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The role of the pharmacist in the treatment of migraine

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ACPE # 012-999-05-218-H01

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Migraine headache is a painful and debilitating disorder. It accounts for greater than 18 million physician visits per year and affects approximately 18% of women and 6% of men in the United States. Nearly 57% of migraine patients report moderate to severe disability as a result of their headaches.

The financial burden of migraine in the United States is also notable. It is estimated that 6.3 to 8.7 days per month in women and men, respectively, are lost because of missed work and decreased productivity secondary to migraine. U.S. employers lose an estimated \$13 billion per year because of missed workdays and impaired work function.

Pharmacists, working with other health-care providers, can have an important role in treating migraine patients. Because of their accessibility to patients, community pharmacists in particular can help patients find appropriate care for their headaches and use their medications correctly. This article reviews migraine presentation and treatment principles and outlines the role of the pharmacist in migraine patient care.

Etiology and diagnosis

Migraine headaches are a subset of headache disorders. Migraine headache is generally separated from tension-type headache or cluster headache by diagnostic criteria that have been outlined by the International Headache Society (IHS). These criteria are listed in Table 1. In patients' terms, migraine headaches are generally characterized by severe, throbbing head pain. In contrast, pain associated with tension-type headaches is more commonly described as less severe, dull, and "hat-band"-like in nature, encircling the head. Patients often present with a mixture of tension-type and migraine symptoms, making the headache difficult to classify. Cluster headaches are much less common,

with unilateral, excruciating pain in the ocular, frontal, or temporal areas and often accompanied by eye symptoms such as tearing or redness.

The etiology and pathophysiology of migraine pain are complex and not completely understood. The vascular hypothesis, proposed in the 1930s, stated that the migraine aura results from intracerebral arterial vasoconstriction, which is followed by reac-



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tive cranial vasodilation, causing the associated throbbing pain of migraine. Vascular studies have not borne out this theory, and most researchers now believe that the aura is caused primarily by neuronal changes or dysfunction and not changes in blood flow. The mechanism of the actual pain of a migraine is also not clear, with a neurovascular picture emerging in which migraine pain is caused by a combination of neuronal dysfunction mediated by serotonergic neurons that results in vasodilation, activation of the trigeminovascular system, and head pain.

Migraines are more common in females than in males. They peak in prevalence at age 40 but have the greatest impact on patients between the ages of 25 and 55. They are generally more common in Caucasian patients than in either African-American or Asian-American patients.

Clinical presentation

Most migraine patients do not present to their physician during an acute migraine attack. Thus migraine diagnosis is often based on the patient's description of his/her symptoms. Consistent with the diagnostic criteria, patients describe migraine pain as moderate to severe, throbbing or pulsing, one-sided, and worsened by activity. The pain may be accompanied by nausea and by sensitivity to light and sound. Accordingly, most patients report they get relief when they lie down in a cool, dark room. Acute migraine episodes can vary in length from four to 72 hours, with many patients experiencing migraine pain for 12-24 hours if untreated.

The acute migraine attack can have up to five phases: prodrome, aura, headache, resolution, and postdrome. Over 50% of migraine patients will experience a prodrome, what they will often describe as general feelings of fatigue, fluid retention, muscle pain, and/or food cravings that they experience a day or hours prior to the headache. Only 15% of patients will then experience an aura prior to the headache. The aura usually consists of reversible neurologic symptoms, such as visual or somatosensory changes, that occur prior to the headache pain. The third phase of the migraine attack is the actual headache pain—what patients generally characterize as the migraine symptoms described above. Finally, as the pain begins to resolve, patients enter the resolution phase, followed by the postdrome. The postdrome is characterized by continued fatigue, impaired concentration, tender muscles, and/or food intolerance. Patients may not experience all of these phases, and each migraine presentation may be unique. However, it is easy to see a significant level of disability that a migraine can cause.

GOAL:

To help pharmacists understand the causes and effects of migraine and the therapies used in treating it

CREDIT:

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES:

Upon completion of this article, the pharmacist should be able to:

- ✓ Review the characteristics of migraine, including diagnostic criteria and common symptoms
- ✓ Discuss the options for acute treatment of migraine therapy
- ✓ Distinguish among triptan agents, including comparison of pharmacokinetics, efficacy, and place in therapy
- ✓ Discuss options for preventive treatment of migraine therapy
- ✓ List actions the pharmacist can take to maximize therapeutic response in migraine patients

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

Migraine treatment

Migraine treatment includes both nonpharmacologic and pharmacologic measures. Among the nonpharmacologic measures helpful to patients are the avoidance of foods or activities known to be migraine triggers. Common migraine triggers are listed in Table 2.

During an acute attack, patients often find relief in a cool, dark, quiet environment, using an icepack on their head. Table 3 summarizes nonpharmacologic treatment strategies for migraine headache. Pharmacologic treatment of migraine headache can be divided into strategies to treat the acute migraine episode and those to decrease the frequency or intensity of headaches.

Acute treatment

Agents for acute treatment of migraine can generally be divided into simple analgesics (aspirin, acetamino-

Table 1
International Headache Society
diagnostic criteria for migraine

Migraine type	Diagnostic criteria
Migraine without aura (At least five attacks fulfilling criteria A-D)	<p>A. Headache attacks last four to 72 hours</p> <p>B. Headache has at least two of the following characteristics:</p> <ol style="list-style-type: none"> 1. Unilateral location 2. Pulsating character 3. Moderate or severe intensity 4. Aggravation by routine physical activity <p>C. During headache, at least one of the following occur:</p> <ol style="list-style-type: none"> 1. Nausea and/or vomiting 2. Photophobia and phonophobia. <p>D. No evidence of organic disease</p>
Migraine with aura (At least two attacks fulfilling criteria A and B)	<p>A. Headache has at least three of the following characteristics:</p> <ol style="list-style-type: none"> 1. One or more fully reversible aura symptom 2. At least one aura symptom develops gradually over more than four minutes, or two or more symptoms occur in succession 3. No aura symptom lasts more than 60 minutes; if more than one aura symptom is present, accepted duration is proportionally increased 4. Headache follows aura with a free interval of less than 60 minutes <p>B. No evidence of organic disease</p>

Source: Headache Classification Committee of the International Headache Society. *Cephalalgia* 2004;24(Suppl 1):24-36.

phen, ibuprofen, etc.), opioid analgesics and butalbital containing products, ergotamines, and first- and second-generation serotonin 1B/1D agonists, or triptans. There are evidence-based guidelines available for the treatment of migraine that were published in 2000 and can be accessed at the American Academy of Neurology Web site: www.aan.com.

Treatment considerations

When using any agent to treat migraine, it is important to remember some treatment issues specific to migraine headache that drive the appropriate choice of an acute treatment agent. First, migraine is often associated with gastric stasis during the acute attack. This slowing down of the gastrointestinal tract that accompanies a migraine may cause some oral medications to work more slowly than they would normally. This is very important, since it is known that the earlier in the time course of a headache that effective treatment is started, the more effectively it treats the headache. Second, many patients with migraine may be nauseous or vomiting and unable to tolerate oral medications. This phenomenon has understandably driven the development of the many available non-oral dosage forms for migraine therapies (e.g., intranasal sprays, subcutaneous injections, orally dissolving tablets). Finally, med-

ication overuse in migraine headache can lead to an escalating cycle of head pain, or “rebound” headache. Therefore, the strategy for treating patients who are experiencing frequent headaches should include preventive medications to help patients avoid overuse of acute treatments, and the subsequent rebound or chronic headaches. For this reason, many clinicians encourage headache patients to limit their use of any acute medication to no more than two days per week.

Nonspecific agents

Simple analgesics, opioids, and butalbital-containing products are nonspecific analgesics used to relieve migraine pain. While these agents work by different mechanisms to address

pain, they do not target the pain of a migraine specifically. As such, they are not ideal for migraine-specific pain but may provide some relief for mild headaches. Many representative agents in these classes have been shown to be more effective than placebo in treating migraine pain.

Clinically, there are a few considerations to keep in mind when using these agents for migraine. First, they should be used only for patients with mild to moderate migraine. If possible, severe migraines should be treated with a migraine-specific agent (e.g., a triptan). Second, many of these agents cause nausea or vomiting, especially if taken without food. Patients should be counseled accordingly if they have migraine-associated nausea or vomiting. Finally, the risk of rebound headache is particularly high with nonspecific analgesic agents. Some researchers believe these agents are more likely to cause rebound headache than migraine-specific agents, although this is debatable. More important, many of these agents are available without a prescription and are marketed specifically toward migraine sufferers. If patients with severe migraine are seeking relief from a nonprescription dose of an analgesic, it is likely they will self-escalate that dose to achieve relief. Doing so can put them at risk for adverse drug reactions or rebound headache. Patients

Table 2**Common triggers associated with migraine**

•Food triggers	•Environmental triggers	•Behavioral/physiologic triggers	•Medications
alcohol caffeine/caffeine withdrawal chocolate monosodium glutamate (e.g., in some instant foods, seasoned salts) nitrate-containing foods (e.g., processed meats) saccharin/aspartame sulfites	glare or flickering lights high altitude loud noises strong smells or fumes tobacco smoke weather changes	excess or insufficient sleep fatigue menstruation, menopause skipped meals stress or post-stress strenuous physical activity	analgesic overuse benzodiazepine withdrawal cimetidine decongestant overuse ergotamine overuse estrogen therapy indomethacin nifedipine nitrates oral contraceptives

Source: King DS, Herndon KC. Headache Disorders. In Dipiro JT et al. *Pharmacotherapy: A Pathophysiologic Approach*, 6th Edition. McGraw-Hill (New York):2005.

with migraine should be encouraged to closely follow the package instructions for nonprescription products to ensure they are receiving appropriate care for severe or persistent head pain.

Migraine-specific agents

Migraine-specific agents include ergot alkaloids, dihydroergotamine, and serotonin 1B/1D agonists (triptans). Although these agents are effective, use of ergot alkaloids and dihydroergotamine has largely fallen out of favor since the agents are generally not as well tolerated as triptans and are sometimes less effective. Of the currently available agents, intranasal dihydroergotamine is tolerated best, with a relatively long duration of action and good efficacy.

The most commonly used acute migraine-specific treatments are the triptans. The class includes sumatriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, eletriptan, and almotriptan. The mechanism of action of these drugs is not completely understood, as with the mechanism of migraine pain. Triptans have

multiple pharmacologic effects that have been identified and that may be associated with their effectiveness, including stimulation of presynaptic 5-HT_{1D} receptors to inhibit vasodilation and inflammation, inhibition of nociceptive neurotransmission, and vasodilation of intracranial extracerebral blood vessels. It is known that the availability of triptans, offering both safe and effective migraine-specific therapy, revolutionized migraine treatment. For the first time, migraine patients had access to effective medications that worked by targeting migraine pain, and the drugs were relatively well tolerated.

The first triptan available was sumatriptan, which is often referred to as the “first-generation” triptan. It is very effective and is available in subcutaneous, intranasal, and oral dosage forms. Table 4 lists dosing guidelines for triptans. When patients take sumatriptan subcutaneously, approximately 75% report relief 15 minutes after an injection. The one-hour efficacy rate of the subcutaneous injection is approximately equivalent to the two-hour efficacy rate of both the oral and intranasal dosage forms, with the majority of patients experiencing relief two hours after taking sumatriptan in these forms. As with all triptans, sumatriptan is well tolerated, but it can be associated with adverse effects, including paresthesias, flushing, chest pain or tightness, dizziness, drowsiness, or nausea/vomiting. Chest symptoms, in particular, can be a troublesome side effect for patients. Additionally, although sumatriptan is effective in relieving head pain in most patients, up to 40% of patients will experience headache recurrence within 24 hours of taking a dose.

Tolerability and efficacy issues with sumatriptan led to the development of the “second-generation” triptans, or all other available agents. In the development phase, it was

Table 3**Nonpharmacologic treatment strategies for migraine headache**

When to use	What patients can do
Before headache attack (incorporated into lifestyle to prevent onset)	Behavioral therapy, such as biofeedback, relaxation, and stress management Regular aerobic exercise Trigger avoidance
During headache attack (to relieve symptoms)	Application of ice to the head Sleep Quiet Rest in a dark room

Source: Adapted from Saper JR. Diagnosis and symptomatic treatment of migraine. *Headache* 1997;34(suppl 1):S1-S14.

Table 4
Triptans for acute migraine treatment

Drug	Dose*	Max. in 24 hrs.	Dosage adjustment	
			Renal	Hepatic
sumatriptan	SC: 6 mg NS: 5 to 20 mg PO: 25 to 100 mg	12 mg 40 mg 200 mg	N — —	N — —
zolmitriptan	PO: 1 to 5 mg NS: 5 mg	10 mg 10 mg	N N	Y Y
rizatriptan	PO: 5 to 10 mg	30 mg	N	N
almotriptan	PO: 6.25 to 12.5 mg	25 mg	Y	Y
naratriptan	PO: 1 to 2.5 mg	5 mg	Y	Y
frovatriptan	PO: 2.5 mg	7.5 mg	N	N
eletriptan	PO: 20 to 40 mg	80 mg	N	N

Source: *Clinical Pharmacology On-line*. Available at www.cpip.gsm.com.
*SC = subcutaneous NS = nasal spray PO = oral

initially thought that if an agent was developed that possessed greater potency at the receptor site, increased lipophilicity and therefore increased central nervous system penetration, and increased bioavailability and/or half-life, it may be more effective, better tolerated, and cause less headache recurrence. It was these principles that were behind the development of second-generation triptans, all of which differ slightly from sumatriptan in one or more of these areas. Pharmacokinetic parameters of triptans are listed in Table 5.

Second-generation agents

Each of the second-generation agents will be discussed in more detail below. Sumatriptan will be used as a comparison point whenever possible, since it is considered the gold standard in this class.

Zolmitriptan is currently available as an oral tablet, an orally disintegrating tablet, and a nasal spray. This agent is very effective, with a response rate similar to that of sumatriptan. It has demonstrated good response consistency in clinical trials, meaning that patients who respond to zolmitriptan initially will continue to do so, even with repeated attacks. The orally disintegrating tablet is helpful for patients who do not want to swallow an oral tablet secondary to nausea or vomiting but do not want to use a nasal spray. Zolmitriptan is generally considered a good alternative to sumatriptan and may have a lower headache recurrence rate in some patients.

Rizatriptan is available as an oral tablet and an orally

disintegrating tablet. This agent is generally considered effective, with a rapid onset of action. The two-hour response rate of rizatriptan has been shown to be up to 70%-77%, slightly higher than sumatriptan's. Its headache recurrence rate, though, is similar to sumatriptan's at approximately 40%. Rizatriptan also interacts significantly with propranolol, an agent commonly used for migraine prevention. When taken with propranolol 240 mg per day, the mean AUC of rizatriptan can increase up to 70%. Because of this, the recommended dose of rizatriptan is 5 mg, up to a maximum of 15 mg in 24 hours, when given with propranolol. With minor differences, rizatriptan and zolmitriptan are very similar to sumatriptan.

In contrast, *naratriptan* was the first of the second-generation triptans to differ markedly from sumatriptan in patient response and tolerability. Its pharmacokinetic profile differs from that of sumatriptan, resulting in a longer onset of action and less headache recurrence than is seen with sumatriptan. The two-hour efficacy rate of sumatriptan is approximately equal to the four-hour efficacy rate of naratriptan. Naratriptan's recurrence rate is lower, though, at 17%-28%. Patients also appear to tolerate naratriptan better than many other triptans. It is most appropriate for patients who have long-lasting migraines, or recurrence or tolerability problems with other triptans. Its slower onset of action may limit its clinical utility.

Of the three most recently released triptans—almotriptan, eletriptan, and frovatriptan—only almotriptan seems to offer significant benefits over sumatriptan. Almotriptan has a similar pharmacokinetic and efficacy profile to sumatriptan, but it appears to be better tolerated than sumatriptan. Its onset and recurrence rate are also lower compared with sumatriptan. Eletriptan has been shown to be as efficacious as or even more so than sumatriptan in European trials in doses of 80 mg. Unfortunately, this dose is not approved in the United States and these results have not been duplicated with the 40-mg dose used in the United States.

Similar to naratriptan, *frovatriptan's* pharmacokinetic profile differs significantly from that of sumatriptan. Its half-life of 26 hours is the longest of any of the available triptans. Clinically, frovatriptan appears to be similar to naratriptan, with a two-hour response rate of only 37%-46%, much less than sumatriptan's. It does, however, show less headache recurrence, with only 7%-25% of patients experiencing recurrence after a dose.

Choosing a triptan

Clinicians are often asked to choose an agent among this relatively large class of similar drugs. Because most of the clinical trials of triptans have been done with single agents compared with placebo, it is relatively simple to establish efficacy but more difficult to say which agent is "better" than another, since they have not been directly compared.

To address this, a meta-analysis was published in *Lancet* in 2001 by Ferrari and others, comparing the results of 53 trials involving 24,089 patients. In summary, the authors concluded that patients had the highest likelihood of finding consistent headache relief with 10-mg rizatriptan, 80-mg eletriptan, or 12.5-mg almotriptan. They also stated that sumatriptan 50 mg and 100 mg offered a good efficacy/tolerability profile with the longest clinical experience and the availability of non-oral dosage forms. The authors concluded that naratriptan 2.5 mg offered good tolerability with a slower onset, and that zolmitriptan was a good alternative to sumatriptan. Frovatriptan was not included in this meta-analysis. Table 6 summarizes select comparison results from this meta-analysis. In more general terms, some authors have gone on to group triptans into two separate categories, with general features of each category. Table 7 summarizes this grouping.

When one is asked to make a recommendation for an alternate triptan if the first product has failed, keep a few things in mind. First, patients may respond differently to each agent in this class. It is definitely reasonable to continue to try alternate agents if patients did not get relief or tolerate the first agent tried. Second, using a series of directed questions can help guide the choice of alternate agents. Determine why the patient failed the first triptan tried. Was it because of slow onset of action? lack of a consistent response? headache recurrence? drug intolerance? You can then use these responses in the choice of a second agent. Finally, remember that some therapeutic principles apply to all triptans: Take them as soon as possible at the

onset of head pain to maximize response, and try not to take them more than two days out of each week in order to avoid rebound headache.

Maximizing therapeutic response

In the case of acute treatment of migraine, it is also important to consider not just the drug therapies used but also the approach to treatment. Acute treatment strategies for migraine headache can be classified as step care or stratified care. Using the step-care approach, patients are given one medication for a series of attacks, then "stepped" up to a stronger medication if they do not find relief with that agent. Under this model, patients may initially be treated with ibuprofen, then stepped up to a butalbital-containing agent, then stepped up to a triptan, such as sumatriptan, if they get no relief from the first drugs tried.

Using the stratified-care approach, patients are evaluated initially when they present to their physician with headache to determine the level of severity or disability of the headache. The treatment approach is then matched to the level of severity of their headache. Under this model, a patient that presents with mild migraines that last only six hours and are not disabling would be treated with ibuprofen, while patients with severe, disabling headache would immediately be treated with a triptan agent.

Historically, many migraine patients have been treated using the step-care approach. While patients with severe migraine pain are eventually treated with targeted therapies using this strategy, there are some significant drawbacks. Patients who find effective therapy

Table 5
Pharmacokinetics of triptans

Drug	C _{max} (ng/ml)	t _{max} (h)	F* (%)	T 1/2 (h)	Metabolism	Vd (L/kg)	CL (mL/min/kg)
sumatriptan 100 mg	54-78.4	1.5-2.3	14	2	MAO-A	2.4-3.3	3.5-3.9
almotriptan 12.5 mg	49.5	1.4-3.8	70-80	3.0-3.7	CYP3A	2.5	8.6
eletriptan 80 mg	107-190	1.0-1.5	50	3.6-6.9	CYP3A4	2.4	6.6
frovatriptan 2.5 mg	4.2-7.0	2-4	24-30	25	CYP1A2	3-4	1.9-3.1
naratriptan 2.5 mg	7.8-14.4	0.8-4.1	63-74	4.5-6.6	CYP 450	2.4-2.9	2.7-3.8
rizatriptan 10 mg	20	1-3	40-45	1.8-3	MAO-A	1.3-2.5	3.2-5.3
zolmitriptan 2.5 mg	1.3-4.7	0.5-6.0	40-49	1.5-3.6	CYP1A2 MAO-A	7.0-8.3	2.0-3.1

Source: Deleu, D. *Journal of Clinical Pharmacology* 2000;40:687-700 *F = bioavailability

may suffer for months or years before doing so, increasing costs and decreasing their quality of life. Patients may also drop out of their headache care, or be lost to follow-up during the treatment escalation phase, thinking that their headaches are not treatable or that clinicians cannot help their headaches.

Given the significant disability associated with migraine, these outcomes are less than optimal. However, some critics of the stratified-care approach have argued that this method increases costs associated with treatment and needlessly exposes patients to adverse effects of migraine-specific therapy, such as the triptans. The Disability in Strategies of Care (DISC) study, published in the *Journal of the American Medical Association (JAMA)* in 2000 investigated this issue. The study authors used the same medications but different treatment approaches for the 835 patients enrolled in the trial. They found that using a stratified-care approach resulted in a greater percentage of patients experiencing a headache treatment response at two hours, with lower disability time.

Preventive treatment

If patients have extremely long-lasting, frequent, or severe migraines, they may be candidates for prophylactic or preventive therapy. Patients may also need preventive therapy if they have contraindications to or failure with acute agents, are unable to tolerate acute treatment agents, or just prefer to take preventive medications. These agents are taken daily to decrease the frequency and intensity of migraine attacks. They are generally considered successful if they decrease either of these parameters by 50%. When used properly, preventive therapy can also improve responsiveness to acute attacks, improve patient functioning, and reduce disability associated with migraine.

The most commonly used preventive migraine agents are beta-blockers, anticonvulsants, and selected antidepressants. Table 8 lists dosages and evidence of efficacy for individual preventive agents. Beta-blockers are considered first-line agents in patients who

Table 6
Comparison of triptans

Drug (strength in mg)	Two-hour relief	Tolerability
sumatriptan (50)	=	=
zolmitriptan (2.5,5)	=	=
naratriptan (2.5)	-	++
rizatriptan (5)	=	=
rizatriptan (10)	+	=
eletriptan (20)	-	=
eletriptan (40)	=/+	=
almotriptan (12.5)	=	++

Source: Adapted from Ferrari et al. *Lancet*. 2001;358:1668.
Note: = indicates no difference when compared with sumatriptan
+ indicates better when compared with sumatriptan
- indicates inferior when compared with sumatriptan

are able to tolerate them. The best-studied agent is propranolol, which has been shown to be up to 80% effective. Unfortunately, it is not the best tolerated of the beta-blockers; metoprolol or atenolol are often used in its place for greater tolerability.

Anticonvulsants and antidepressants can also be used for migraine prevention. The most commonly used anticonvulsant is divalproex sodium, or sodium valproate. This agent also has a high efficacy rate but is limited by adverse effects that include weight gain, hair loss, and teratogenicity. Of the antidepressants, the tricyclic

class (TCA) has the most data to support efficacy. Within this class, amitriptyline has been effective in the most clinical trials. Like propranolol, though, amitriptyline is not always well tolerated, so nortriptyline is often substituted. These agents are usually given at bedtime to avoid daytime oversedation. TCAs have shown particular efficacy in patients that have mixed migraine and tension-type headaches, so they may be the first choice for prevention in these patients. Selective serotonin reuptake inhibitors (SSRIs) have also been studied but have not been shown to be effective and may even cause headache as an adverse effect.

More recently, topiramate showed very promising results in published trials and was recently FDA-approved for the prevention of migraine headaches in adults. A 2004 report by Brandes and others in *JAMA* showed a 50% response to 100 mg or 200 mg daily within the first month. Adverse drug events that resulted in discontinuation in this trial include paresthesias, fatigue, and nausea.

With any preventive medication, keep a few points in mind. As mentioned previously, these agents are

Table 7
Triptan generalizations by group

Group	Features	Examples
Group I	Faster onset, higher potency, higher recurrence	sumatriptan, zolmitriptan, rizatriptan, almotriptan, eletriptan
Group II	Slower onset, lower potency, lower recurrence	naratriptan, frovatriptan

Source: Rapoport AM et al. *CNS Drugs*. 2003(17):431-47.

considered successful if they decrease the frequency, duration, or intensity of attacks by 50% or more. Patients should understand that these agents will likely not make their migraines go away, and should have realistic expectations with their use. They may also take up to two months to take effect, so a preventive medication trial may take two to three months before its effect is determined. Clinicians may consider tapering or discontinuing these drugs after six months to assess effect.

Finally, consider coexisting conditions when choosing a preventive therapy. Patients with hypertension may be able to have both their migraines and blood pressure controlled by the addition of a beta-blocker. Alternatively, clinicians may want to avoid the use of propranolol and use an antidepressant instead in patients with coexisting migraine and depression.

Role of the pharmacist

As with many other chronic disease states, pharmacists can play a role in therapy of migraine headache. This role is even more important with migraine, though, given the accessibility of the pharmacist and the reliance patients have historically had on their community pharmacists for headache care. It is known that 57% of migraine patients exclusively take nonprescription medications for their headaches. In addition, pharmacists recommend a "headache product" over 53,000 times per day, more often than most other products are recommended in community pharmacies. Patients depend on their pharmacists for treatment of their headaches.

Pharmacists can begin to help headache patients by first identifying those patients that may need to pursue further diagnosis and treatment. Many patients have classic migraine symptoms and need migraine-specific prescription therapy. They will not be able to have access to this therapy until they are seen by a physician and appropriately diagnosed. Appropriate diagnosis and subsequent treatment can improve outcomes and reduce disability in these patients.

Pharmacists can also encourage appropriate use of nonprescription medications for migraines. As discussed earlier, nonprescription NSAIDs and combination products are appropriate for mild to moderate migraine. In contrast, acetaminophen alone has not been shown to be effective in treating even mild migraines. Pharmacists can encourage selection and appropriate use of an effective agent and counsel patients to avoid overuse and subsequent rebound headache or adverse drug reactions.

Once patients are on prescription drug therapy, pharmacists can encourage appropriate treatment. As

Table 8
Medications for prevention of migraine

Drug	Dose	Evidence of efficacy
Beta-blockers		
propranolol*	40-120 mg BID	High
timolol*	20 mg QD	High
nadolol	40-240 mg/day	Moderate
atenolol	50-150 mg/day	Moderate
metoprolol	50-250 mg/day	Moderate
Antidepressants		
amitriptyline	10-150 mg QHS	High
venlafaxine	37.5-150 mg QD	Low
nefazodone	100-450 mg/day	Low
fluoxetine	20-40 mg QD	Low
Calcium-channel blockers (CCBs)		
verapamil	160-320 mg/day	Low
amlodipine	5-10 mg QD	Low
nimodipine	60 mg QID	Moderate
Anticonvulsants		
divalproex sodium*	250-500 mg BID	High
topiramate*	25-200 mg/day	Moderate
gabapentin	900-2400 mg/day	Promising
Source: Clinical Pharmacology Online. Available at: www.cpip.gsm.com and <i>Guidelines for Migraine Prevention</i> , available at www.aan.com .		
* FDA-approved for prevention of migraine		

discussed earlier, patients should be treated using a stratified-care approach, with specific triptans used to target patient-specific migraine characteristics. If patients have failed therapy, pharmacists can make recommendations for alternate agents or recommend an alternate dosage form. Non-oral dosage forms may be particularly helpful and may significantly impact the success of a therapy in patients experiencing nausea or vomiting with their headache. Patients are often not aware of the principles governing preventive therapy or even the rationale for its use. They may gain further understanding about these agents and their role in migraine treatment from their pharmacist.

CONTINUING EDUCATION

Conclusion

Migraine headaches are complex in their presentation and treatment. Providing care for this disabling condition involves many challenges to both patients and clinicians in diagnosis and treatment. The pharmacist can play an important role in an interdisciplinary

team in helping to maximize a therapeutic response for migraine patients. Because of their accessibility and the availability of nonprescription migraine medications, community pharmacists can have a significant impact in the care of the migraine patient.

References are available upon request.

TEST QUESTIONS

Write your answers on the answer form appearing on page 31 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

- Approximately what percentage of migraine patients report moderate to severe disability as a result of their headaches?
 - 10%
 - 25%
 - 60%
 - 100%
- Patients generally describe migraine pain as:
 - Mild
 - “Hat-band” like
 - Accompanied by eye tearing and redness
 - Throbbing and one-sided
- Which one of the following proposed migraine mechanisms attributes migraine pain to reactive cranial vasodilation?
 - Vascular hypothesis
 - Cranial hypothesis
 - Migraine theory
 - Trigeminal hypothesis
- Which one of the following terms describes the migraine phase that is characterized by reversible neurologic symptoms, such as visual or somatosensory changes?
 - Prodrome
 - Aura
 - Resolution
 - Postdrome
- Nonpharmacologic treatment measures for acute migraine include which one of the following?
 - Exposure to bright light
 - Application of heat to the head
 - Exercise
 - Resting in a quiet environment
- Which of the following statements regarding migraine treatment considerations is true?
 - Migraine medications are most effective when taken late in the migraine attack.
 - Migraine is often associated with gastric stasis during the acute attack.
 - Oral dosage forms are ideal for all migraine patients.
 - There are no negative consequences of acute treatment medication overuse in migraine headache.
- Nonspecific agents used to treat acute migraine include which one of the following?
 - Sumatriptan
 - Dihydroergotamine
 - Simple analgesics
 - Propranolol
- The most commonly used acute migraine specific treatments are in the class of:
 - Triptans
 - Ergot alkaloids
 - Analgesics
 - Preventive medications
- Which one of the following triptans is considered to be the gold standard?
 - Zolmitriptan
 - Naratriptan
 - Almotriptan
 - Sumatriptan
- Sumatriptan’s headache recurrence rate is approximately:
 - 10%
 - 20%
 - 40%
 - 60%
- Which of the second-generation triptans was the first to differ significantly clinically from sumatriptan?
 - Rizatriptan
 - Naratriptan
 - Zolmitriptan
 - Almotriptan
- The triptan with the longest half-life is:
 - Almotriptan
 - Sumatriptan
 - Frovatriptan
 - Naratriptan
- According to the triptan meta-analysis discussed in the article, patients are most likely to have success with which one of the following in treating acute migraine?
 - 12.5-mg almotriptan
 - 50-mg sumatriptan
 - 20-mg eletriptan
 - 2.5-mg naratriptan
- Which one of the following has been shown to be the optimal treatment approach to migraine patients?
 - Stepped care within attacks
 - Stepped care across attacks
 - Usual care
 - Stratified care
- Which study demonstrated the benefits of this approach to care in migraine patients?
 - EPIC
 - PROVE-IT
 - DISC
 - APEX
- The most commonly used preventive migraine treatments include:
 - Calcium channel blockers
 - Triptans
 - NSAIDs
 - Antidepressants

TEST QUESTIONS

- 17.** Which class of drugs is considered to be first-line for prevention of migraine?
 a. Tricyclic antidepressants c. Anticonvulsants
 b. Beta-blockers d. Selective serotonin reuptake inhibitors
- 18.** According to the article, which one of the following anti-epileptic agents has recently shown very promising results for migraine prevention?
 a. Carbamazepine c. Topiramate
 b. Amitriptyline d. Valproic acid
- 19.** Preventive medications may take up to how long to take effect in migraine patients?
 a. Seven days c. Four weeks
 b. 14 days d. Two months
- 20.** Approximately what percentage of migraine patients take exclusively nonprescription medications for their headaches?
 a. 60% c. 80%
 b. 70% d. 90%

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ANSWER FORM

THE ROLE OF THE PHARMACIST IN THE TREATMENT OF MIGRAINE

OCTOBER 24, 2005 012-999-05-218-H01

Test questions start on preceding page

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