence on the topics of pharmacologic management and a comprehensive reference list.
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 24. Dahlof C. Integrating the triptans into clinical practice. *Curr Opin Neurol* 2002;15:317–322. This paper is the most user-friendly of the triptan review articles. It also reviews some of the common gastrointestinal side effects caused by the oral triptan formulations.
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Reality is merely an illusion, albeit a very persistent one.

—Albert Einstein