Management of Migraines

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EDUCATIONAL OBJECTIVES
After the completion of this activity pharmacists will be able to:
• Describe the clinical presentation of migraine headaches.
• Discuss medications used in acute migraine treatment.
• Discuss common medications for migraine prevention.

INTRODUCTION
Migraine is one of the most common reasons adults in the United States present to the emergency department (ED). It accounts for almost 3% of ED visits and annually costs anywhere between $1 to $17 billion. Migraines are known to affect approximately 23 million people in the U.S. alone. Those affected are most likely to be between the ages of 20 to 55, but migraines are also seen in children as young as five as well as in the elderly. Of the patients that experience migraines, 63% have between one and four attacks per month, 23% have less than one attack per month, and 14% have more than four migraine attacks per month.

The International Headache Society (IHS) classifies migraine as a primary headache disorder, along with tension-type and cluster headaches. There are two major subtypes of migraine, which include migraine with aura and migraine without aura. A aura is a group of neurologic symptoms that affects approximately 31% of migraineurs on some occasions.

PATHOPHYSIOLOGY
The vascular hypothesis was an early theory that described migraine aura as being caused by intracerebral vasoconstriction followed by extracranial vasodilation. More recently, there have been regional blood flow studies that do not support this hypothesis. The currently accepted theory is that migraines are caused by neuronal dysfunction. This dysfunction is caused by a wave of depressed electrical activity that advances across the brain cortex at a rate consistent with the spread of aura symptoms.

The pain associated with migraines is believed to originate in the trigeminalvascular system. This system provides a pathway in which pain from the meningeal blood vessels can be transmitted to higher centers within the central nervous system (CNS). This system also innervates the pain-sensitive intracranial extracerebral blood vessels, dura mater, and large venous sinuses.

When the nerves in the trigeminal system are activated, they release various neuropeptides including calcitonin gene-related peptide, neurokinin A, and substance P. These neuropeptides cause vasodilation, which results in dural plasma extravasation and ultimately neurogenic inflammation. This process causes pain impulses to be transmitted to higher cortical pain centers, which allows the migraine to be perceived.

This system may also be regulated in part by serotonin. If there is a dysfunction in the calcium channels responsible for mediating serotonin and excitatory neurotransmitter release, then a migraine may result. This dysregulation of serotonin can cause vasodilation of intracranial extracerebral blood vessels and subsequent activation of the trigeminalvascular system.

CLINICAL PRESENTATION
Migraine, cluster, and tension-type headaches are all considered primary headache disorders, but each presents slightly different. Cluster headaches are a group of headaches that appear in a pattern very close to each other but may not reoccur for months to years. Tension-type headaches are characterized by a dull, persistent pain in a band around the largest part of the head. These headaches usually occur around a time of stress and may persist for months. These types of headaches differ from migraines in that they lack aura; they are also more prominent in men, whereas migraines are more common in women.

A migraine attack can be divided into several phases that include the premonitory phase, migraine aura (if present), the migraine phase, and the resolution phase.

The premonitory phase is experienced by 20% to 60% of migraineurs and is characterized by a wide variety of symptoms. Neurologic symptoms (e.g., sensitivity to light, sound, or smells and difficulty concentrating) are most common, but some people may also experience psychological symptoms (e.g., anxiety, depression, euphoria, irritability, drowsiness, or excitability), autonomic symptoms (e.g., frequent urination, diarrhea, or constipation), or constitutional symptoms (e.g., stiff neck, yawning, thirst, food cravings, or anorexia).

In people who experience aura, it may occur before or during a migraine attack. It usually evolves over 5 to 20 minutes and lasts less than 60 minutes; pain from the migraine usually occurs within 60 minutes of the end of the aura. The most common sensory abnormality with aura is visual, often characterized by flickering lights or loss of vision, but the symptoms could be motor related as well, such as numbness and tingling.

The migraine headache itself may occur at any time of day but most patients seem to experience migraine upon wakening in the early morning. There is a gradual onset that may peak in minutes and last anywhere from 4 to 72 hours. The pain is usually accompanied by fatigue, irritability and nausea. Some less common symptoms include anorexia, certain cravings, gastrointestinal discomfort as well as sensitivity to light and sound.

The resolution phase is the final phase of a migraine attack and is characterized by feeling tired and exhausted. Some of the sensory sensitivities as well as impaired concentration and scalp tenderness may persist; however, the length of this phase is highly variable among patients.

DIAGNOSIS
The IHS provides guidelines to follow when diagnosing migraine headaches. It is important to note that there are different criteria depending on the presence of aura. The International Headache Society Diagnostic Criteria for Migraine are provided in Table 1.

TRIGGERS
Several triggers have been identified that increase one’s risk of experiencing a migraine attack. These may include different kinds of foods, environmental factors, and behavioral-physiologic factors. It is important for migraineurs to identify and avoid the triggers that cause their migraines in order to decrease the likelihood of experiencing an attack. Common triggers are described in Table 2.
ACUTE TREATMENT

Migraines can be debilitating and often interfere with patients’ day-to-day routines. Although some non-pharmacologic therapy, such as sleeping in a dark & quiet room, may help to minimize pain, pharmacologic therapy is the mainstay treatment for acute migraine symptoms.2,4,5 Pharmacologic therapy is divided into two types: specific and non-specific medications. Non-specific medications include analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and other miscellaneous agents. These medications are often used for migraines of mild to moderate severity. The 5-HT serotonin receptor agonists, referred to as the triptans, as well as the ergot alkaloids are classified as specific medications. These agents are used for more severe migraines and work directly on the vasculature to treat the cause of the migraine symptoms. Regardless of the type of medication being used, it is important to treat migraines as early as possible in order to achieve the best results.

Although acute therapies help relieve the pain and symptoms associated with migraine, they may actually be implicated in causing headaches if medication is used too frequently.2,4,5 Acute medication therapy should be limited to 2 to 3 days per week in order to prevent the development of medication overuse (or rebound) headaches. These headaches are characterized by the return of symptoms as soon as the medication wears off; this then leads to consumption of more acute migraine medication. Analgesics and opioids are the most common agents to cause medication overuse headaches.

Another important issue that must be considered when treating patients for migraines is that nausea and vomiting often accompany other migraine symptoms.2 When nausea and vomiting occur, alternate dosage forms, such as orally disintegrating tablets, rectal suppositories, and parenteral routes of administration are preferred over oral dosage forms. Antiemetics may also be used as adjunctive therapy in patients who experience severe nausea and vomiting associated with migraines. Metoclopramide, chlorpromazine, prochlorperazine, and 5HT3 antagonists such as ondansetron are common antiemetics that may be used.

Non-pharmacological therapy is limited for the acute treatment of migraines.2 Applying ice to the head; sleeping in dark, quiet rooms; and relaxation techniques may help minimize migraine symptoms.

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| Table 1. IHS Diagnostic Criteria for Migraine |

| Migraine with Aura | • At least 5 attacks  
| • Headache attack lasts 4-72 hours in an untreated or unsuccessfully treated patient  
| • Headache has at least two of the following characteristics:  
| o Unilateral location  
| o Pulsating quality  
| o Moderate or severe intensity  
| o Aggravation by or avoidance of regular routine  
| • During headache at least one of the following  
| o Nausea or vomiting:  
| o Photophobia or phonophobia  
| o Not attributed to another disorder |

| Migraine with Aura (Classic Migraine) | • At least two attacks  
| • Migraine aura fulfills criteria for typical aura (see below), hemiplegic aura (characterized by reversible motor weakness), or basilar-type aura (characterized by bilateral, reversible visual, sensory, or speech symptoms but no motor weakness)  
| • Not attributed to another disorder |

| Typical Aura | • Fully reversible visual, sensory, or speech symptoms but no motor weakness  
| • Homonymous or bilateral visual symptoms including  
| o Positive features (flickering light)  
| o Negative features (loss of vision)  
| • Unilateral sensory symptoms  
| o Positive features (pins and needles)  
| o Negative features (numbness)  
| • At least one of the following  
| o Each symptom lasts for at least 5 minutes and for no longer than 60 minutes  
| o Headache that meets criteria for migraine without aura begins during the aura or follows aura within 60 minutes |

Table adapted from Pharmacotherapy 8th ed. Dipiro et al. c2011. Pg. 1064
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Dichloralphenazone, typically an alternative agent for migraine headaches, although they are commonly used in clinical practice. They are used to treat patients with more severe migraines if they have provided adequate relief in the past. Most commonly, NSAIDs or combination analgesics, such as Midrin or butalbital-containing products, are used as second line therapy when first line agents do not provide adequate relief.

Use of these products should be limited due to concerns of the development of medication overuse headache.

Opioids. Narcotic analgesics are typically reserved to treat moderate to severe migraines in cases when first line therapies are contraindicated or for use as rescue medications after initial therapy has failed. Meperidine, oxycodone, hydromorphone, and butorphanol nasal spray are the more commonly used opioids in migraine treatment. These medications may lead to dependency; therefore, they should only be used as last line therapy and only when the patient’s migraines are infrequent. Butorphanol should be reserved for use as last line therapy to prevent emergency room visits and treatment with parenteral migraine therapies. Some adverse effects associated with use of these drugs are constipation, rebound headache, and most notably, dependency. Patients who use opioids should be assessed regularly to ensure medication misuse and dependency do not develop.

Triptans. There is strong evidence to support the use of triptans as first line therapy for patients with moderate to severe migraines. Triptans may also be used in any patient or as rescue treatment when non-specific medications have failed. This class is divided into first and second generation agents. Sumatriptan is the lone first generation triptan, and it is also the most extensively studied. It is available in a wide variety of dosage forms including oral, subcutaneous, and intranasal delivery. Second generation triptans include zolmitriptan, naratriptan, rizatriptan, almotriptan, frovatriptan, and eletriptan. Second generation triptans have better oral bioavailability and longer half-lives as compared to sumatriptan, which can help improve symptom control and prevent migraine recurrence. Two of these agents, frovatriptan and naratriptan, may be favored for patients who have migraines with a slow onset but extended duration, as these two medications have a slower onset of action while also having the longest half-lives within the drug class. When choosing a triptan for acute treatment of migraines, it is difficult to predict a how a patient will respond to a specific agent. In general, triptans have similar efficacy and safety profiles; thus, therapy should be chosen based on cost, patient compliance, and patient preference. If a patient fails therapy with one of the agents in this class, then another may be effective. Once an effective medication and dosing regimen is established, the patient should continue using this regimen for subsequent attacks.

Adverse effects of the triptans are common, but are usually mild in severity and only last for a brief period. Some of the more common side effects that may be seen with these agents include fatigue, chest tightness, dizziness, and flushing. Because triptans cause vasoconstriction of blood vessels, these medications may rarely lead to adverse cardiac events such as myocardial ischemia and angina. Although these cardiac adverse events rarely occur in patients who are not predisposed to ischemic conditions, these medications are contraindicated in patients who have ischemic heart disease, uncontrolled hypertension, and cerebrovascular disease. These medications should also not be used in hemiplegic or basilar migraine, which are rare types of migraines in which the patient experiences aura and other atypical symptoms such as unilateral numbness and tingling, dizziness, and vertigo. Lastly, these medications should not be given within 24 hours of ergotamine derivatives, as the effects on the vasculature may be compounded.

**Table 1. IHS Diagnostic Criteria for Migraine**

| Food triggers | • Alcohol  
| • Caffeine/caffeine withdrawal  
| • Chocolate  
| • Pickled foods  
| • Monosodium glutamate  
| • Processed meats  
| • Diet foods/diet drinks  
| • Tyramine foods such as aged cheeses, chocolate and beer/wine  
| Environmental triggers | • Glare or flickering lights  
| • High altitude  
| • Loud noises  
| • Strong smells/perfumes  
| • Tobacco smoke  
| • Weather changes  
| Behavioral-physiologic triggers | • Excess or insufficient sleep  
| • Fatigue  
| • Menstruation/ menopause  
| • Sexual activity  
| • Skipped meals  
| • Strenuous physical activity  
| • Stress/post-stress  

Table adapted from Pharmacotherapy 8th ed. c2011 Dipiro et. al pg. 1068

**Analgesics and NSAIDs.** These medications are first line therapies for the treatment of mild to moderate migraines. They may also be used to treat patients with more severe migraines if they have provided adequate relief in the past. Most commonly, NSAIDs or a combination of acetaminophen/ aspirin/caffeine are used as first line therapy for mild to moderate migraines. Other combination analgesics, such as Midrin or butalbital-containing products, are used as second line therapy when first line agents do not provide adequate relief.

The following NSAIDs and combination therapies have the largest body of evidence supporting their use in the treatment of migraines: aspirin, ibuprofen, naproxen, tolfenamic acid and the combination of acetaminophen/ aspirin/caffeine. These medications are relatively efficacious, with the acetaminophen/ aspirin/caffeine combination having the most consistent efficacy. Many NSAIDs are available over-the-counter, which makes them an inexpensive and convenient therapeutic option. Common adverse effects seen with these medications are gastrointestinal effects such as nausea and dyspepsia. Patients who have a past medical history of renal or peptic ulcer disease should use these medications with caution. Due to lack of evidence, acetaminophen alone is not routinely recommended for the treatment of migraine symptoms.

Combination analgesics such as Midrin or butalbital with acetaminophen or aspirin are other treatment options. Midrin, a combination of acetaminophen/ isometheptene/ dichloralphenazone, is typically an alternative agent for migraine therapy because only modest benefits have been shown in clinical trials. There are no well-designed clinical studies to support the use of butalbital-containing products in the treatment of migraine headaches, although they are commonly used in clinical practice.
Ergot Alkaloids. Ergotamine tartrate and dihydroergotamine (DHE) may be used for patients with moderate to severe migraines or for patients that did not respond to treatment with non-specific agents.

Overall, there is inconsistent evidence regarding the efficacy of ergotamine in the treatment of migraines. It is supplied as an oral and sublingual tablet, as well as a rectal suppository. The oral and rectal forms of this medication are formulated in combination with caffeine in order to increase absorption and analgesic activity. It is important to note that strict dosing restrictions must be followed to prevent rebound headaches from occurring.

DHE is mostly used in the emergency setting for treatment of moderate to severe migraines; however, patients can be instructed on how to use this medication at home. It may be administered via the intranasal or parenteral route (subcutaneous, intramuscular, or intravenous). One advantage of DHE is that it is not believed to cause rebound headache. It is thought to be relatively equally effective and safe as other acute migraine treatment options.

The most common side effect that may be seen with use of these medications is nausea and vomiting due to stimulation of the chemoreceptor trigger zone. Pretreatment with an antiemetic should be considered in patients taking these medications. One very rare, but serious side effect of these medications is peripheral ischemia, also known as ergotism. Some signs and symptoms of ergotism include cold and numb extremities, consistent paresthesias, and diminished pulses in the extremities. These symptoms are a direct result of the vasoconstrictive properties of these agents. These medications should not be used in patients who have renal or hepatic failure, vascular disease, uncontrolled hypertension, or sepsis.

Corticosteroids. Parenteral hydrocortisone and dexamethasone may be used as a rescue medication to treat status migrainosis, which is a migraine headache that persists for up to one week. Corticosteroids are thought to work by decreasing the peptide-mediated inflammation in the brain; however the evidence supporting the efficacy of steroids in acute migraine treatment is inconsistent.

MIGRAINE PROPHYLAXIS
Epidemiologic studies suggest that approximately 38% of people who suffer from migraines need preventative therapy; however, it is estimated that only 3% to 13% currently use prophylaxis. Preventative therapy has the potential to significantly improve quality of life for these patients, and pharmacists have the opportunity to recognize this need as well as help with the decision to initiate appropriate prophylaxis therapy. Therefore, it is important for pharmacists to understand when migraine prophylaxis is warranted, which medications are effective, and in which cases particular medications may be preferred.

Preventative therapy should be considered in patients whose migraine attacks have a significant impact on their quality of life despite appropriate use of acute treatments and lifestyle modifications or trigger management strategies. This usually includes people whose migraines occur two or more times per month with disability lasting three or more days per month. People who fail, have contraindications for, or experience adverse events from acute treatments are also candidates for migraine prophylaxis. Prevention would also be preferred in people who use acute treatment medications more than twice per week and in those with uncommon migraine conditions such as hemiplegic migraine, migraine with prolonged aura, or migraineous infarction (which is a stroke that occurs in the setting of a migraine attack). Patient preference and cost of therapy should also be considered. The primary goal of migraine prophylaxis is to improve patients’ quality of life by reducing the frequency, severity, and duration of migraines and also by increasing responsiveness to acute treatment when migraines occur.

Therapy should be initiated with medications that are proven to be most effective with the lowest potential for adverse effects; these agents should be started at low dosages and slowly titrated (usually every 2 to 4 weeks) to a therapeutic response or until side effects prevent any further increase in dose. An adequate trial to assess efficacy may take approximately 2 to 6 months at the target dose or at the maximum tolerated dose. Prophylactic medications are usually considered effective if the frequency or duration of migraine attacks is reduced by 50% or more per month. A reduction in migraine frequency less than 50% may be worthwhile, especially if the medication is well tolerated. Other factors to consider include reductions in migraine severity and migraine-related disability.

Patients using prophylactic medications should be assessed periodically to monitor both efficacy and tolerability. Because of its utility in assessing the efficacy of migraine prophylaxis, patients should be strongly encouraged to keep a headache diary or calendar. After 6 to 12 months of successful prophylaxis, consideration should be given to tapering and discontinuing therapy, although some patients may benefit from continuing treatment much longer. If migraine frequency increases as the prophylactic drug is being tapered down, the dosage may be increased again or restarted if the drug has been discontinued.

Several medications have been shown to be effective for the prevention of migraines. The various drug classes used include beta-blockers, anticonvulsants, antidepressants, angiotensin blockade agents, triptans, NSAIDs, botulinum toxin type A (Botox), as well as a variety of complimentary treatments. A summary of common agents used for migraine prophylaxis is provided in Table 4.

Beta-blockers. There is considerable evidence to support the use of beta-blockers for migraine prophylaxis. Although the precise mechanism for migraine prevention is unknown, beta-blockers may raise the migraine threshold by modulating adrenergic or serotonergic neurotransmission in cortical pathways throughout the brain. The most commonly used agent is propranolol; however, metoprolol, timolol, atenolol, nadolol, and nebivolol are also used. Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, have been used; however, newer evidence suggests that these agents should be avoided because they have the potential to worsen migraine symptoms.

In general, if a patient fails a trial with one beta-blocker, another within the class may be effective. The general response to these agents is gradual, and it may take at least a month to see an effect. It should be noted that beta-blockers are not effective in reducing aura. Adverse effects associated with beta-blockers include fatigue, reduced exercise tolerance, dizziness, nausea, insomnia, and depression. They should be avoided or used cautiously in patients with asthma, hypoglycemia associated with diabetes treatment, heart block, and hypotension. Beta-blockers may be especially useful in patients with concomitant cardiovascular disorders (e.g. hypertension, angina, or post-myocardial infarction), tremors, or anxiety.

Anticonvulsants. Anticonvulsants have been shown to be effective for the prevention of migraines. The beneficial effects of these agents are likely linked to several mechanisms including enhancement of
γ-aminobutyric acid (GABA)-mediated inhibition, modulation of the excitatory neurotransmitter glutamate, and inhibition of sodium and calcium ion channel activity. The most commonly used anticonvulsants are divalproex sodium, sodium valproate, and topiramate.

Drug concentrations of divalproex sodium and sodium valproate should only be monitored if toxicity or compliance are in question; a serum drug concentration of 50 to 120 mg/L is considered to be in the therapeutic range. Adverse effects associated with these agents include nausea, vomiting, fatigue, tremor, weight gain, dizziness, and hepatotoxicity. Gastrointestinal side effects usually diminish with continued use. Valproic acid derivatives should be avoided or used with extreme caution in patients with liver disease, pregnancy, and young children. Valproic acid derivatives may be ideal in patients with prolonged or atypical aura, cluster or tension-type headaches, or patients with concurrent seizure, anxiety, or manic-depressive disorders.

Several studies evaluated the efficacy of topiramate in migraine prophylaxis; improvement in migraine frequency usually occurs within the first month of treatment. Adverse effects include paresthesia, fatigue, nausea, and weight loss. Because of its propensity to promote weight loss, topiramate is particularly useful in patients who are overweight, patients who are particularly concerned about weight gain, and in patients with co-morbid conditions that might be exacerbated by weight gain (i.e., diabetes).

**Antidepressants.** The tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs) are the most commonly used antidepressants in migraine prophylaxis. The beneficial effects of these agents in migraine are independent of their antidepressant activity and may be related to down-regulation of central 5-HT2 receptors, increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor activity. Amitriptyline is the only TCA with consistent evidence to support its efficacy for this indication. Adverse effects of amitriptyline include drowsiness, weight gain, and anticholinergic symptoms such as dry mouth. Nortriptyline is the active metabolite of amitriptyline and has a slightly better side effect profile making it an acceptable, although a less evidence-based, alternative. The only SNRI with evidence for use is venlafaxine. The most common adverse effects of venlafaxine include nausea, vomiting, and drowsiness.

These antidepressants should be avoided or used with caution in patients with arrhythmias, urinary retention, closed-angle glaucoma, seizures, as well as patients who are obese, pregnant, or concurrently treated with other medications.
using monoamine oxidase inhibitors (MAOIs). Antidepressants may be especially useful for migraine prophylaxis in patients with concurrent anxiety, depression, insomnia, and chronic pain.10,11

**Angiotensin blockade agents.** Recent studies have shown that angiotensin blockade agents are useful in the prevention of migraine. Although the exact mechanism is unknown, inhibition of angiotensin II has several effects that may be relevant to migraine such as modulation of cerebrovascular flow and effects on autonomic pathways, neuroendocrine systems, and fluid and electrolyte homeostasis.13

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications and Dosing</th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>Propranolol: initial 20 to 40 mg BID, increased by 20 mg BID every one to two weeks; target 80 to 160 mg daily, divided BID, or use LA product once daily</td>
<td>First-line therapy, especially in patients with hypertension, angina, post-MI, tremors, or anxiety</td>
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<td></td>
<td>Metoprolol: 100 to 200 mg once daily (metoprolol succinate) or divided BID (metoprolol tartrate)</td>
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<td></td>
<td>Timolol: 10 mg BID or 20 mg once daily; range 10 mg once daily to 30 mg daily, divided</td>
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<tr>
<td><strong>Anticonvulsants</strong></td>
<td>Amitriptyline: initial 10 mg HS, increased by 10 mg every one to two weeks; target 20 to 40 mg HS; max 150 mg per day</td>
<td>Second-line therapy, especially in patients with depression, anxiety, insomnia, or chronic pain</td>
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<td></td>
<td>Venlafaxine: initial 37.5 mg once daily for one week, increased weekly by 37.5 to 75 mg/day; target 150 mg once daily</td>
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<tr>
<td><strong>Angiotensin blockade agents</strong></td>
<td>Lisinopril: target 20 mg once daily</td>
<td>Third-line therapy, especially in patients with hypertension, heart failure, or diabetes</td>
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<td>Candesartan: target 16 mg once daily</td>
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<tr>
<td><strong>Triptans</strong></td>
<td>Frovatriptan: 2.5 mg BID for six days</td>
<td>Frovatriptan: First-line therapy for MRMs</td>
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<td></td>
<td>Naratriptan: 1 mg BID for five days</td>
<td>Naratriptan, Zolmitriptan: Second-line therapy for MRMs</td>
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<td></td>
<td>Zolmitriptan: 2.5 mg BID for seven days</td>
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<td>*Begin therapy 2 days before menses</td>
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<tr>
<td><strong>NSAIDs</strong></td>
<td>Naproxen: 250 to 550 mg BID</td>
<td>Good choice for predictable migraines, especially MRMs or other predictable triggers</td>
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<td>Naproxen sodium: 220 or 440 mg once, then 220 mg every 8 to 12 hours</td>
<td>Good for concurrent arthritis or dysmenorrhea</td>
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<td></td>
<td>Ibuprofen: 400 mg once daily</td>
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<td>*Begin therapy 2 or 3 days before anticipated headache and continue during the at-risk period</td>
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<tr>
<td><strong>Botulinum toxin type A (Botox)</strong></td>
<td>Administered intramuscularly as 0.1 mL (5 units) injections in 31 to 39 sites around the head and back of the neck every 12 weeks</td>
<td>Good for chronic migraines when at least 3 other prophylaxis therapies have failed</td>
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The angiotensin-converting enzyme inhibitor (ACEI) lisinopril has demonstrated some effectiveness in the prevention of migraine.10 Approximately 30% of patients experienced migraine half as often when compared to no therapy. It is generally well tolerated; the most common adverse effect is cough. The angiotensin receptor blocker (ARB) candesartan showed similar results; approximately 40% of patients had their migraine frequency reduced by half or more. Adverse effects associated with candesartan were similar to placebo. Although the evidence for the use of these agents in migraine prophylaxis is limited, they have a good side effect profile. Thus,
angiotensin blockade agents would be good alternatives to beta-blockers in patients with concurrent hypertension as well as other cases these agents are used such as heart failure or diabetes.¹

**Triptans.** The triptans are typically used for acute treatment of migraines; however, a few of these agents have evidence to support their use in the prophylaxis of menstrually related migraines (MRM).¹ Frovatriptan has established efficacy for the short-term prevention of MRM. When used for six days, beginning two days prior to the anticipated MRM, frovatriptan significantly reduced the frequency and severity of MRM.¹⁴,¹⁵ The long duration of action and good tolerability of frovatriptan makes it a good choice for prevention of MRM. Based on currently available evidence, naratriptan and zolmitriptan may also be considered for the short-term prevention of MRM.³

The triptans are generally well tolerated; adverse effects are similar to placebo, with the most common being asthenia, dizziness, and nausea.² These agents should be avoided in patients with concurrent uncontrolled hypertension as well as cardiovascular or cerebrovascular disease.² Overall, frovatriptan, naratriptan, and zolmitriptan are considered safe and effective for the prevention of MRM.

**NSAIDs.** The majority of evidence supports the use of naproxen sodium and naproxen for migraine prevention; however, other NSAIDs including ibuprofen, ketoprofen, fenoprofen, flurbiprofen, and mafenamic acid have some evidence to support their use.¹² NSAIDs are commonly used intermittently when predictable migraine triggers, such as menstruation, are identified.¹⁰,¹¹ In the case of menstruation, NSAIDs may be especially helpful if used 2 to 3 days prior to menses and continued throughout the period. Not only are these good choices for patients with MRM, they are also very helpful in patients with co-existing dysmenorrhea. Chronic use of NSAIDs in patients with concurrent arthritis may also be useful for migraine prevention.¹¹

Adverse effects tend to be infrequent with short-term therapy; however, chronic use of NSAIDs may cause dyspepsia, erosive gastritis, peptic ulceration, gastrointestinal bleeding, and hematologic complications.¹⁰,¹¹ NSAIDs should be avoided or used with caution in patients with hypersensitivity to aspirin, active gastrointestinal bleeding, coagulopathies, hypertension, elderly patients, and patients with peptic ulcer, liver, or kidney disease. It should also be noted that regular or daily use of NSAIDs for the treatment of frequent migraine attacks may exacerbate headache due to the development of medication overuse (or rebound) headaches. Use of NSAIDs for the treatment of migraine attacks for 15 days or more per month increases the likelihood that the headache attacks are due to medication overuse.⁷ Clinicians should be aware of this condition when assessing patients who use NSAIDs for migraine prophylaxis.

**Botulinum toxin type A (Botox).** Recent evidence supports the use of Botox for the prevention of chronic migraines, which are defined as headaches that occur on at least 15 days per month with at least 8 days being migraine headaches.¹⁶ Botox should be considered in patients who have not responded to at least three prior pharmacological prophylaxis therapies and whose condition is appropriately managed for medication overuse. It should be noted that there is insufficient evidence to support the use of Botox in patients with episodic migraines, which is defined as fewer than 15 headache days per month for three consecutive months.¹⁶,¹⁷

When used for migraine prevention, Botox is injected into 31 to 39 sites around the head and back of the neck; for best results, this should be repeated every 12 weeks.¹⁶ Common side effects associated with the use of Botox include ptosis (drooping upper eyelids), blurry vision, local transient pain at the site of the injection, and bruising.¹² Botox should be discontinued in people who do not adequately respond to therapy or in people whose condition changes to episodic migraine. An inadequate response to therapy is defined as less than a 30% reduction in headache days per month after two treatment cycles. Overall, Botox seems to be a safe and effective option for the prevention of chronic migraines when other prophylactic therapies have failed.

**Complementary treatments.** Several complementary or alternative treatments have been used for migraine prophylaxis, although the evidence supporting the use of many of these agents is still unclear. Complementary treatments that may be used include Petasites (butterbur), MIG-99 (feverfew), magnesium, riboflavin (vitamin B2), coenzyme-Q10, and estrogen.¹⁰,¹¹ Specific recommendations and evidence supporting the use of these complimentary agents is beyond the scope of this manuscript.

**CONCLUSION**

In conclusion, migraine headaches continue to be a difficult condition to treat due to lack of understanding of the condition as well as the difficulty in predicting individual patient responses to available therapies.³ Migraines significantly affect patients’ lives as they may lead to significant impairment of daily function and quality of life. Pharmacists have the opportunity to help patients achieve control of their migraines by recommending the appropriate treatment. It is important to individualize both acute and prophylactic migraine therapy based on patient specific characteristics and specific migraine symptoms.

For best results, acute migraine therapy should be administered as early as possible when migraine symptoms occur. If migraines are severe and debilitating, occurring frequently, or if acute migraine therapies are ineffective or cannot be used, then preventative therapy should be considered. To achieve optimal outcomes, patients should try different migraine therapies to see which is best suited for them. Further research is needed to fully understand the underlying causes of migraines and to help in the development of medications with increased efficacy and more favorable adverse effect profiles. ♦
REFERENCES


