REVIEW

LISA K. MANNIX, MD*
Headache specialist,
Cincinnati, Ohio

Relieving migraine pain: Sorting through the options

ABSTRACT

Although triptans are a major advance in the treatment of migraine, the optimal approach for acute treatment involves a combination of lifestyle modifications, nonpharmacologic symptom relief, and drug therapy.

KEY POINTS

Patients should be alert to early symptoms of a pending attack. Early drug treatment provides the best opportunity for complete pain relief and reduces the need for retreatment.

Treatment is based on the severity of the headaches, time to peak intensity, coexisting conditions, response to prior treatment, patient preferences, and other factors.

Patients with migraine should be encouraged to take an active role in managing their headaches by avoiding common triggers, making lifestyle changes, and taking their medication at the first sign of migraine pain.

For patients with mild migraine, nonspecific drug therapy (eg, nonprescription analgesics) may be sufficient.

Clinical differences among the triptans are small; they should be selected on the basis of scientific data, clinical experience, and patient preference.

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PHYSICIANS NOW HAVE AN ARRAY of migraine treatments available, including new drugs in convenient dosage forms. The key to effective treatment, however, is still a good working relationship between the physician and patient to tailor treatment to the severity and frequency of headaches.

Although therapy for migraine has advanced, patients often have unrealistic expectations and need to understand that instant pain relief and total headache prevention are usually not achievable.

DISTINGUISHING MIGRAINE FROM OTHER HEADACHES

The International Headache Society classifies headaches as primary or secondary. The most common types of primary (ie, benign) headaches are migraine, tension-type headache, and cluster headache; each has subtypes.[1]

Migraine, the most common cause of recurrent severe or disabling headache, is diagnosed on the basis of a clinical history of intermittent headache with autonomic, constitutional, and neurologic disturbances (TABLE 1).[1]

About 12% of the US population has migraine—7% of men and 18% of women.[2] The peak prevalence is in midlife in women and somewhat earlier in men.

Migraine has characteristic signs and symptoms that distinguish it from other types of headache (TABLE 2).[3,4] Migraine pain is usually unilateral and pulsating and varies in intensity from mild to incapacitating. Migraine pain typically is accompanied by neurologic signs and symptoms such as nausea, vomiting, photophobia, and phonophobia. Aura occurs in only 15% to 20% of people with migraine. The most common aura symptoms are visual distur-

TABLE 1

Diagnostic criteria for migraine

MIGRAINE WITHOUT AURA

At least five headache attacks that:
Last 4 to 72 hours if untreated or unsuccessfully treated
Have at least two of the following characteristics
- Unilateral location
- Pulsating quality
- Moderate to severe intensity
- Aggravated by walking up stairs or similar routine physical activity

Are accompanied by at least one of the following symptoms
- Nausea, vomiting, or both
- Photophobia and phonophobia

No evidence of related organic diseases

MIGRAINE WITH AURA

At least two attacks with at least three of the following characteristics:
One or more completely reversible aura symptoms that indicate focal cerebral cortical dysfunction, brain stem dysfunction, or both
At least one aura symptom develops gradually over more than 4 minutes or two or more symptoms occur in succession
No aura symptom lasts more than 60 minutes
Headache follows aura in less than 60 minutes
No evidence of related organic disease

ADAPTED FROM HEADACHE CLASSIFICATION COMMITTEE OF THE INTERNATIONAL HEADACHE SOCIETY. CLASSIFICATION AND DIAGNOSTIC CRITERIA FOR HEADACHE DISORDERS, CRANIAL NEURALGIAS AND FACIAL PAIN. CEPHALALGIA 1988; 8(SUPPL 7):1–96.

bances and paresthesias, which usually disappear within 60 minutes of onset and are followed by headache.

Tension-type headache, in contrast, is steady, bilateral, of modest intensity, and not associated with other significant symptoms.[5]

Cluster headache is usually severe, of shorter duration than migraine, and accompanied by nasal congestion and ptosis of the upper eyelid on the involved side.[6]

Chronic daily headache can develop in patients with a history of episodic migraine who report an increased frequency of migraine accompanied by a decreased frequency or severity of constitutional symptoms.[7] Most often, it results from overuse of analgesics.

Predisposing and precipitating factors

The onset, frequency, duration, and severity of migraine can be influenced by a variety of predisposing and precipitating factors (**TABLE 3**).[4,8] Identifying these factors helps establish the diagnosis and develop individualized management strategies.[9]

About 80% of patients with migraine have a family history of the disorder.[9] Other predisposing factors include psychologic and psychiatric disorders such as depression, anxiety, and sleep disturbances; neurologic disorders such as epilepsy and multiple sclerosis; a history of other types of headache; and a history of motion sickness beginning in childhood.

Patients should be screened for psychological and neurologic disorders. Preventive measures such as education, stress management, and lifestyle changes should be implemented if indicated.[3,10]

Complete prevention of migraine is not realistic

WHAT CAUSES MIGRAINE?

In migraine, trigeminovascular sensory nerves are activated, and neuropeptides that mediate vasodilation are subsequently released.[11,12] Local vasodilation of intracranial extracere-

TABLE 2

Headaches: Migraine, cluster, and episodic tension-type

FEATURE	MIGRAINE	CLUSTER	EPISODIC TENSION-TYPE
Predisposition by sex	Female (3:1)	Male (10:1)	Female (< 2:1)
Onset	Variable	During sleep	Variable
Location of pain	Usually unilateral	Behind or around one eye	Bilateral in band around head
Type of pain	Pulsating	Stabbing, boring	Nonpulsating
Duration if untreated	4–72 hours	15–90 minutes	30 minutes–7 hours
Frequency	Variable (1–2 attacks per year to 8 or more per month)	1–8 attacks per day for 3–16 weeks; completely remits for months to years	Variable (1–2 attacks per year to 3–4 attacks per week); chronic tension-type headache occurs more than 15 days per month
Associated signs and symptoms	Nausea, vomiting, photophobia, phonophobia, aura	Sweating, flushing, nasal congestion, ptosis, lacrimation, pupillary changes	No nausea, mild photophobia or phonophobia

ADAPTED FROM CUNNINGHAM SM. MIGRAINE: HELPING CLIENTS CHOOSE TREATMENT AND IDENTIFY TRIGGERS. BR J NURSING 1999; 8:1515–1523 AND DUBOSE CD, CUTLIP AC, CUTLIP WD. MIGRAINE AND OTHER HEADACHES: AN APPROACH TO DIAGNOSIS AND CLASSIFICATION. AM FAM PHYSICIAN 1995; 51:1498–1509.

bral blood vessels and stimulation of surrounding trigeminal sensory nerve pathways are the key mechanisms.

Activation of the trigeminovascular system results in transmission of nociceptive information to central neurons in the brain stem, which relay pain signals to higher centers where pain is perceived. Dysfunction of these brain stem nuclei and surrounding areas may play a critical role in migraine.[13]

TREATMENT GOALS: INSTANT RELIEF, TOTAL PREVENTION UNREALISTIC

In managing migraine, it is important to establish appropriate goals with the patient, who may have unrealistic expectations.

Pain relief. Patients expect pain relief within 30 minutes of taking an antimigraine medication,[14] but a more reasonable goal, at least with oral medications, is complete relief of pain and a return to normal function within 2 hours. With the new migraine-specific drugs, rapid and complete relief is possible.

Reduction of migraine frequency is another reasonable goal. Prophylactic medications such as amitriptyline, propranolol, or valproic acid may be indicated if migraines are frequent or significantly interfere with daily activities despite acute treatment. They also are a good alternative for patients who have contraindications to, do not respond to, or overuse acute therapies.[15]

It is unrealistic to expect to completely prevent migraines, because the disorder is chronic. Patients should be aware that even with preventive treatment, future migraines may occur and require acute treatment.

Patients want *no* pain, not *less* pain

PATIENT EDUCATION AND LIFESTYLE MODIFICATIONS

Physicians need to explain the chronic nature of migraine, the importance of lifestyle modifications, the treatment goals, and the therapeutic options.

A headache diary can help identify migraine triggers and gauge responses to lifestyle modifications and drug therapy.[3] The patient should record events and activ-

TABLE 3

Precipitating factors for migraine

Diet
- Tyramine (bananas, pods of broad beans, avocado, aged cheese, yogurt, sour cream, nuts)
- Phenylethylamine (chocolate, red wine)
- Sodium nitrite (food coloring, preservatives, processed meats and fish)
- Monosodium glutamate
- Alcohol
- Caffeine (including changes in daily intake)
- Artificial sweeteners

Lifestyle
- Excessive sleep, change of routine, fasting or dieting, stressful events, exertion, depression, fatigue, lack of sleep

Hormonal
- Menstruation, ovulation, perimenopause, estrogen replacement, oral contraceptives

Environmental
- Excessive sun, strong odors, loud noise, bright lights, smoke, glare from water or snow, flickering lights, computer monitors, weather changes, high altitude

Medications
- Antibiotics (trimethoprim-sulfamethoxazole, griseofulvin)
- Antihypertensives (nifedipine, captopril, atenolol, metoprolol, prazosin, reserpine)
- Histamine$_2$ blockers
- Nonsteroidal anti-inflammatory drugs
- Vasodilators

ADAPTED FROM DUBOSE CD, CUTLIP AC, CUTLIP WD. MIGRAINE AND OTHER HEADACHES: AN APPROACH TO DIAGNOSIS AND CLASSIFICATION AM FAM PHYSICIAN 1995; 51:1498–1509 AND LEWIS TA, SOLOMON GD.ADVANCES IN MIGRAINE MANAGEMENT. CLEVE CLIN J MED 1995; 62:148–155.

A headache diary can help identify migraine triggers

ities associated with the migraines, headache characteristics, and treatment responses.

Avoidance of triggers (TABLE 3) should be encouraged, but it is not always effective because patient responses to triggers are variable and many triggers are unavoidable.[16] The effects of migraine triggers can be additive, and exposure to combinations of triggers may cause migraine. Patients obsessed with identifying and avoiding individual triggers should be discouraged from inflating the importance of any one trigger.

Patients should stick to a regular schedule for sleeping and eating.

Stress management and relaxation techniques can help patients whose migraines are triggered by short-term episodes of stress and who may be experiencing significant stress due to concern about the effectiveness of migraine treatment and future attacks.

NONPHARMACOLOGIC SYMPTOM RELIEF

Nonpharmacologic interventions—locally applied heat or cold, massage, hot showers, and rest in a quiet, darkened room—may reduce pain and medication use in some patients.

Without intervention, most migraines resolve during sleep.[9]

Patients also may benefit from complementary or alternative therapies such as relaxation techniques, biofeedback, yoga, aromatherapy, acupuncture, spinal manipulation, and homeopathic remedies.

ACUTE DRUG THERAPY

The US Headache Consortium has developed guidelines for acute migraine treatment. Underlying principles are that patients should participate in their own management and that treatment should be individualized (TABLE 4).[17]

TABLE 4

Principles of acute migraine treatment

Educate patients about their condition and its treatment and encourage them to participate in their own treatment

Use migraine-specific agents (triptans, dihydroergotamine, ergotamine) in patients with more severe migraine and in those whose headaches respond poorly to nonsteroidal anti-inflammatory drugs or combination analgesics

Select a nonoral route of administration for patients whose migraines present early with nausea or vomiting as a significant component of the symptom complex

Consider a self-administered rescue medication for patients with severe migraine that does not respond well to other treatments

Guard against medication-overuse headache (rebound or drug-induced headache)

ADAPTED FROM MATCHAR DB, YOUNG WB, ROSENBERG JH, ET AL. EVIDENCE-BASED GUIDELINES FOR MIGRAINE HEADACHE IN THE PRIMARY CARE SETTING: PHARMACOLOGIC MANAGEMENT OF ACUTE ATTACKS. AVAILABLE AT WWW.AAN.COM/PROFESSIONALS/PRACTICE/PDFS/GL0087.PDF.

Patients should maintain a daily sleeping and eating schedule

Treatment is based on the severity of the headaches, time to peak intensity, comorbid and coexisting conditions, response to prior treatment, patient preferences, and other factors.[18] Patients prefer rapid and complete pain relief, no headache recurrence, and no adverse effects.[19]

Algorithmic and other approaches to the acute management of migraine have been developed (FIGURE 1). However, evidence to support a definitive algorithmic approach to acute migraine drug treatment is lacking.[17] Nonetheless, patients should be alert to early symptoms of a pending attack.[9] Early drug treatment provides the best opportunity for complete pain relief within 2 hours of dosing and reduces the need for retreatment.[20]

Published data on migraine drugs are a useful starting point but provide little basis for selecting a medication in individual patients. The optimal approach incorporates a combination of scientific evidence, clinical experience, and patient preferences.

Nonprescription drugs

Many patients use nonprescription medications for migraine pain. All nonprescription analgesics are potentially effective and have a wide safety margin.[21] These drugs are a reasonable first-line option in patients with mild or infrequent migraine attacks. However, those with moderate or severe migraine usually need more potent, migraine-specific prescription drugs.

Nonprescription analgesics widely marketed for treating headache include aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Aspirin alone generally is not recommended because it has limited efficacy and a high incidence of gastrointestinal toxicity.

Acetaminophen has only limited evidence supporting its efficacy in the acute treatment of migraine.[17]

Nonprescription NSAIDs have proved superior to placebo for migraines, but their beneficial effects were marginal or without clinical relevance in some studies.[22]

Combination nonprescription drugs are an option for patients with mild or moderate migraine or severe attacks that have not responded to NSAIDs or nonopiate analgesics.[17]

The nonprescription combination of acetaminophen, aspirin, and caffeine is safe, well tolerated, and significantly more effective than placebo in relieving migraine pain and nausea, photophobia, phonophobia, and functional disability in patients with moderate or severe migraine attacks who do not require bed rest.[23] Significant differences in pain relief between this combination and placebo have been observed as early as 30 minutes after dosing, and 59% of patients treated with the combination report mild or no pain at 2 hours.

Acute treatment of migraine

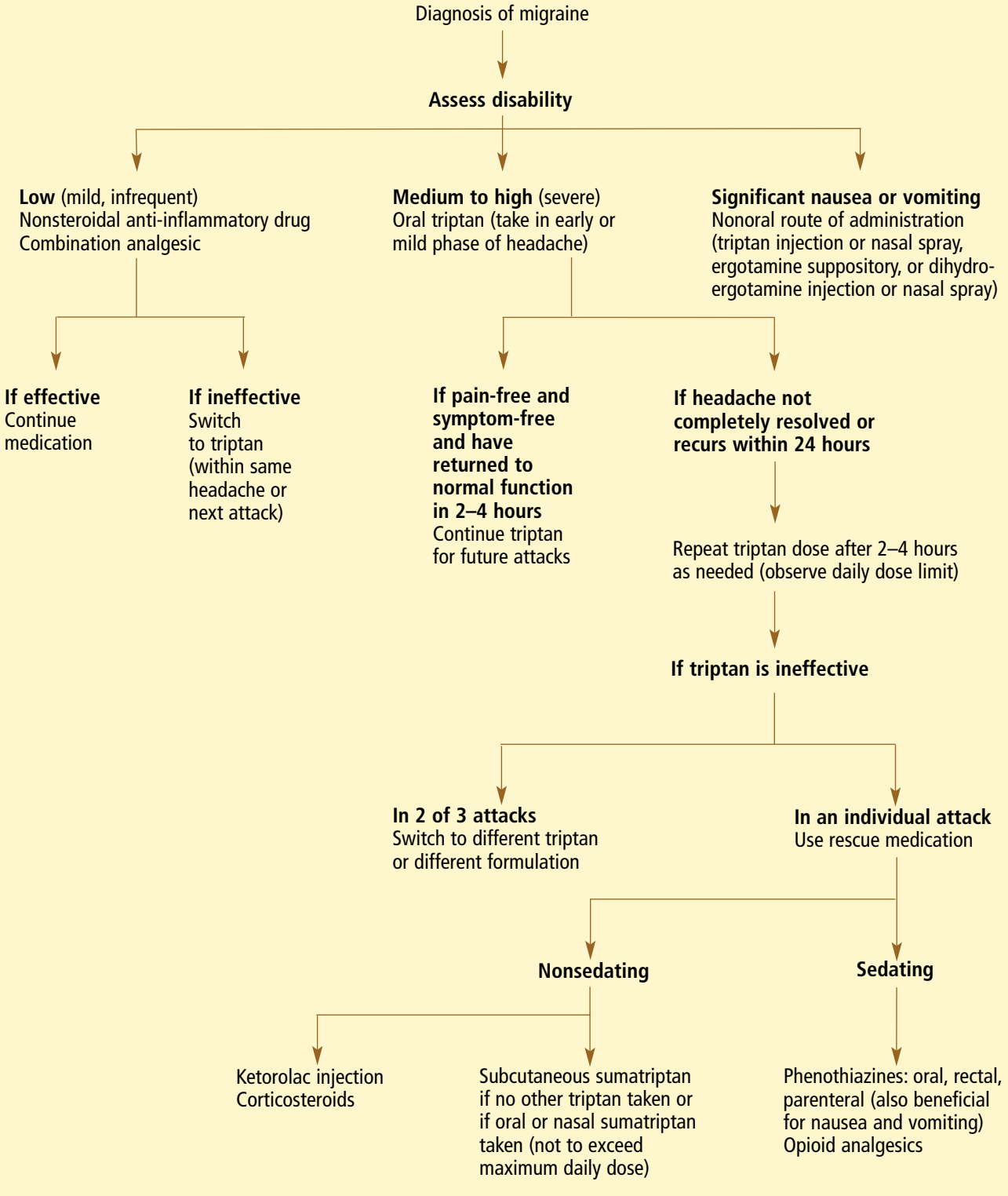

FIGURE 1

TABLE 5

Triptan efficacy at 2 hours after dosing

DRUG	% OF PATIENTS WITH PAIN RELIEF*	% OF PATIENTS PAIN-FREE
Sumatriptan (Imitrex)		
Subcutaneous (6-mg injection)	81–82[31]	67[38]
Oral (25-mg tablets)	52[32]	21[39]
Oral (50-mg tablets)	50–61[32]	16–32[39]
Oral (100-mg tablets)	56–62[32]	23[39]
Intranasal (nasal spray)	55–64[33]	42[38]
Zolmitriptan (Zomig)		
Oral (2.5-mg tablets)	62–65[34]	22–39[38]
Oral (2.5-mg wafers)	63[34]	No data
Oral (5-mg tablets)	59–67[34]	14–39[40]
Naratriptan† (Amerge)		
Oral (2.5-mg tablets)	No data[35]	No data[35]
Rizatriptan (Maxalt)		
Oral (10-mg tablets)	67–77[36]	40–44[38]
Oral (10-mg wafer)	66[36]	42[41]
Almotriptan (Axert)		
Oral (12.5-mg tablets)	57–65[37]	18[38]

*Pain relief is defined as a decrease in pain from moderate or severe to mild or none.
†In naratriptan clinical trials, pain relief was assessed at 4 hours, not 2 hours as in other triptan trials. Pain relief at 4 hours was reported by 60% to 66% of patients treated with naratriptan 2.5 mg. A pain-free state at 4 hours was reported by 33% of patients treated with naratriptan 2.5 mg.

Clinical differences among the triptans are small

Ergot alkaloids and derivatives

Ergotamine has been used for the acute treatment of migraine for more than 70 years, but there is little agreement on its place in clinical practice.

Ergotamine and dihydroergotamine are serotonin receptor agonists with vasoconstrictor and anti-inflammatory effects.[24]

Ergotamine has a prolonged half-life and should not be used more than once every 4 days or within 24 hours of any triptan. Regular use of ergotamine can lead to rebound headaches, ie, daily headaches that worsen when the drug is withdrawn.[8,24]

Ergotamine is available as an oral tablet, injection, sublingual formulation, and rectal suppository; dihydroergotamine is available as an injection and a nasal spray.[8] However, the commercial availability of all ergot formulations in the United States has been limited recently.

European researchers recently reviewed the preclinical and clinical data on ergotamine in the acute treatment of migraine. Their report states that ergotamine is the drug of choice for some patients who have infrequent or prolonged migraine and are likely to comply with dosing restrictions.[25] Patients who do well on ergotamine without dose escalation do not need to switch to an alternative agent.

The recommended initial dose of ergotamine is 0.5 mg to 2 mg taken early in the migraine; the rectal route results in better absorption than oral delivery.

The most common adverse effects of ergotamine (and, to a lesser extent, of dihydroergotamine) are nausea, vomiting, worsening of headache, numbness, and dizziness.

Triptans

Triptans, a new class of compounds, represent a major advance in the acute treatment of migraine.

Triptans are serotonin (5-HT) derivatives with highly selective and potent agonist activity at the vascular and neuronal 5-HT receptors.[26] They have at least three distinct modes of action, all of which may be additive in their antimigraine effects: vasoconstriction of distended intracranial extracerebral vessels, inhibition of neurogenic inflammation around intracranial vessels, and inhibition of central impulse transmission within the trigeminovascular system.[27]

At recommended doses, triptans are extremely effective in relieving migraine pain and associated symptoms. According to the US Headache Consortium recommendations, triptans are appropriate for patients with moderate or severe migraine who have no contraindications to their use.[17] Contraindications include a history, signs, or symptoms of cardiovascular or cerebrovascular disease, uncontrolled hypertension, and basilar or hemiplegic migraine.

Common adverse effects include dizziness, somnolence, fatigue, paresthesia, and chest tightness, pressure, and heaviness.

Is one triptan superior to the others?

If not pain-free in 2 hours, repeat the triptan dose

Clinical differences among the triptans are small, and considerations for selecting a triptan should include tolerability, available formulations, headache characteristics, relief of associated symptoms, consistency of response, headache recurrence, and patient preferences.

Generally, patients prefer oral formulations, although they will use a nasal spray or injection for rapid onset and relief. Wafers are convenient because no water is needed to aid in swallowing. For patients with significant nausea and vomiting, an oral formulation might not be practical, and a nasal spray or injection would be preferred.

Sumatriptan (Imitrex), available in injectable, oral, and intranasal formulations, was the first triptan to be approved for clinical use in patients with migraine. Since the release of sumatriptan in the early 1990s, several other triptans have become available: zolmitriptan (Zomig), naratriptan (Amerge), rizatriptan (Maxalt), and almotriptan (Axert). All are available as oral tablets; zolmitriptan and rizatriptan also are available as wafers. (An additional triptan, frovatriptan [Frova], was introduced to the US market after completion of this manuscript.)

The efficacy of individual triptans as reported in clinical trials cited in the manufacturers' prescribing information is summarized in **TABLE 5**.[27–41] In each of these studies, response was defined as the percentage of patients experiencing pain relief within 2 hours of initial dosing; in the case of naratriptan, response was measured at 4 hours after initial dosing. Pain relief was defined as a decrease in pain from moderate or severe to mild or none.

The end point of "pain relief" is now being supplanted by the end point "pain-free," which is defined as a decrease in pain from moderate or severe to none. The pain-free end point more accurately reflects a drug's efficacy, and patients' preference for complete relief of pain. Data on pain-free rates reported in various trials are given in **TABLE 5**.

Triptans cannot be compared by reviewing clinical trial results in manufacturers' prescribing information. To accurately gauge the efficacy and safety of various triptans, head-to-head comparisons are required. Even though such trials provide better comparative data, results of direct comparisons of triptans with each other and with other migraine medications can be influenced by patient randomization methods, potential bias from prior exposure to one of the study drugs, differences in the analysis of time to study end points, and other factors.[38] Data derived from these comparisons must be considered carefully when making therapeutic decisions for individual patients.

Subcutaneous sumatriptan is the gold standard for acute migraine treatment in view of its rapid onset of action and favorable response rate. The intranasal formulation of sumatriptan is also fast-acting because of absorption through the nasal mucosa and is similar in efficacy to the oral tablet.

However, in comparative trials with oral sumatriptan, zolmitriptan and rizatriptan were shown to have a better response rate at 2 hours and a shorter time to pain relief.[39–41] Almotriptan has been shown to be similar in efficacy to oral sumatriptan but has a lower rate of treatment-related adverse effects.[42] Naratriptan is the only triptan shown to be

TABLE 6

Recommended triptan dosages for acute migraine

TRIPTAN	INITIAL DOSE	REPEAT DOSE
Sumatriptan		
Subcutaneous[31]	6 mg	Maximum recommended dose in 24 hours is two 6–mg injections separated by at least 1 hour
Oral tablet[32]	25 mg, 50 mg, 100 mg	Optimal starting dose is 50 mg; can repeat initial dose after 2 hours if needed, not to exceed 200 mg in 24 hours
Intranasal[33]	5 mg, 20 mg	Usual starting dose is 20 mg; can repeat initial dose once after 2 hours if needed, not to exceed 40 mg in 24 hours
Zolmitriptan[34]		
Oral tablet or wafer	2.5 mg, 5 mg	Repeat initial dose after 2 hours if needed; not to exceed 10 mg in 24 hours
Naratriptan		
Oral tablet[35]	1 mg, 2.5 mg	Usual starting dose is 2.5 mg; repeat initial dose once after 4 hours if needed, not to exceed 5 mg in 24 hours
Rizatriptan		
Oral tablet or wafer[36]	5 mg, 10 mg	Usual starting dose is 10 mg*; repeat initial dose after 2 hours if needed, not to exceed 30 mg in 24 hours
Almotriptan		
Oral tablet[37]	6.25 mg, 12.5 mg	Usual starting dose is 12.5 mg; repeat initial dose after 2 hours if needed, not to exceed two doses in 24 hours

*Decrease rizatriptan dose to 5 mg if the patient is taking propranolol, with the total rizatriptan dose not to exceed 15 mg in 24 hours

Serious disease masquerading as migraine is uncommon

less effective than oral sumatriptan[43]; in a direct comparison, it also was less effective than rizatriptan.[44]

IF ACUTE TREATMENT FAILS

No response. Patients who do not respond to acute drug therapy should be interviewed carefully to determine the possible causes of treatment failure. Timing of the initial dose in relation to headache onset, the initial dose used, and whether the initial dose was repeated can affect response to treatment. Delaying treatment until the headache is severe is a possible cause of treatment failure.

With the short-acting oral triptans (except naratriptan) and sumatriptan nasal spray, a second dose can be taken 2 hours after the initial dose. If a patient is not pain-free 2 hours after the initial dose, I recommend repeating the dose. A second dose also can be effective if the pain is relieved initially but recurs. If a patient consistently requires repeat dosing, increasing the initial dose to the highest available or recommended dose should be considered.

Little evidence suggests that not responding to one triptan influences the likelihood of responding to a different one.[45]

Nonresponsiveness to oral triptans might

be due to low or inconsistent absorption, inadequate dose, delayed administration, and variability in individual response. Several episodes of nonresponsiveness to treatment initiated early in the course of migraine should be verified before a patient is categorized as a nonresponder. Nonresponders to a particular triptan might benefit from a different one. Another option is a trial of a nonoral formulation (eg, nasal spray, injection), which allows more rapid onset of action.

Recurrence. Headache recurrence is the return of migraine pain within 24 hours of initial pain relief. Patients with recurrent headache should repeat the initial dose at the first sign of recurrence; maximum recommended doses for the triptans are listed in TABLE 6. Treating migraine when the pain is mild is effective in achieving a pain-free state and might decrease the rate of recurrence.[20]

Partial response and recurrence. Patients with frequent migraines who achieve only a partial therapeutic response followed by a return of head pain are prone to rebound headache because of analgesic overuse.[46] Discontinuing analgesics, ergotamine, sedatives, triptans, and other overused medications and starting appropriate preventive therapy is usually successful. Withdrawal symptoms can be severe in patients who overuse ergotamine or analgesics in combination with opioids or barbiturates; such patients may require hospitalization for detoxification and management of symptoms during the withdrawal.

RESCUE THERAPY OF PROLONGED, REFRACTORY MIGRAINE

Patients with prolonged, incapacitating migraine refractory to oral conventional treatments may benefit from rescue therapy. Such therapy might also be indicated in patients with serious underlying medical disorders that could be worsened by prolonged migraines.

Corticosteroids, phenothiazines, and parenteral antinauseants and antimigraine medications provide the foundation of rescue treatment.[16] These are not intended for frequent use and should be considered only after first-line therapies fail.

Subcutaneous sumatriptan is a reasonable first-line approach to migraine rescue therapy.[47] Treatment with subcutaneous sumatriptan is cost-effective and convenient for use in home and emergency department settings and usually achieves rapid pain relief.

Phenothiazines. Chlorpromazine and prochlorperazine are potent antiemetics and can be given with parenteral antimigraine medications, including sumatriptan and dihydroergotamine.[48] Intravenous chlorpromazine (25 mg) and prochlorperazine (10 mg) are effective in the emergency setting. The phenothiazines have anticholinergic properties and are alpha-adrenergic antagonists with hypotensive effects. The principal adverse effects of phenothiazines in short-term use are dystonia and sedation.

Parenteral nonsteroidal agents and corticosteroids are empirically justified as a "last resort" in patients with severe, prolonged migraine in whom other preparations are ineffective or contraindicated.[16]

Ketorolac tromethamine (15 to 30 mg) can be given intramuscularly or intravenously every 6 hours, not to exceed 120 mg in 24 hours. Success rates of about 60% have been reported in patients with acute migraine treated with intramuscular ketorolac.[49]

Long-acting dexamethasone or methylprednisolone given intramuscularly also is effective in patients with prolonged migraines, and these drugs can be given with antiemetics or dihydroergotamine if necessary.

Opioid analgesics such as butorphanol tartrate nasal spray, oral hydrocodone bitartrate, and parenteral opiates, although effective for pain relief, should be used with caution as rescue therapy because of the potential for habituation. With the availability of other nonhabituating drugs, opioid analgesics should also be avoided as first-line therapy in most patients.

Nonresponders to one triptan might benefit from a different one

WHEN TO REFER

Migraine usually can be managed successfully in the primary care setting. Referral to a headache specialist may be indicated in patients who do not achieve a satisfactory therapeutic response despite multiple trials of appropriate medications and other interventions.

Such patients should be assessed carefully

regarding the characteristics and frequency of their headaches, associated symptoms, and the circumstances surrounding therapeutic failure. When patients fail to respond to treatment, try to determine if they are compliant with recommendations about lifestyle modifications, trigger avoidance, and medications.

Referral is also usually recommended for patients who require additional diagnostic evaluation.[50] Indications for diagnostic evaluation in patients include abrupt-onset headaches, headaches with neurologic symptoms lasting more than 1 hour, and headaches with syncope or seizure.[51] Migraine can be a sign of serious underlying disease, including brain tumor, cerebral aneurysm, and intracranial hemorrhage. Serious disease masquerading as migraine is uncommon, but appropriate identification of these disorders is fundamental to their successful management.

Referral options. Patients can be referred to a neurologist, psychologist, headache specialist, or pain management center.

Neurologic consultations may be indicated in patients with suspected underlying disorders and are usually obtained before computed tomographic scans and other expensive evaluations.

Psychological referral may be useful in patients with migraine accompanied by anxiety and depression and may provide patients with a sense of control over the frequency and severity of their headaches.

Patients referred to a headache specialist typically receive a comprehensive diagnostic evaluation followed by management recommendations and return to the care of their primary care physician.

NEW RECEPTOR TARGETS, BETTER PREVENTIVE THERAPIES NEEDED

In the future, other migraine-specific drugs may be developed. Current research is focusing on targets other than the 5-HT receptors. Research also continues in the area of prophylactic therapy for migraine, but no treatment is completely effective in preventing migraine in most patients. Methods of better identifying migraine are also being developed, improving physicians' ability to distinguish migraine from other headaches.

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ADDRESS: *Lisa K. Mannix, MD, 4760 E. Galbraith Road, Suite 206, Cincinnati, OH 45236; email LKMannixMD@aol.com.*

CME ANSWERS

Answers to the self-test on page 71 of this issue

1 **E** 2 **A** 3 **D** 4 **E** 5 **D** 6 **A** 7 **E** 8 **D** 9 **D** 10 **B** 11 **F** 12 **C**