The Pharmacological Management Of Migraine, Part 1
Overview and Abortive Therapy
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Educational Objectives
After reviewing this article, readers should be able to:
- Describe, in general terms, the epidemiology, pathophysiology, and public health implications associated with migraine.
- Identify the comorbidities and risk factors associated with migraine.
- Recognize the clinical presentations of migraine.
- Identify nonpharmacological treatments used in the management of migraine.
- Describe the abortive therapies used in the pharmacological treatment of migraine, including the risks and benefits of these agents.
- Understand the etiology and management of medication-overuse headache.

This is part 1 of a two-part series. Preventative therapy and treatment of special populations will be presented as part 2 in the August issue of P&T.

Introduction

Although tension headache is the most common headache type, migraine is the most common headache complaint in clinical practice. Migraine affects approximately 13% of adults in the U.S., and its prevalence ranges between 12% and 20% in various countries around the world.¹ Migraine is more common in females than males, with a prevalence of 19% and 7%, respectively. Approximately 80% of patients report a family history.¹⁻³

Because migraine affects people during their most productive years (the 25- to 50-year-old age group), direct and indirect costs have a significant impact on society. The direct costs are approximately $1 billion annually, and the indirect costs of lost time at work, school, and home result in an estimated $5.56 billion to $17.2 billion per year.¹,⁴⁻⁵ The pharmacotherapy of migraine is complex, and the appropriate use of abortive agents and preventative medications requires an understanding of the various medications available and when they are best used in migraine management.

Pathophysiology

Migraine is best described as a neuronal event that may be caused by a hereditary susceptibility of the brain and various environmental triggers. It may occur in patients who have a genetically sensitive nervous system. The pathophysiology of migraine continues to be studied, and numerous theories have been proposed.

The most recent and widely studied theory involves the trigeminovascular system, which—under the influence of a variety of external and internal triggers—results in the release of various inflammatory peptides, including calcitonin gene-related peptide (CGRP), substance P, neurokinin A, and nitric oxide. The resultant perivascular inflammatory response influences the trigeminal nucleus caudalis in the brainstem (the migraine generator) and cervical cord area, transferring pain data to the upper areas of the brain, including the thalamus and cortex. This leads to a state of hyperexcitability or cortical sensitization, resulting in the pain of migraine and associated features, including gastrointestinal (GI) and visual changes.⁶⁻⁷

Although other neurotransmitters may be involved in the pathophysiology of migraine, the serotonergic (serotonin, or 5-hydroxytryptamine [5-HT]) system may have significant involvement. Documented changes in 5-HT processing and metabolism during a migraine attack suggest that migraine is a result of a central neurochemical imbalance secondary to dysfunction of the serotonergic system. Although the exact series of events involved is not fully understood, low levels of 5-HT appear to cause activation of the trigeminovascular system.⁸

Clinical Presentation and Diagnosis

The clinical presentation of migraine may vary from patient to patient, and even within the same individual, it may vary from one attack to another. The proper diagnosis may require...
the assistance of physicians who have experience in headache management. Migraine may remain undiagnosed in many patients because of a wide continuum of presentations, often resulting in an improper diagnosis of sinus or tension headache. Such misdiagnoses may lead to inadequate or improper treatment.9,10 The Headache Classification Subcommittee of the International Headache Society (IHS) has developed a comprehensive system for classifying migraine that can be useful along with other tools to assist in the diagnostic process.11–14

Migraine may occur in three clinical phases:11

1. The pre-headache phase includes the premonitory phase and the migraine aura. This phase may precede the headache by hours to days, affecting up to 20% to 60% of patients. Features of the premonitory phase are both physical and somatic, compared with the aura phase, which manifests with more neurological features.

2. During the headache phase, the migraine itself usually presents with throbbing, pulsatile pain in the frontotemporal region, usually lasting from 4 to 72 hours. The pain may vary in severity from mild to severe and may escalate over the course of the headache. Other clinical features that may be present during this phase include nausea, vomiting, autonomic symptoms, nasal congestion, and lacrimation.10,11,14 Nausea and vomiting during a migraine are thought to be a result of the direct activation of trigeminal thalamic and spinal thalamic tracts.6 Many female patients experience migraines in relation to their monthly menstrual periods, offering targeted periods for treatment.15

3. The resolution (postdromal) phase consists of fatigue and irritability, lasting a day or two; this is sometimes referred to as the “migraine hangover.”10–12

Although these three phases characterize the stages of migraine, many patients do not present in such a typical fashion; they might experience only some of these clinical features, or the pain might present in a more atypical fashion.10–14 The IHS criteria of the International Headache Classification (ICHD-2) require two of the four pain characteristics and only one of the two associated symptoms for the clinical diagnosis of migraine.11

Migraine is associated with a wide range of comorbidities, including depression, bipolar disease, fibromyalgia, irritable bowel syndrome, overactive bladder, sleep disorders, obsessive–compulsive disorders, and anxiety, which may have a significant impact on the care of the patient.16,17

Migraine Triggers and Precipitating Factors

The therapeutic approach to migraine should always include an evaluation of potential triggers or precipitating factors. Although limited evidence implicates the role of diet as a trigger, some patients report benefits when they avoid certain foods and their chemical content. Numerous chemical substances found in various foods or medications, psychological and physical factors, and other triggers may exacerbate or precipitate migraine; an exhaustive list is beyond the scope of this article. Clinicians should evaluate patients for factors that might be causing or contributing to migraine.18–23

Managing the Patient with Headache

The initial assessment of patients with headache should include a complete medical evaluation to rule out reversible causes, including rare serious causes such as tumors or other cerebrovascular abnormalities. When migraine is diagnosed, the initial management should involve an assessment of potential triggers or exacerbating factors. Further management should include education for patients and their families, because migraine can have a significant impact on family life.19,22,24

Nonpharmacological treatment. Non-drug therapies include biofeedback, behavior modification, and psychosocial interventions, including relaxation and stress management. These therapies can be effective alone or in combination with medications in some populations.25–27 Other nonpharmacological therapies that may benefit some patients include acupuncture, applications of heat and cold, impulse magnetic-field therapy, photic stimulation, and physical approaches (e.g., aerobic exercise, isometric neck exercises, and chiropractic manipulations).28–30 Patients should take an active role in their care. Developing a headache diary and documenting headache frequency, associated triggers, and response to pharmacotherapy can be an excellent place to start.31

Pharmacotherapy. The pharmacotherapy of migraine involves medications used in acute (abortive) management and other agents that are used in preventative (prophylactic) management. The complex pathophysiology of migraine supports numerous targets for pharmacotherapy. Medications that interact with various vasoactive neurotransmitters—including serotonin, tyramine, norepinephrine, gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA), dopamine, and many other substances (e.g., bradykinin, histamine, and prostacyclin)—continue to be studied and utilized.32,33 Pharmacists, who are often the first health care contact for migraine patients, should have a good understanding of migraine and its pharmacological management.40

Part 1 of this continuing education article covers the abortive pharmacotherapy of migraine. A subsequent article in next month’s issue of P&T (part 2) will discuss prophylactic (preventative) pharmacotherapy.

Acute (Abortive) Migraine Treatment

The use of abortive therapy alone in the acute management of migraine may be an appropriate option for patients who experience fewer than two migraines per month or who use abortive medications less than two days per week. Other important factors to be considered include the effectiveness of abortive medications, a patient’s tolerance to these agents, the migraine’s disabling effects, and interference with daily routines.39 The appropriate choice depends on one’s history of abortive and concurrent medication use, comorbidities, contraindications, associated symptoms (e.g., nausea and vomiting), the severity and frequency of attacks, and cost.1–4,10,35,36,38,41,42

Table 1 lists common pharmacotherapies used in the abortive management of migraine, including the simple and various combination analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, 5-hydroxytryptamine (5-HT) receptor agonists (triptans), antiemetic agents, and
others. In some cases, the use of more than one of these agents in combination may be necessary to relieve a migraine attack.10,35,36,41–45

Obtaining a patient’s headache history, including responses to previous therapies, onset of effect, and recurrent patterns, may also be helpful in selecting an appropriate abortive therapy. Patients’ input and acceptance of their therapeutic plan is an important but often overlooked component of migraine management.40,44,45

### Analgesic Agents

Analgesics for the management of migraine include three general classes. They can be used as monotherapy or in various combinations (see Table 1). The simple analgesics include:

- acetaminophen (APAP).
- aspirin (acetylsalicylic acid, ASA), which can be used alone or in combination.
- NSAIDs.

Two other commonly used analgesic classes include barbiturate and opiate combination products containing aspirin or acetaminophen.41,42,46,47

### Simple Analgesics

Limited clinical data support the role of APAP as monotherapy in the acute management of migraine. One placebo-controlled trial reported benefits with 1,000 mg in mild-to-moderate migraine,65 although comparison trials with NSAIDs reported greater efficacy with NSAIDs.66,67 APAP’s mechanism of action is probably achieved through a central mechanism related to central prostaglandin inhibition.68 A trial of acetaminophen may be considered in mild-to-moderate migraine, especially in patients who do not tolerate NSAIDs,36 although most patients will have already tried simple an-

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**Table 1 Medications Used in the Abortive Management of Migraine**

<table>
<thead>
<tr>
<th>Medications Used in the Abortive Management of Migraine</th>
<th>Some combination OTC products</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA, numerous generics 650–1,000 mg q 4–6 hours (maximum 4,000 mg daily)</td>
<td>• Anacin (ASA) 400 mg, caffeine 32 mg</td>
</tr>
<tr>
<td>APAP (e.g., Tylenol) 325–1,000 mg q 4–6 hours (maximum 4,000 mg daily)</td>
<td>• Bayer Extra Strength (APAP 500 mg, caffeine 32.5 mg)</td>
</tr>
<tr>
<td>• Butalbital and ASA/caffeine (Fiorinal) 1–2 tablets q 4–6 hours (also available with codeine)</td>
<td>• Exceldrin Extra Strength and Exceldrin Migraine® (APAP 250 mg, ASA 250 mg, caffeine 65 mg)</td>
</tr>
<tr>
<td>• Butalbital and APAP/caffeine (Fioricet) 1–2 tablets q 4–6 hours (also available with codeine)</td>
<td>• Vanquish (APAP 194 mg, ASA 227 mg, caffeine 33 mg)</td>
</tr>
<tr>
<td>Restrict use to avoid rebound; 4 tablets daily; not more than 2 days per week</td>
<td></td>
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</tbody>
</table>

**Barbiturate combinations**

- Butalbital and ASA/caffeine (Fiorinal) 1–2 tablets q 4–6 hours (also available with codeine)
- Butalbital and APAP/caffeine (Fioricet) 1–2 tablets q 4–6 hours (also available with codeine)

**Serotonin receptor agonists (triptans)**

- Sumatriptan (Imitrex) Intranasal, Oral, SQ
- Rizatriptan (Maxalt) Oral, MLT (dissolving product)
- Zolmitriptan (Zomig) Oral, ZMT (dissolving product), Nasal
- Naratriptan (Amerge) Oral
- Almotriptan (Axert) Oral
- Frovatriptan (Frova) Oral
- Eletriptan (Relpax) Oral

**NSAIDs**

- Ibuprofen 200–400 mg q 4–6 hours (maximum 1,200 mg daily OTC)
  - Advil Migraine Liqui-Gels
  - Advil Migraine
- Naproxen sodium 220 mg q 6–8 hours (maximum 660 mg daily, OTC Aleve
  - Numerous other products: diclofenac potassium ( Cataflam), ketorolac (Toradol)

**Ergot alkaloids**

- Dihydroergotamine mesylate (DHE) injection/1 mg/mL Nasal Spray (Migranol)
- Ergotamine tartrate (numerous brands with various contents, including belladonna alkaloids, caffeine, and phenobarbital)

**Sympathomimetics**

- Isometheptene 65 mg, dicyclomethazone 100 mg, APAP 325 mg (Midrin)

**Anticonvulsants**

- IV valproate (Depacon)

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APAP = acetaminophen; ASA = aspirin; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; OTC = over the counter; SQ = subcutaneous.

* Regular weekly usage requires medical evaluation and determining the need for preventative therapy.

Adapted from references 10, 36, 41, 42, and 46.
algesics and over-the-counter (OTC) anti-inflammatory drugs before seeking care from a health care professional.

Monotherapy with aspirin (ASA) may also benefit some patients, although the doses required are not always tolerated in patients with concurrent GI symptoms. Aspirin’s mechanism of action is probably similar to that of other NSAIDs that act on the anti-inflammatory response in migraine. Clinical trials of aspirin have been conducted in patients with mild-to-severe migraine in both monotherapy versus placebo and in comparison trials with sumatriptan succinate (Imitrex, GlaxoSmithKline) and ibuprofen. Studies with 900 to 1,000 mg reported benefits when compared with placebo and similar efficacy when compared with sumatriptan 50 mg and ibuprofen 400 mg, although more pain-free effects were reported in one trial with sumatriptan. Most of these studies used effervescent formulations that are not available in the U.S., thereby making the role of aspirin in the treatment of acute migraine attacks unclear. Aspirin, therefore, should probably be reserved as a second-line or third-line choice. The combination of aspirin and metoclopramide (Reglan, Baxter) has also demonstrated efficacy and may offer improved tolerability over aspirin alone.

Combination therapy with the simple algesics APAP and ASA, with caffeine added to enhance absorption and to possibly potentiate activity, may also be used in acute migraine. In clinical trials involving two tablets of this combination, patients with mild-to-moderate migraine reported relief of headache intensity and of migraine-associated symptoms (e.g., nausea and vomiting) and similar or greater efficacy, compared with other simple algesics, was also observed. Higher or more frequent doses of this combination have not been studied. In addition to the potential for medication-overuse headache (see page 408), the caffeine in these products can lead to insomnia, restlessness, and palpitations. These combination algesics may have a place in mild-to-moderate migraine, but their role in moderate-to-severe migraine is not supported by clinical trials.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs have been effective in the abortive therapy of mild-to-severe migraine in both placebo-controlled and comparison trials with other abortive agents, including the triptans (see Table 1). Numerous agents have been studied at various doses, with trials showing improvements in pain-free periods and reductions in pain intensity and in migraine-associated symptoms (e.g., nausea, vomiting, and sensory disturbances).

The proposed mechanism of action is achieved via anti-inflammatory effects on vasoactive peptide–induced inflammation, which may occur during migraine.

The use of NSAIDs in combination with caffeine or other abortive agents, including triptans, may offer additive benefits in some patients. The properties of NSAIDs, including drug interactions and adverse drug reactions, are well documented elsewhere. NSAID-induced GI side effects may be problematic in migraine patients who experience nausea and vomiting, thus limiting their utility in these patients, although the addition of metoclopramide may improve tolerability.

The role of NSAIDs in the abortive management of migraine is appropriate in patients with infrequent, mild-to-severe attacks who experience minimal GI symptoms.

Barbiturate Analgesics

Barbiturate combination products containing butalbital, an intermediate-acting barbiturate, have been used for years for migraine (see Table 1). Butalbital is available in various combinations with APAP (Fioricet, Watson) or ASA (Fiorinal, Watson) with or without the addition of codeine. Barbiturates cause central nervous system (CNS) depression and confusion, and they can affect cognition and may cause paradoxical excitation. Although butalbital has a long history of use in migraine patients, no data are available that support its utility. Use of this agent has also resulted in abuse and dependency problems, often leading to medication-overuse headache in patients.

Products containing this barbiturate have been banned in Eastern Europe and in non-Western countries, and expert panels throughout the world have pointed to its potential for abuse. Although butalbital continues to be considered an abortive therapy in migraine, patients who are using barbiturates on a regular basis should be evaluated and provided with an alternative therapy.

Opioid Analgesics

Similar to the barbiturate combinations, opioid analgesics in the abortive management of migraine should be limited or avoided altogether because of similar concerns with overuse, abuse, tolerance, and the risk of medication-overuse headache. The mechanism and pharmacological profile of these agents is described elsewhere. Various opiate products are often used in combination with acetaminophen or aspirin (see Table 1).

Although some trials support the use of opioids in migraine, the use of alternative therapies is suggested because of concerns about medication-overuse headache. Butorphanol (Stadol, Apothecon), a mixed opioid agonist/antagonist, has been used extensively in acute migraine. It has a high potential for abuse and should be restricted or avoided as an abortive agent.

More recent data report the concept of opioid-induced hyperalgesia, which may be unique in patients with migraine. This event supports the lack of utility of these agents and an escalation of their use in some patients. The role of opioid-containing analgesics should be restricted in most migraine patients, although their short-term use may be justified in women with intractable menstrual migraine, women who are pregnant, elderly patients, or patients with severe and debilitating headache who are intolerant of or unresponsive to other agents. If opioid analgesics are used, they should be vigilantly monitored by patients, their family members, and their health care professionals.

Isometheptene/Dichloralphenazone/Acetaminophen (Midrin)

Another analgesic combination with a history of use as a migraine abortive agent is the combination drug Midrin (Excellium). Midrin is composed of isometheptene, a mild vasoconstrictor; dichloralphenazone, a mild sedative; and acetamin-
ophthalmometric properties suggesting a vasoconstriction mechanism. Clinical trials dating back to the 1970s reported modest benefits in mild-to-moderate migraine, although one comparison trial reported similar efficacy in patients with mild-to-moderate migraine when sumatriptan was used early in attacks. The agent’s side effects include sedation and GI tract problems, and its vasoconstrictive properties may be a concern in patients with hypertension. Dosing should be limited based on the potential for medication-overuse headache (see Table 1).

Drug interactions may include additive sedation with other central-acting drugs and monoamine oxidase inhibitors (MAOIs). The risk of APAP overuse should be monitored in patients using multiple APAP-containing analgesics. This combination analgesic may have a limited role as a second-line or third-line agent in some migraine patients, although its use should be restricted and monitored.

**Analgesic Overuse (Medication-Overuse Headache)**

The consequence of analgesic overuse is the clinical phenomenon known as medication-overuse headache. This unrecognized epidemic might involve millions of patients in the U.S. alone. It results from the overuse of analgesics, primarily prescription opiate and barbiturate combinations, but it can also occur with simple analgesics. It has also been reported with triptans and ergot alkaloids (see Table 1).

The IHS defines “medication overuse” as the use of simple analgesics for more than 15 days per month and the use of triptans, ergots, opioids, barbiturates, or combination medication for more than 10 days per month. The phenomenon occurs in patients with primary headache disorders, and it may prevent successful treatment if it is not addressed.

The mechanism of action in medication-overuse headache is not clear, but it is thought to be related to dysregulation in serotonergic transmission. The clinical consequences are chronic daily headaches that may result in the need for extensive supportive care, such as inpatient-management programs, various treatment protocols, and preventive therapy. Practitioners as well as patients and their families should become part of the evaluation and monitoring process of analgesic use by keeping diaries to evaluate effectiveness and frequency of use.

**Serotonergic Drugs**

Disturbances in serotonin (5-HT) regulation appear to be part of the pathogenesis of migraine, including neuropeptide release and inflammatory responses. The 5-HT receptor system involves numerous receptor subtypes, including 5-HT1, with additional subtypes (5-HT1A, 5-HT1D, 5-HT1E). Agonist activity at these receptors, specifically the 5-HT1D receptors, has been proposed as beneficial in migraine treatment, and two serotonergic drug classes—the ergotamine derivatives and the 5-HT receptor agonists (triphtans)—have demonstrated efficacy.

**Ergot Alkaloids**

The ergot alkaloids were the first specific agents indicated for the abortive management of migraine. In recent years, their use has declined because of the emergence of the more selective 5-HT receptor agonists (triphtans). The ergot alkaloids that are used as migraine abortives include ergotamine tartrate (ET) and dihydroergotamine mesylate (DHE) (Migranal, Valeant), which are available in injectable and nasal spray formulations (see Table 1). The oral formulations of ET may also contain caffeine, belladonna alkaloids, and phenobarbital, which contribute to their side-effect profile.

The ergot multireceptor action at serotonergic subtypes 5-HT1A, 1D, and 5-HT1, effects in their results on neurotransmitter release and neurogenically induced inflammation, which is their proposed mechanism of action in migraine. Additional receptor interactions, including activity at the alpha-adrenergic and dopaminergic systems, may also contribute to their action but also result in more side effects.

The pharmacokinetic properties of the ergots are dependent on the formulation; intravenous (IV) DHE has the fastest onset. Both ET and DHE are metabolized in the liver and excreted in bile. Clinical data for both ET and DHE have reported efficacy in 50% to 90% of patients, with most of the data favoring DHE. Data comparing DHE with meperidine (Demerol, Sanofi-Synthelabo) and sumatriptan reported similar efficacy, and the fastest onset is noted with sumatriptan. Fewer headache recurrences were observed with DHE.

One systematic review of DHE reported efficacy similar to that of opiates, ketorolac, and valproate and less effective responses when compared with sumatriptan and phenothazines. The DHE nasal product, an alternative formulation, was reported to be superior to sumatriptan in one trial. The longer half-life of DHE nasal spray may offer an advantage of a lower frequency of headache recurrence, although self-administration of this product may be difficult for some patients.

The side-effect profile of the ergot’s derivatives include nausea and vomiting, muscle cramps, tingling in the extremities, sense of difficulty swallowing, chest discomfort, nasal congestion, depression, and fatigue. Any chest discomfort must be appropriately evaluated, because effects on cardiac function have been reported secondary to the ergot vasoconstrictive properties and because heart disease is considered a contraindication.

**Ergotism**, a general term describing ischemic complications of major body systems, including the myocardium, can result from prolonged use or overuse. Additional complications may include fibrosis and retroperitoneal fibrosis. Medication-overuse headache is another potential complication of ergot derivative overuse that may warrant similar care and monitoring, as with the analgesics.

Potential drug interactions with the ergot derivatives include triptan use within 24 hours and other agents with serotonergic properties, including some antidepressants. Inhibitors of the cytochrome CYP 450 3A4 metabolic pathway (e.g., various antifungal agents, antibiotics, and macrolides) may increase their effects and potentiate toxicity. The ergot alkaloids are alternatives in the abortive treatment of migraine, but the emergence of the triptan class of migraine-specific agents has limited their use.
Triptans: 5-Hydroxytryptamine (Serotonin Receptor Agonists)

The triptans have emerged as drugs of choice in the abortive management of migraine, especially in patients who have not responded to or who cannot tolerate simple analgesics or NSAIDs. With seven agents on the market (Table 2), they are available in various dosage forms that offer numerous delivery options.

The mechanism of action of the triptans, although similar to that of ergots, has a more selective serotonin agonist receptor profile, acting on 5-HT₁b,d receptors and lacking interactions with adrenergic and dopaminergic receptors. Actions at these receptors result in their proposed migraine mechanism, including vasoconstriction of intracranial blood vessels; inhibition of vasoactive neuropeptide release; blocking transmission of pain signals; and influencing the plasma vasodilation, extravasation, and inflammation that occur in migraine. The pharmacokinetic properties of the triptans include differences in their bioavailability, onset of action, metabolism pathways, half-lives, and mode of excretion (see Table 2).

Bioavailability ranges from 15% with sumatriptan to 70% with naratriptan (Amerge, GlaxoSmithKline), even though these differences do not appear to correlate with clinical efficacy.

Table 2  Serotonin Receptor Agonists (Triptans)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation/Dosage</th>
<th>Pharmacokinetics</th>
<th>Comment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan (Imitrex)</td>
<td>Cost considerations with the SQ form</td>
<td>• SQ 6 mg; may repeat in 1 hour, max. 12 mg q 24 hours (autoinjector)</td>
<td>Metabolism (MAO-A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intranasal 5–20 mg, 1 spray in 1 nostril per dose; may repeat MR in 2 hours, max. 40 mg/day</td>
<td>Fast onset, especially SQ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Oral 25–50 mg; may repeat q 2 hours, max. 200–300 mg/24 hours</td>
<td>A new combination product with naproxen (Treximet) is now available.</td>
</tr>
<tr>
<td>Rizatriptan (Maxalt)</td>
<td>Oral 5–10 mg; may repeat in 2 hours, max. 20–30 mg daily, 15 mg if taking propranolol; MLT product dissolves on tongue; no need for water</td>
<td>Onset: 30–120 minutes</td>
<td>Metabolism (MAO-A)</td>
</tr>
<tr>
<td>Maxalt-MLT (dissolving form)</td>
<td></td>
<td>Half-life 2–3 hours</td>
<td>Fast onset</td>
</tr>
<tr>
<td>Zolmitriptan (Zomig)</td>
<td>Oral 2.5–5 mg; may repeat in 1–2 hours, max. 10 mg daily; ZMT product dissolves on tongue; no need for water</td>
<td>Onset: 45 minutes to 1 hour</td>
<td>Metabolism (CYP 450, 1A2)</td>
</tr>
<tr>
<td>Zomig-ZMT (dissolving form)</td>
<td></td>
<td>Half-life: 3 hours</td>
<td>MAO-A, active metabolite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioavailability: 40%</td>
<td>Two to six times more potent vs. parent drug</td>
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<tr>
<td></td>
<td></td>
<td>ZMT: perceived as faster onset</td>
<td>Fast onset</td>
</tr>
<tr>
<td>Naratriptan (Amerge)</td>
<td>Oral 1–2.5 mg; may repeat in 4 hours, max. 5 mg daily</td>
<td>Onset: 1–3 hours</td>
<td>Metabolism (CYP 450)</td>
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<tr>
<td></td>
<td></td>
<td>Half-life: 6 hours</td>
<td>50% excreted unchanged by kidneys</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioavailability: 60%–70%</td>
<td>Slow onset, long duration</td>
</tr>
<tr>
<td>Almotriptan (Axert)</td>
<td>Oral 6.25–12.5 mg; may repeat in 2 hours, max. 25 mg daily</td>
<td>Onset: 30 minutes – 2 hours</td>
<td>Metabolism (CYP 450, 3A4, 2D6 MAO-A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 3–4 hours</td>
<td>40% excreted unchanged by kidneys</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioavailability: 70%</td>
<td></td>
</tr>
<tr>
<td>Frovatriptan (Frova)</td>
<td>Oral 2.5 mg; may repeat in 2 hours, max. 7.5 mg daily</td>
<td>Onset: 2–4 hours</td>
<td>Metabolism (CYP 1A2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 26 hours</td>
<td>Slow onset, longer duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioavailability: about 30%</td>
<td></td>
</tr>
<tr>
<td>Eletriptan (Relpax)</td>
<td>Oral 20–40 mg; may repeat one time, max. 80 mg daily</td>
<td>Onset: 1–2 hours</td>
<td>Metabolism (CYP 450, 3A4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Half-life: 4–6 hours</td>
<td>Fast onset</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bioavailability: 50%</td>
<td></td>
</tr>
</tbody>
</table>

CYP = cytochrome; MAO = monoamine oxidase; max. = maximum; SQ = subcutaneous.

* Monitor usage and side effects of all agents.

Adapted from references 121, 148–154, 159, 164, and 169.
For most of the oral triptans, the onset of action ranges from 30 to 60 minutes, with a faster onset reported for rizatriptan (Maxalt, Merck), zolmitriptan (Zomig, AstraZeneca), and eletriptan (Relpax, Pfizer), possibly because of their greater bioavailability or CNS penetration.169,154

Differences in half-life may affect headache recurrence, suggesting a lower frequency of recurrence with frovatriptan (Frova, Endo) and naratriptan,148,150,153,153,160. The triptans are metabolized by two major pathways (see Table 2), the CYP 450 system, and/or the monoamine oxidase A (MAO-A) system; as a result, dose adjustments and assessment of potential drug interactions are necessary for patients with hepatic disease.166,167 Because some triptans such as naratriptan and almotriptan (Axert, Ortho-McNeil) depend on renal elimination, alternative dosing formulations (see Table 2), including subcutaneous (SQ) and intranasal products, have the fastest onset of action, although the oral dissolution products have only a perception of faster onset.148,149,151 The pharmacokinetic differences among the triptans have limited significance on clinical efficacy, but they may influence the most appropriate choice or preference for a given patient.162–166

Clinical efficacy among the triptans continues to be evaluated, although placebo-controlled trials with each of these agents have demonstrated efficacy.169–174 Differences in efficacy among the triptans are not clinically significant, and the American Academy of Neurology supports the role of all the triptans in the abortive management of moderate-to-severe migraine.36,175,176 The data suggest similar efficacy among the various triptans, but there is evidence to support the concept that failure or intolerance to one triptan warrants the trial of an alternative agent.177–183

Comparison trials with triptans and other migraine-abortive agents have included analgesics, NSAIDs, trimethobenzamide, diphendyrmamine, metoclopromide, and ergot derivatives.55,61,184–186 Sumatriptan 50 mg was reported to be similar to ibuprofen 400 mg and to 1,000 mg effervescent ASA in reducing moderate-to-severe migraine pain, although sumatriptan provided greater pain-free effects at two hours.55 An emergency room study reported that sumatriptan was more effective at two hours in treating acute migraine pain compared with trimethobenzamide and diphendyrmamine.180 A comparison trial of rizatriptan (Maxalt) and analgesics, NSAIDs, or ergot derivatives revealed an improved response at two hours in the triptan group.187,188 Trials with sumatriptan plus naproxen sodium (e.g., Aleve, Bayer; Naprosyn, Roche) showed additive effects and good tolerability in the acute management of migraine.84,189

Adverse Effects
The selective pharmacotherapy with the triptans suggests a tolerable side-effect profile, and perhaps because the triptans have been primarily used and studied in young healthy patients, they are reported to be well tolerated and safe. Side effects include dizziness, paresthesias, somnolence, asthenia, fatigue, flushing sensations, myalgias, and transient increases in blood pressure. GI effects, including nausea, vomiting, and digestive complaints, can occur, but they may be a result of the migraine itself. Other effects, including chest and neck symptoms, may require follow-up (see Contraindications).148–154 SQ sumatriptan may be associated with injection-site reactions. The intranasal products may also cause some local reactions, nasal cavity discomfort, and taste disturbances.190,191 Although the adverse effects of the triptans are similar, there may be some differences in tolerability, and intolerance to one triptan may warrant a trial of an alternative agent.

Contraindications
Contraindications to the triptans are usually the result of their vasoconstrictive properties.192 The triptans and their association with chest symptoms, in contrast to true ischemic changes, contribute to one adverse event that is still not completely understood. The incidence of cardiac problems with the triptans is reported to be low, although cardiac events have been reported in patients with and without a significant cardiovascular history. It is not clear whether the etiology of these symptoms is a result of a true vascular pathology, esophageal effects, pulmonary mechanisms, reductions in skeletal muscle energy metabolism, or a central mechanism. Because of these potential adverse effects, appropriate evaluation is necessary when the triptans are used, especially among patients at risk.192–197

Because of the potential for ischemic complications, the triptans are contraindicated in patients with coronary artery disease, cerebrovascular disease, uncontrolled hypertension, rhythm disturbances, peripheral vascular disease, ischemic bowel disorders, and hemiplegic or basilar migraine. To avoid potential complications, pretreatment screening should be conducted in postmenopausal women, men older than 40 years of age, smokers, obese patients, and those with diabetes mellitus or a strong family history of cardiac disease.199–200 Other ischemic complications reported with the triptans include splenic and renal infarction and intestinal ischemia.198–200 Although the triptans are not recommended for pregnant patients, as a result of their class C status, there is no evidence of early or late pregnancy loss, onset of premature or preterm labor, placental abruption, or malformations. Triptans should be used in pregnancy only after the risk–benefit ratio for individual patients is evaluated.148–154, 201–203

Drug–Drug Interactions
Potential drug interactions with the triptans can be caused by other serotonergic agents (Table 3) that can increase the risk of serotonin syndrome, an adverse reaction to medications that enhance serotonergic activity. The risk of serotonin syndrome from triptans alone is low, but it can result from their 5-HT1 receptor activity profiles, which may differ from agents involved with this syndrome.204–206 Triptans that are metabolized by the CYP 450 system, specifically 3A4 and 2D6 (see Table 2), may require dose adjustments when they are used with inhibitors of these pathways, such as paroxetine (Paxil, GlaxoSmithKline) and erythromycin. Because of potentially significant drug interactions, triptans should not be taken concurrently with ergots or other triptans within 24 hours of use. Monitoring triptans metabo-
lized by the MAO-A pathway (see Table 2), when used concurrently with propranolol, should be avoided. This interaction will be detailed in part 2 of this series next month.207-210

Clinical Recommendations
To select the appropriate triptan for each patient, prescribers should consider the past efficacy and tolerability of migraine-abortive medications, the characteristics of the patient’s migraine, and the patient’s preference.211 The various triptans and their available dosage forms allow for alternative delivery methods and flexibility in administration (see Table 2). The SQ and intranasal formulations are excellent options for patients who are experiencing GI effects, who prefer a faster onset, or who have a history of poor response to oral therapies (see Table 2).212-216

The oral dissolution tablets, available with some formulations (see Table 2), can be placed directly on the tongue. These products are an option for patients experiencing GI effects, although they offer only a perception of faster onset; they may actually be more slowly absorbed than the regular oral formulation. Some oral formulations, particularly frovatriptan (Frova), have a slower onset, compared with others (e.g., rizatriptan); this may be a consideration for some patients.151,153,217

The triptans are reported to be effective in 50% to 90% of patients with moderate-to-severe migraine attacks, and they are indicated as a first-line agent or as an alternative in patients who have not responded to or who are intolerant of simple analgesics or NSAIDs. Early use is recommended in the pre-headache phase. Failure to respond to one agent warrants a trial of another medication but not within the same 24-hour period. Although limited evidence supports medication-overuse headache with triptan use, appropriate monitoring and usage are important. When dispensing triptans, pharmacists play a major role in monitoring and educating patients about their appropriate use, potential side effects, and expected efficacy.36,189,218-222

Table 3 Common Drugs with Serotonergic Properties

<table>
<thead>
<tr>
<th>Monoamine oxidase inhibitors</th>
<th>Phenelzine (Nardil)</th>
<th>Selegiline (Zelapar, Eldepryl, Emsam)</th>
<th>Isocarboxazid (Marplan)</th>
<th>Tranylcypromine (Parnate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Tricyclics: amitriptyline, others</td>
<td>SSRIs: fluoxetine (Prozac), others</td>
<td>Miscellaneous: nefazodone (Serzone®), trazodone (Desyrel), venlafaxine (Effexor), bupropion (Wellbutrin)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Buspirone (BuSpar)</td>
<td>Dextromethorphan</td>
<td>Lithium</td>
<td>Amantadine (Symmetrel)</td>
</tr>
</tbody>
</table>

SSRI = selective serotonin reuptake inhibitor. * Serzone has been discontinued, but generic brands are available. Adapted from references 204-208.

Other Abortive Agents
The phenothiazines, butyrophenones, and metoclopramide (Reglan) have shown clinical efficacy in the abortive management of migraine. The antiemetic properties of these agents, along with their IV and rectal dosage formulations, are options for patients with significant nausea and vomiting. The proposed mechanism of these agents may result from their dopamine antagonist properties and the dopamine hypersensitivity reported during a migraine.41,42

IV prochlorperazine (Compazine, GlaxoSmithKline), chlorpromazine (Thorazine, GlaxoSmithKline), promethazine (Phenergan, Wyeth), droperidol (Inapsine, Janssen), and haloperidol decanoate (Haldol, Ortho-McNeil) have shown efficacy as migraine-abortive drugs in clinical trials.223-226 The antiemetic metoclopramide has been effective,227,228 with one trial reporting efficacy similar to that of sumatriptan when used in high doses in persistent migraine.185 Using metoclopramide in combination with the triptans or ergots may provide additional efficacy as well as antiemetic benefits.238,239

The side effects and toxicities of these agents are well documented elsewhere; however, when these medications are given intravenously, they must be administered cautiously because of concerns about potential hypotension, arrhythmias (an electrocardiogram should be performed before the dose is given), or dystonic reactions. These agents should be considered an alternative in the abortive management of migraine if they are administered in the proper setting in patients who do not respond to triptans or ergot derivatives.36

Other agents that may be used in the abortive management of migraine include IV valproic acid (Depacon, Abbott). This anticonvulsant was found to be more effective than placebo, and it had comparative efficacy with DHE in refractory cases.240-244

Case reports have shown efficacy for Pfizer’s IV verapamil (e.g., Calan) and sublingual nifedipine (Procardia) in complicated migraine.245,246 Tramadol (Ultram, Ortho-McNeil), a dual-mechanism analgesic, had efficacy similar to that of the NSAID diclofenac potassium ( Cataflam, Novartis).247 Other agents and supplements that may have a role in the abortive management of migraine include corticosteroids and herbal supplements (e.g., feverfew and magnesium sulfate).248-250

Conclusion
In selecting the most appropriate pharmacotherapy for the abortive management of migraine, prescribers must consider the severity of the pain. Patients with mild-to-moderate migraine attacks can often be treated with simple analgesics or NSAIDs, with the triptans or ergots reserved for moderate-to-severe pain. Other options may have a role in refractory migraine or when contraindications exist for first-line agents.36

Combination therapy may be necessary for some patients, and triptans or ergots combined with NSAIDs or other potential agents may provide additional benefits in refractory migraine.35,36,41,42,84,189

Preventative pharmacotherapy may also be necessary for many patients.251,252 Prophylaxis will be covered in part 2 of this two-part series in the next issue of P&T.
References


50. Hamalainen ML, Hope K, Valkila E, et al. Ibuprofen or acetaminophen for the acute treatment of migraine in children: A double-
Continuing Education Questions for Physicians and Pharmacists

P&T® 2008;33(7):404–416
ACPE Program # 079-000-08-017-H01-P
Expiration Date: July 31, 2009

**TOPIC: The Pharmacological Management of Migraine, Part 1: Overview and Abortive Therapy**

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## Continuing Education Questions for Physicians and Pharmacists

**TOPIC:** The Pharmacological Management of Migraine, Part 1: Overview and Abortive Therapy

ACPE Program # 079-000-08-017-H01-P

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**Multiple Choice**  
Select the one correct answer.

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer Options</th>
</tr>
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</table>
| 1. Which of the following is not true regarding migraine headaches? | a. Migraine is more common in females than males, with a prevalence of 19% and 7%, respectively.  
b. Because migraine affects people during their most productive years (in the 25- to 50-year-old age group), the direct and indirect costs have a significant impact on society.  
c. The direct costs are reported to be approximately $1 billion annually, and the indirect costs of lost time at work, school, and home result in an estimated $5.6 billion to $17.2 billion per year.  
d. The prevalence of migraine is reported to range between 2% and 5% in various countries around the world. |
| 2. The acute treatment of migraines is appropriate for those who experience: | a. fewer than two migraines per week.  
b. more than 10 migraines per month.  
c. fewer than two migraines per month.  
d. none of the above |
| 3. According to the article, which of the following pharmacological agents should be avoided in the abortive treatment of migraine? | a. barbiturates  
b. aspirin  
c. opiates  
d. a and c |
| 4. Which of the following statements is not correct regarding the pharmacological agents used in the acute treatment of migraines? | a. Most patients will have already tried simple analgesics and over-the-counter anti-inflammatory medications before seeking care from a health care professional.  
b. Combination analgesics may have a role in moderate-to-severe cases of migraines supported by clinical trials.  
c. Although butalbital with APAP or ASA has a long history of use in migraine patients, no data are available that support its utility.  
d. The isometheptene component of Midrin has sympathomimetic properties that suggest a vasoconstriction mechanism. |
| 5. Caffeine is added to combination therapy with the simple analgesics APAP and ASA: | a. to enhance absorption.  
b. to possibly potentiate activity.  
c. a and b  
d. none of the above |
| 6. Which of the following statements regarding pharmacological activity of triptans is not true? | a. Central nervous system penetration is correlated with clinical efficacy.  
b. Bioavailability is not correlated with clinical response.  
c. Triptans block pain signal transmission and vasoactive neuropeptide release.  
d. Headache recurrence may be affected by differences in half-life. |
| 7. A side effect associated with the use of ergots is: | a. excitability.  
b. insomnia.  
c. chest discomfort.  
d. dry mouth. |
| 8. An advantage of triptans is: | a. their more selective serotonin agonist receptor profile.  
b. an increased interaction at adrenergic receptors.  
c. their use as a drug of choice for migraine prophylaxis.  
d. an increased interaction at dopaminergic receptors. |
| 9. Triptans are contraindicated for all of the following except: | a. coronary artery disease.  
b. cerebrovascular disease.  
c. diabetes mellitus.  
d. ischemic bowel disorders. |
| 10. Other abortive agents that can be used include: | a. phenothiazines, butyrophenones, and oral valproic acid.  
b. metoclopramide, intravenous valproic acid, and halo-peridol.  
c. droperidol, haloperidol, and gabapentin.  
d. chlorpromazine, methylphenidate, and prochlorperazine. |
CE Registration and Evaluation Form

Date of publication: July 2008
Title: The Pharmacological Management of Migraine, Part 1: Overview and Abortive Therapy
Authors: George DeMaagd, PharmD, BCPS
Submission deadline: July 31, 2009
ACPE Program # 079-000-08-017-H01-P

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Certification: I attest to having completed this CE activity. ___________________________________________________________
Signature (required) Date _______________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a [ ] b [ ] c [ ] d [ ] 6. a [ ] b [ ] c [ ] d [ ]
2. a [ ] b [ ] c [ ] d [ ] 7. a [ ] b [ ] c [ ] d [ ]
3. a [ ] b [ ] c [ ] d [ ] 8. a [ ] b [ ] c [ ] d [ ]
4. a [ ] b [ ] c [ ] d [ ] 9. a [ ] b [ ] c [ ] d [ ]
5. a [ ] b [ ] c [ ] d [ ] 10. a [ ] b [ ] c [ ] d [ ]

Evaluation

Rate the extent to which:

<table>
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<tr>
<th>Very High</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
<th>Very Low</th>
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</table>
1. Objectives of this activity were met
2. You were satisfied with the overall quality of this activity
3. Content was relevant to your practice needs
4. Participation in this activity changed your knowledge/attitudes
5. You will make a change in your practice as a result of participation in this activity
6. This activity presented scientifically rigorous, unbiased, and balanced information
7. Individual presentations were free of commercial bias
8. Adequate time was available for Q&A
9. Which ONE of the following best describes the impact of this activity on your performance:
   [ ] This program will not change my behavior because my current practice is consistent with what was taught.
   [ ] This activity will not change my behavior because I do not agree with the information presented.
   [ ] I need more information before I can change my practice behavior.
   [ ] I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   [ ] Discuss new information with other professionals
   [ ] Consult the literature
   [ ] Discuss with industry representative(s)
   [ ] Participate in another educational activity
   [ ] Other ____________________________

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