

The Pharmacists Role in Migraine Management: Challenges and Opportunities

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Learning Objectives:

Pharmacists:

After this completing this continuing education program, pharmacists will be able to:

1. Understand the etiology of migraine and be able to distinguish it from other types of headache
2. Understand the OTC and prescription medication therapy currently available to treat migraine
3. Understand non-pharmacological interventions that can assist in migraine prevention and treatment.
4. Identify problems associated with medication use in individuals with migraine, particularly overuse of some OTC and prescription medications.

Pharmacy Technicians:

After completing this lesson, pharmacy technicians should be able to:

5. Understand the etiology of migraine and be able to distinguish it from other types of headache
6. Understand the OTC and prescription medication therapy currently available to treat migraine
7. Understand non-pharmacological interventions that can assist in migraine prevention and treatment.
8. Identify problems associated with medication use in individuals with migraine, particularly overuse of some OTC and prescription medications.

One person in every four American households, or 28 million people, will experience migraine headaches. Eighteen percent of American women experience migraine, and 6% of men report migraine at some time in their lives. Migraines are reported to be responsible for over 112 million bedridden days per year at a cost of \$13 billion to employers. Attacks range from mild to severe, and can last from 4 hours to 72 hours. In the most severe attacks, migraine sufferers are unable to pursue basic daily activities. No cure currently exists for migraine, and therefore each patient must be treated based on individual symptoms, responsiveness to medication therapy, and other non-pharmacological interventions that provide relief.

Introduction

One person in every four American households, or 28 million people, will experience migraine headaches. Eighteen percent of American women experience migraine, and 6% of men report migraine at some time in their lives. The incidence peaks during adolescence, and the prevalence is greatest between the ages of 25 and 55 years of age. Migraines are reported to be responsible for over 112 million bedridden days per year at a cost of \$13 billion to employers. The incidence of migraine varies among race, gender, and household income. Individuals of African American descent appear to be less likely to experience migraine. This is believed to be because of higher levels of an enzyme that metabolizes dietary tyramine and thus seems to provide additional protection against migraine. Women generally experience more severe symptoms, including more intense pain, nausea and vomiting, and are more likely to be bedridden than men. The rationale for the differences among women and men are thought primarily to be hormonal. In general, individuals of lower socioeconomic status have a greater incidence of migraine than individuals with higher incomes. No measurable difference has been observed in urban or rural areas.

The average migraine sufferer experiences the first attack during the early teen years, and the attacks generally continue throughout adulthood. Migraine is characterized by recurring attacks of throbbing headache pain, often associated with visual, auditory, or gastrointestinal disturbances. Attacks range from mild to severe, and can last from 4 hours to 72 hours. In the most severe attacks, migraine sufferers are unable to pursue basic daily activities. While the precise mechanism of migraine is unknown, researchers believe

migraine attacks are caused by acute inflammation surrounding selected blood vessels in the head. Migraine sufferers often experience a “postdromal” period described as washed out or feelings of being hungover after the headache symptoms subside.

No cure currently exists for migraine and therefore, each patient must be treated based on individual symptoms, responsiveness to medication therapy, and other non-pharmacological interventions that provide relief.

Headache Classification

This classification system listed below in **Table 1** is based upon the second edition of International Classification of Headache Disorders (ICHD-II) criteria for identifying headache etiology and aids in diagnosis.

Diagnosing migraine

Diagnosis will first include ruling out other types of headache based upon ICHD-II criteria. Then, an individual will be asked about their environmental surroundings, stress level, and diet and exercise routine. Information on common dietary, hormonal, stress, sleep, environmental and physical triggers can be found at the following website:

<http://www.uhs.berkeley.edu/home/healthtopics/pdf/riggers.pdf>. Generally, the diagnosis is based upon the neurologic evaluation, physical examination, and assessment of patient history. MRIs, CT scans, and other imaging are generally not used unless the neurologic exam shows potential for abnormalities.

General treatment options for migraine

Treatment is based upon the level of pain experienced by the patient and level of debilitation with the goal of restoration of normal function and headache relief. Successful treatment depends primarily on initiation of therapy as close to onset of migraine pain as possible. If an individual experiences symptoms prior to the onset of a migraine, treatment can begin to prevent progression.

Generally, physicians used a stepped approach that first includes the use of mild OTC or prescription analgesics including non-steroidal anti-inflammatories (NSAID) or aspirin therapy. If an individual fails to respond appropriately to these therapies, then classes of medications specifically approved to treat migraine, triptans or dihydroergotamine (DHE) or other ergot alkaloid, are initiated. Other treatment options that are not specific for treating migraine pain include barbiturates and narcotic pain medications. Antiemetic agents are often used if migraine therapy alone does not

cure nausea.

Measuring medication efficacy is generally based upon assessing patient's response to medications regarding migraine relief. A simple, standard questionnaire has been developed to assess response to migraine therapy. According to the questionnaire, answering "no" to any of the following would potentially require a change of migraine medication:

- Does your migraine medication work consistently in the majority of attacks?
- Does your headache pain disappear within 2 hours?
- Are you able to function normally within 2 hours?
- Are you comfortable enough with your medication therapy to be able to plan your daily activities?

Migraines should not be overtreated with medication therapy because prolonged use often exacerbates an existing headache or causes rebound or withdrawal headaches. ICHD-II defines medication overuse as 15 or more consistent days of analgesic therapy or 10 consistent days per month for 3 months of use of a migraine-specific therapy, opioid analgesic, or other combination of medications. Individuals who exceed medication utilization limits should be evaluated for migraine prevention therapy.

Current pharmacological treatment for migraine

Classification systems accepted for migraine treatment and prevention include the American Academy of Neurology (AAN) and American Academy of Family Practitioners and the American College of Physicians–American Society of Internal Medicine (AAFP/ACP-ASIM), and the US Headache Consortium. These organizations sometimes provide slightly different recommendations for treatment but both provide clinicians with acceptable protocols. Pharmacists should recognize both systems and understand the differences.

NSAIDs and other analgesics

OTC NSAID treatment includes naproxen and ibuprofen available in a variety of generic and brand names. Prescription NSAID pain relievers include ketorolac and diclofenac as well as prescription strengths of ibuprofen and naproxen. AAFP/ACP-ASIM recommends NSAIDs as first-line therapy for migraine. AAN suggests use of NSAIDs as first-line therapy only in the case of mild-moderate migraine or when an individual has responded to similar therapy in the past.

OTC acetaminophen is used by some migraine sufferers in a combination of OTC "migraine" products that include caffeine as an active ingredient. Neither AAFP/ACP-ASIM nor AAN recommends acetaminophen alone.

If an individual fails to respond to basic analgesic therapy, then the next level of therapy should be initiated with either triptans or DHE medications specific for migraine treatment. Pharmacists should evaluate the need for these products using the sample questionnaire described above or by assessing patient need through regular interactions.

Triptans

Triptans are a class of agents specifically approved for use in migraine. **Table 2** provides a list of triptans currently approved in the United States, general dosing information, and the pros and cons for selecting a particular product. AAN guidelines recommend triptans as a first-line class of therapy for moderate to severe migraine, and AAFP/ACP-ASIM recommends these agents after failure of NSAIDs or other analgesics or as first-line therapy for more severe, debilitating migraine.

As a class, these medications are fast acting to provide immediate relief of migraine and are generally well tolerated. These agents are also available in a variety of dosing formats, including nasal sprays, oral tablets, dissolving tablets, and injectables to allow for flexible dosing options depending upon the needs of individuals. Non-oral administration is available for individuals who experience nausea and vomiting.

Triptans work by stimulating the 5-HT receptors on cranial vessels, thereby producing vasoconstriction, and may also act by blocking sensitization of central trigeminovascular neurons. They inhibit the release of neurotransmitters involved with vasodilatation and inflammation.

Triptans are contraindicated in some patients with a history of, or at risk for, heart disease or stroke, and individuals with hypertension because of the vasoconstriction properties. Other common side effects include warmth, tingling, and fatigue. Some individuals may also experience tightness in the chest or throat. Most triptans are contraindicated with the use of MAOI agents and some are contraindicated with propranolol or oral contraceptive pills. Some also have unique reactions with cimetidine or ergot alkaloids, which are also indicated for migraine relief. The side effect profile and contraindications should be examined before selecting a triptan. (Most are compared to sumatriptan because it was the first in class and considered the standard therapy.) Furthermore, most have monthly limits on the dosage and/or number of tablets recommended.

Ergot alkaloids

Two agents in this class are currently available in the United States: DHE and ergotamine tartrate with caffeine. These products work by producing vasoconstriction in intracranial vessels and reduce

neurogenic inflammation in the trigeminovascular system. AAN considers these agents as first-line therapy for the treatment of migraine. DHE is available as a nasal spray and for injectable use in emergency situations. Ergotamine is available generically in oral tablets and rectal suppositories. Generally, these agents are less effective than sumatriptan and other triptan therapy, especially when given as monotherapy. When combined with an antiemetic, the use of DHE is as effective as NSAIDs or opioid therapy. Side effects of ergotamine derivatives include ergot poisoning, tachycardia, bradycardia, localized edema, cardiovascular events, GI events, and dry mouth. Rhinitis may occur with the nasal spray and nausea and vomiting has been associated with the intravenous injection.

These agents cannot be used in combination with triptans because of the cumulative effect of stimulating 5-HT receptors. Ergotamine and its derivatives are also contraindicated in pregnancy because it has properties that may induce labor.

DHE has specific interactions with β -blockers, antihypertensive, selective serotonin reuptake inhibitors (SSRIs), dopamine, macrolide antibiotics or nitrates, and therefore are contraindicated. Patients with diagnoses of angina, coronary artery disease, hypertension, history of heart attack, peripheral vascular disease, or renal impairment should not use DHE.

Narcotic analgesics

Narcotic analgesics are not specifically indicated to treat migraine, rather the indication for generalized pain suppression in the hypothalamus. Individuals who do not respond to non-narcotic analgesics or medications specifically for migraine may receive butorphanol nasal spray, intramuscular meperidine or methadone. Use of these medications may cause addiction or other unwanted debilitating side effects and therefore should not be considered first-line therapy.

Other medications

Other medications have been used in the treatment of migraine, but little clinical research exists that prove the benefit of these agents. A summary of the use of these agents is below:

- Butalbital, a barbiturate, should be very limited because of withdrawal potential.
- Isometheptene has shown clinical effectiveness compared to placebo and is recommended by AAN for mild to moderate migraine.
- Corticosteroids are generally used for rescue therapy.
- Topical lidocaine may be beneficial for some

individuals who do not experience an aura with migraine but intranasal lidocaine has shown little effectiveness.

Antiemetics for use in nausea and vomiting

AAN and AAFP/ACP-ASIM guidelines suggest that antiemetics be administered in a preventive manner even without vomiting because of the debilitating effects of nausea. Antiemetics include oral antiemetics, intramuscular metoclopramide; intravenous, intramuscular, or rectal prochlorperazine, or 5-HT antagonists (contraindicated for use with triptans because they work against the clinical benefit of stimulating 5-HT receptors). All of these agents can cause sedation, drowsiness or dizziness so individuals should be cautioned that falls may occur and not to drive or operate heavy machinery while using.

Avoiding overuse of medication

Overuse of migraine medications is a problem that can create physical and psychological dependency as well as result in recurrent headaches or cause more regular occurrences. To avoid overuse, gradually taper the overused medication and replace with another therapy; temporarily switch the medication to a transitional medication and then taper the transitional medication; and provide a transitional medication quickly and then begin preventive therapy to stop the onset of a migraine.

Quick hints for managing overuse:

- Agents that can be discontinued quickly: triptans, ergot alkaloids, and nonopioid analgesics.
- Gradual tapering is necessary to avoid side effects or withdrawal with opioids, barbiturates and caffeine.
- Transitional therapies may include a 3-day to 7-day taper of oral steroids, a daily triptan, or a short course of NSAIDs.

Medication therapy for migraine prevention

Prevention of migraine is the goal of therapy for individuals with recurrent headaches, those who fail on migraine therapy, and those for whom therapy is contraindicated or cannot tolerate therapy. Differing guidelines exist to determine the need for preventive therapy. AAN and U.S. Headache Consortium guidelines suggest that any recurring migraines that the patient perceives as significantly interfering with daily routines, despite acute treatment, may be considered for prevention. AAFP/ACP-ASIM guidelines require preventive therapies be considered for patients who have two or more attacks per month that result in 3 or more days of disability per attack.

Medications used as first-line therapy for migraine prevention:

- FDA has approved beta-blockers, specifically propranolol and timolol, for this purpose. Other effective agents - although not specifically FDA approved for migraine prevention - include atenolol, metoprolol, or nadolol. These agents may take up to 12 weeks to take effect. Beta-blockers are most effective for individuals with existing hypertension, tremors, or anxiety.

Contraindications for the use of beta-blockers include asthma, type 1 diabetes, cardiac conduction abnormalities, or Raynaud's disease. Adverse effects include fatigue, reduced exercise tolerance, sexual dysfunction, depression, nausea, bradycardia, orthostatic hypotension, and insomnia.

- Tricyclic antidepressants (TCAs), especially amitriptyline, are the only class of antidepressants that have shown efficacy in preventing migraine. TCAs are most effective in individuals who also have depression, coexisting migraines and tension headaches.

Contraindications to use of TCAs include wide-angle glaucoma, enlarged prostate, heart disease, hypotension, cardiac dysrhythmia, bowel obstruction, and urinary bladder retention. Side effects include dry mouth, weight gain, blurred vision, constipation, urinary retention, orthostatic hypotension, palpitations, and sexual dysfunction.

- Two antiepileptic agents (AEDs) have been approved for migraine: divalproex sodium and topiramate. Divalproex is approved for long-term prevention with effectiveness shown up to 3 years. However, in recent years, topiramate has been shown to be the most effective agent with benefits beginning in the first month of therapy. When using antiepileptic agents, research suggests beginning with low doses and gradually increasing over time. General side effects of AEDs include fatigue, nausea, dry mouth, memory loss, dizziness, and vertigo. Weight gain is often a side effect of these agents but not with use of topiramate; in fact, it may cause weight loss or anorexia. Other side effects specific to topiramate include taste perversion, cognitive dysfunction, angle-closure glaucoma, and predisposition to kidney stones. Divalproex has slightly more serious side effects and therefore should be used with greater caution. These side effects include severe drowsiness, hair loss, polycystic ovary syndrome, hepatotoxicity, and hemorrhagic pancreatitis. Individuals prescribed

divalproex must undergo liver testing prior to beginning therapy and undergo testing throughout treatment. Divalproex is also contraindicated in individuals with a pre-existing liver condition.

Pharmacists' role in preventing and treating migraines

As a publicly accessible health care professional, pharmacists play a key role in helping individuals manage migraine therapy. Appropriate utilization of migraine medications is low and many individuals improperly self-medicate or take dangerous doses of other medications. Pharmacists can assist individuals with migraines by monitoring their medication therapy regimens, particularly refills of migraine specific medications. If a pharmacist suspects overuse of a medication, then he or she should, in conjunction with a physician, recommend the tapering/switching techniques described above. Furthermore, a pharmacist can use the questionnaire to determine whether medication therapy is adequate and then recommend appropriate changes and tapering techniques.

Pharmacists can also help migraine sufferers to understand non-pharmacological interventions that often help to prevent migraine. For example, pharmacists should provide information regarding foods and medications that can cause or exacerbate a migraine. Other behavioral factors that can help prevent a migraine include ensuring proper sleep patterns, stress reduction, and curbing environmental factors such as indoor pollutants that may lead to migraine. Finally, pharmacists should educate individuals about the potential warning signs associated with migraine and if the person experiences these effects, recommend appropriate preventive therapy or begin migraine treatment prior to onset.

Summary

Migraine is a problematic condition that affects millions of Americans and results in billions of dollars of lost productivity in the workforce. Even worse, for individuals who experience migraine, the effects can be devastating and debilitating. Medication therapy is often difficult to manage appropriately and many individuals are improperly or ineffectively treated. Pharmacists often have access to these individuals on a regular basis and could monitor treatment and therapy to ensure adequacy and appropriateness. Given the prevalence of migraine, all pharmacists should be armed with adequate information about migraine therapy and understand the signs and symptoms.

Table 1

Type of headache	ICHD-II diagnostic criteria	Other important characteristics
Migraine	<p>A. At least 5 attacks fulfilling criteria B-D below</p> <p>B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)</p> <p>C. Headache has at least two of the following characteristics:</p> <ul style="list-style-type: none"> • unilateral location • pulsating quality • moderate or severe pain intensity • aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs) <p>D. During headache at least one of the following:</p> <ul style="list-style-type: none"> • nausea and/or vomiting • photophobia and phonophobia <p>E. Not attributed to another disorder</p>	<p>May occur in children.</p> <p>More common in women than men.</p> <p>Some individuals describe a visual or sensory “aura” prior to onset of headache. (Only about 30% of migraine sufferers experience the aura so it is no longer considered in the criteria for diagnosis.)</p> <p>Often exacerbated by physical activity.</p> <p>Can be precipitated by certain foods and beverages, stress, hormones, and environment.</p>
Tension-type headache (TTH)	<p>A. At least 10 episodes occurring on <1 day per month on average (<12 days per year) and fulfilling criteria B-D below</p> <p>B. Headaches lasting from 30 minutes to 7 days</p> <p>C. Headache has at least two of the following characteristics</p> <ul style="list-style-type: none"> • Bilateral location • Pressing/tightening (nonpulsatile) quality • Mild or moderate intensity • Not aggravated by routine physical activity such as walking or climbing stairs <p>D. Both of the following:</p> <ul style="list-style-type: none"> • No nausea or vomiting (anorexia may occur) • No more than one of photophobia or phonophobia <p>E. Not attributed to another disorder</p>	<p>Most common headache type occurring in 30-78% of population at some point in their lives.</p> <p>Have been known as muscle contraction type headache, psychomyogenic headache, ordinary headache, idiopathic headache and, psychogenic headache.</p> <p>Usually bilateral pain described as a tension or pressing feeling</p> <p>Not exacerbated by physical activity and no nausea present.</p>
Cluster headache	<p>A. At least 5 attacks fulfilling criteria B-D</p> <p>B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated</p> <p>C. Headache is accompanied by at least one of the following</p> <ul style="list-style-type: none"> • Ipsilateral conjunctival injection and/or lacrimation • Ipsilateral nasal congestion and/or rhinorrhea • Ipsilateral eyelid edema/ipsilateral forehead and facial sweating • Ipsilateral miosis and/or ptosis • A sense of restlessness or agitation <p>D. Attacks have a frequency from one every other day to 8 per day</p> <p>E. Not attributed to another disorder</p>	<p>Occur in approximately 1% of population.</p> <p>Most common in men age 20-40 years old.</p> <p>Attacks do not last all day, but generally occur every other day up to 8 times daily.</p> <p>Unilateral pain accompanied by tearing on the same side as headache. Sweating, salivation, runny nose, and drooping or swelling eyelids may occur.</p>

Table 2

Triptans available in the United States

Brand (generic, manufacturer)	General dosing information	Pros/cons for selection
Axert® (almotriptan, Ortho-McNeil Neurologic)	Tablet 6.25–12.5 mg; additional dose may be given after 2h, up to two doses/d	Contraindicated with MAOIs, ketoconazole, and other inhibitors of the cytochrome 3A4 inhibitors (CYP 3A4)—great potential for drug interactions Highest oral bioavailability in class Better sustained response than sumatriptan
Relpax® (eletriptan, Pfizer, Inc.)	Tablet 20–40 mg; additional dose may be given after 2h, up to 80 mg/d	Contraindicated with propranolol and CYP 3A4 inhibitors—great potential for drug interactions Rapid onset with 2-hour response rate
Frova® (frovatriptan, Endo Pharmaceuticals)	Tablet 2.5 mg; a second 2.5 dose may be given 2h, up to three 2.5 mg tablets/d	Contraindicated with oral contraceptive pills, ergotamine, and propranolol Slow onset of action for individuals with slow onset headaches and those with recurrent headaches
Amerge® (naratriptan, GlaxoSmithKline)	Tablet 1–2.5 mg; additional dose may be given once after 4 h, up to 5 mg/d	Contraindicated with oral contraceptive pills Slow onset of action and favorable side effect profile More effective choice for those with a tendency to experience side effects but only those with mild-moderate migraine Long half-life makes recurrent headache less likely
Maxalt®, Maxalt® MLT (dissolving tablet) (rizatriptan, Merck & Company)	Tablet 5–10 mg; additional doses may be given 2h apart, up to 30 mg/d Orally disintegrating tablet 5–10 mg; additional doses may be given 2 h apart, up to 30 mg/d	Contraindicated with MAOIs and propranolol Fast acting and good consistency of response
Imitrex®, Imitrex® Nasal spray, Statdose® injection (sumatriptan, GlaxoSmithKline)	Subcutaneous 6 mg; additional doses 12 min in tablet form may be given up to 100 mg/d, 2 hours apart Tablet 25–100 mg; additional 2–2.5 h doses may be given after 2h, up to 200 mg/d Nasal spray 5–20 mg; additional dose 0.08–4 h may be given once after 2h, up to 40 mg/d	Contraindicated with MAOIs Subcutaneous form provides greatest bioavailability and fastest relief in class Nasal spray has rapid onset and low bioavailability and taste
Zomig®, Zomig® ZMT (dissolving tablet), Zomig® Nasal Spray (zolmitriptan, AstraZeneca)	Tablet ≤2.5mg; additional dose 1.5 h 40% 3 h may be given after 2 h Orally disintegrating tablet 2.5 mg; additional dose may be given after 2 h Nasal spray 5mg; additional dose may be given after 2 h	Contraindicated with MAOIs, propranolol, oral contraceptives, cimetidine, acetaminophen Generally considered a “neutral” agent in class with no real pros and cons Nasal spray has faster rate of absorption and more pleasant taste compared to sumatriptan
Treximet™ (sumatriptan and naproxen sodium, GlaxoSmithKline/Pozen, Inc.)	Tablet 85 mg sumatriptan-500 mg naproxen; 1 tablet daily; no more than 2 tablets in 24 h period.	Contraindicated with MAOIs and NSAID warnings Similar profile to sumatriptan and naproxen without having to take multiple dosages