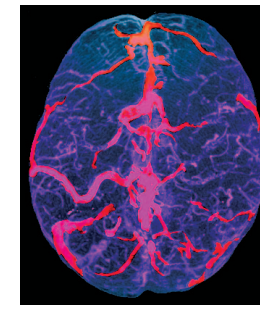
CONTINUING EDUCATION CREDIT



The Pharmacological Management Of Migraine, Part 1

Overview and Abortive Therapy

George DeMaagd, PharmD, BCPS

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 $5.6 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.

Dr. DeMaagd is Professor and Associate Dean of Academic Administration at Union University School of Pharmacy in Jackson, Tennessee.

Accepted for continuing education credit April 10, 2008.

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-hydroxytriptamine [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.[19,23,24]

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).[28–36] 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.[37]

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.[38,39] 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.[6–8,10,35,36,38,41,42]

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-hydroxytriptamine (5-HT) receptor agonists (triptans), antiemetic agents, and

Table 1 Medications Used in the Abortive Management of Migraine

ASA, numerous generics 650–1,000 mg q 4–6 hours (maximum 4,000 mg daily) APAP (e.g., Tylenol) 325–1,000 mg q 4–6 hours (maximum 4,000 mg daily)	***Some combination OTC products*** • Anacin (ASA) 400 mg, caffeine 32 mg) • Bayer Extra Strength (APAP 500 mg, caffeine 32.5 mg) • Excedrin Extra Strength and Excedrin Migraine* (APAP 250 mg, ASA 250 mg, caffeine 65 mg) • Vanquish (APAP 194 mg, ASA 227 mg, caffeine 33 mg)
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) Restrict use to avoid rebound; 4 tablets daily; not more than 2 days per week	***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
Opiate combinations* • Propoxyphene with APAP (Darvocet) • Codeine with APAP (Tylenol #3) • Oxycodone with APAP or ASA (Percocet, Percodan) • Butorphanol nasal spray (Stadol) one spray in one nostril (1 mg); may repeat in 1 hour; maximum four sprays daily	***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)
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)	***Sympathomimetics**** • Isometheptene 65 mg, dichloralphenazone 100 mg, APAP 325 mg (Midrin)
Phenothiazines: prochlorperazine (Compazine), chlorpromazine (Thorazine), metoclopramide (Reglan)	***Anticonvulsants:*** IV valproate (Depacon)

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.

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,[48] although comparison trials with NSAIDs reported greater efficacy with NSAIDs.[49,50] APAP's mechanism of action is probably achieved through a central mechanism related to central prostaglandin inhibition.[46] 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-

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.[40,41,51] 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[51–54] 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.[55,56] 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.[53–56] The combination of aspirin and metoclopramide (Reglan, Baxter) has also demonstrated efficacy and may offer improved tolerability over aspirin alone.[52,53]

Combination therapy with the simple analgesics APAP and ASA, with caffeine added to enhance absorption and to possibly potentiate activity, may also be used in acute migraine.[41,42,46] 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),[57–59] and similar or greater efficacy, compared with other simple analgesics, was also observed.[57–61] 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.[46,62,63] These combination analgesics 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[64–75] and comparison trials with other abortive agents, including the triptans (see Table 1).[76–83] 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).[64–83]

The proposed mechanism of action is achieved via anti-inflammatory effects on vasoactive peptide–induced inflammation, which may occur during migraine.[41,42] The use of NSAIDs in combination with caffeine or other abortive agents, including triptans, may offer additive benefits in some patients.[84,85] 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 tolerabilty.[52,86] 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.[41,42,46]

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 products 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.[87] 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.[88–90] 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.[87–91]

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).[92–94]

Although some trials support the use of opioids in migraine,[95–97] the use of alternative therapies is suggested because of concerns about medication-overuse headache.[75,95,99] 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.[100,101]

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.[102] 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 head pain 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.[102,103]

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-

ophen (see Table 1). The isometheptene component has sympathomimetic properties suggesting a vasoconstriction mechanism.[104] Clinical trials dating back to the 1970s reported modest benefits in mild-to-moderate migraine,[105,106] although one comparison trial reported similar efficacy in patients with mild-to-moderate migraine when sumatriptan was used early in attacks.[107] 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 because of 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.[36,41,42,107]

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).[89,92,108–111]

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.[11,62,63,93,102,103] 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.[111–115]

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-HT_1, with additional subtypes (5-$HT_{1d,1a,\ 1f,1b,1e)}$. Agonist activity at these receptors, specifically the 5-$HT_{1b/1d}$ receptors, has been proposed as beneficial in migraine treatment, and two serotonergic drug classes—the ergotamine derivatives and the 5-HT receptor agonists (triptans)—have demonstrated efficacy.[116–126]

Ergot Alkaloids

The ergot alkaloids were the first specific agents indicated for the abortive management of migraine.[128,129] In recent years, their use has declined because of the emergence of the more selective 5-HT receptor agonists (triptans). The ergot alkaloids that are used as migraine abortives include ergotamine tartrate (ET) and dihydroergotamine mesylate (DHE) (Migranol, Valeant), which are available in injectable and nasal spray formulations (see Table 1).[36,127] The oral formulations of ET may also contain caffeine, belladonna alkaloids, and phenobarbital, which contribute to their side-effect profile.[122,127–132]

The ergot multireceptor action at serotonergic subtypes 5-$HT_{1a,d,f,b}$ and 5-HT_2 results in their effects on neuropeptide release and neurogenically induced inflammation, which is their proposed mechanism of action in migraine.[126–128] 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.[127–130]

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.[121,127–132] Clinical data for both ET and DHE have reported efficacy in 50% to 90% of patients, with most of the data favoring DHE.[132–134] 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.[135,136]

One systematic review of DHE reported efficacy similar to that of opiates, ketorolac, and valproate and less effective responses when compared with sumatriptan and phenothiazines.[137] The DHE nasal product, an alternative formulation, was reported to be superior to sumatriptan in one trial.[138–141] The longer half-life of DHE nasal spray may offer an advantage of a lower frequency of headache recurrence,[141,142] although self-administration of this product may be difficult for some patients.[142]

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.[121,127,129] 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.[129,142,143]

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.[128,129,133,142–147]

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.[121,127,129] 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.[35,36,91]

Triptans: 5-Hydroxytriptamine (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.[35,36,91] With seven agents on the market (Table 2), they are available in various dosage forms that offer numerous delivery options.[148–154]

The mechanism of action of the triptans, although similar to that of ergots, has a more selective serotonin agonist receptor profile, acting on 5-$HT_{1b,1d}$ 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.[155–162] 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

Table 2 Serotonin Receptor Agonists (Triptans)

Drug	Formulation/Dosage	Pharmacokinetics	Comment*
Sumatriptan (Imitrex) Cost considerations with the SQ form	• SQ 6 mg; may repeat in 1 hour, max. 12 mg q 24 hours (autoinjector) • Intranasal 5–20 mg, 1 spray in 1 nostril per dose; may repeat MR in 2 hours, max. 40 mg/day • Oral 25–50 mg; may repeat q 2 hours, max. 200–300 mg/24 hours	• SQ onset: 10–15 minutes Bioavailability: 97% • Intranasal onset: 15–20 minutes Bioavailability: 17% • Oral onset: 0.5 to 1.5 hours High first-pass metabolism Bioavailability: oral 15% Half-life (all dosage forms): about 2 hours	Metabolism (MAO-A) • Fast onset, especially SQ • A new combination product with naproxen (Treximet) is now available.
Rizatriptan (Maxalt) Maxalt-MLT (dissolving form)	• Oral 5–10 mg; may repeat in in 2 hours, max. 20–30 mg daily, 15 mg if taking propranolol; MLT product dissolves on tongue; no need for water	Onset: 30–120 minutes Half-life 2–3 hours Bioavailability: 45% MLT: perceived as faster onset	Metabolism (MAO-A) • Fast onset
Zolmitriptan (Zomig) Zomig-ZMT (dissolving form)	• Oral 2.5–5 mg; may repeat in 1–2 hours, max. 10 mg daily; ZMT product dissolves on tongue; no need for water • Intranasal 5 mg; may repeat q 2 hours, max. 10 mg	Onset: 45 minutes to 1 hour Half-life: 3 hours Bioavailability: 40% ZMT: perceived as faster onset Intranasal onset: 15–20 minutes	Metabolism (CYP 450, 1A2 MAO-A), active metabolite • Two to six times more potent vs. parent drug • Fast onset
Naratriptan (Amerge)	• Oral 1–2.5 mg; may repeat in 4 hours, max. 5 mg daily	Onset: 1–3 hours Half-life: 6 hours Bioavailability: 60%–70%	Metabolism (CYP 450) • 50% excreted unchanged by kidneys • Slow onset, long duration
Almotriptan (Axert)	• Oral 6.25–12.5 mg; may repeat in 2 hours, max. 25 mg daily	Onset: 30 minutes – 2 hours Half-life: 3–4 hours Bioavailability: 70%	Metabolism (CYP 450, 3A4, 2D6 MAO-A) • 40% excreted unchanged by kidneys
Frovatriptan (Frova)	• Oral 2.5 mg; may repeat in 2 hours, max. 7.5 mg daily	Onset: 2–4 hours Half-life: 26 hours Bioavailability: about 30%	Metabolism (CYP 1A2) • Slow onset, longer duration
Eletriptan (Relpax)	• Oral 20–40 mg; may repeat one time, max. 80 mg daily	Onset: 1–2 hours Half-life: 4–6 hours Bioavailability: 50%	Metabolism (CYP 450, 3A4) • Fast onset

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.

response.[148,150,152] 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.[149,151,154]

Differences in half-life may affect headache recurrence, suggesting a lower frequency of recurrence with frovatriptan (Frova, Endo) and naratriptan.[148,150,151,153,165] 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, dose adjustments are required for patients with renal impairment.[150,152,164]

CNS penetration may vary among the triptans, but these differences are not always correlated with clinical efficacy.[164,168] 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, diphenhydramine, metoclopramide, 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 diphenhydramine.[186] 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.[192–197] 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-HT 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.[36,169,218–222]

Table 3 Common Drugs with Serotonergic Properties

Monoamine oxidase inhibitors	Phenelzine (Nardil) Selegiline (Zelapar, Eldepryl, Emsam) Isocarboxazid (Marplan) Tranylcypromine (Parnate)
Antidepressants	Tricyclics: amitriptyline, others SSRIs: fluoxetine (Prozac), others Miscellaneous: nefazodone (Serzone*), trazodone (Desyrel), venlafaxine (Effexor), bupropion (Wellbutrin)
Others	Buspirone (BuSpar) Dextromethorphan Lithium Amantadine (Symmetrel) Cocaine

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.[223–236] The antiemetic metoclopramide has been effective,[237,238] 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

1. Lipton RB, Stewart WF, Scher AI. Epidemiology and economic impact of migraine. *Curr Med Res Opin* 2001;17(Suppl 1)S4–S12.
2. Rozen TD, Swanson JW, Stang PE, et al. Increasing incidence of medically recognized migraine headache in a United States population. *Neurology* 1999;53(7):1468–1473.
3. Stewart WF, Lipton RB, Celentano DD, et al. Prevalence of migraine headache in the United States. *JAMA* 1992;267(1):64–69.
4. Goldberg LD. The cost of migraine and its treatment. *Am J Manag Care* 2005;11:S62–S67.
5. Adelman JU, Adelman LC, Freeman MC, et al. Cost considerations of acute migraine treatment. *Headache* 2004;44:271–285.
6. May A, Goadsby PJ. The trigeminovascular system in humans: Pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cereb Blood Flow Metab* 1999;19:115–127.
7. van de Ven RC, Kaja S, Plomp JJ, et al. Genetic models of migraine. *Arch Neurol* 2007;64:643–646.
8. Hamel E. Serotonin and migraine: Biology and clinical implications. *Cephalalgia* 2007;27(11):1293–1300.
9. Cady R, Dodick D, Levine H, et al. Sinus headache: A neurology, otolaryngology, allergy, and primary care consensus on diagnosis and treatment. *Mayo Clin Proc* 2005:80(7):908–916.
10. Lipton RB, Diamond S, Reed M, et al. Migraine diagnosis and treatment: Results from the American Migraine Study II. *Headache* 2001;41:638–645.
11. Headache Classification Subcommittee of the International Headache Society. International Classification of Headache Disorders, 2nd ed. *Cephalalgia* 2004;24(Suppl.1):1–151.
12. Diener HC, Kaube H, Limmroth V. A practical guide to the management and prevention of migraine. *Drugs* 1998;56(5):811–824.
13. Lipton RB, Bigal ME, Amatniek JC, et al. Tools for diagnosing migraine and measuring its severity. *Headache* 2004;44:387–398.
14. Giffin NJ, Ruggiero L, Lipton RB, et al. Premonitory symptoms in migraine: An electronic diary study. *Neurology* 2003;60:935–940.
15. Tepper SJ. Tailoring management strategies for the patient with menstrual migraine: Focus on prevention and treatment. *Headache* 2006;46(Suppl 2):S61–S68.
16. Rains JC, Poceta JS, et al. Headache and sleep disorders: Review and clinical implications for headache management. *Headache* 2006; 46(9):1344–1363.
17. Tietjen GE, Brandes JL, Digre KB, et al. High prevalence of somatic symptoms and depression in women with disabling chronic headache. *Neurology* 2007;68:134–140.
18. Goadsby PJ, Lipton RB, Ferrari MD. Migraine: Current understanding and treatment. *N Engl J Med* 2002;346:257–270.
19. Adelman JU, Adelman RD. Current options for the prevention and treatment of migraine. *Clin Ther* 2001;23(6):772–788.
20. Blau JN. Thavapalan M. Preventing migraine: A study of precipitating factors. *Headache* 1988;28:481–483.
21. Guarniert P, Radnitz CL, Blanchard EB. Assessment of dietary risk factors in chronic headache. *Biofeedback Self-Regulation* 1990; 15(1):15–25.
22. Bogucki A. Studies on nitroglycerin and histamine provoked cluster headache attacks. *Cephalalgia* 1989;22:90–153.
23. Sensenig J, Johnson M, Staverosky T. Treatment of migraine with targeted nutrition focused on improved assimilation and elimination. *Altern Med Rev* 2001;6(5):488–494.
24. Bigal ME, Lipton RB. The preventive treatment of migraine. *Neurologist* 2006;12:204–213.
25. Earles J, Folen RA, James LC. biofeedback using telemedicine: Clinical applications and case illustrations. *Behav Med* 2001;27: 77–82.
26. Sorbi M, Tellegen B, Du Long A. Long-term effects of training in relaxation and stress. Coping in patients with migraine: A three-year follow-up. *Headache* 1989;29:111–112.
27. Sheffield MM. Psychosocial interventions in the management of recurrent headache disorders: Policy considerations for implementation. *Behav Med* 1994;20:74–77.
28. Melchart D, Linde K, Fischer P, et al: Acupuncture for recurrent headaches: A systematic review of randomized controlled trials. *Cephalalgia* 1999;19:779–786.
29. Streng A, Linde K, Hoppe A. Effectiveness and tolerability of acupuncture compared with metoprolol in migraine prophylaxis. *Headache* 2006;46(10):1492–1502.
30. Pelka RB, Jaenicke C, Gruenwald J. Impulse magnetic-field therapy for migraine and other headaches: A double-blind placebo-controlled study. *Adv Ther* 2001;18(3):101–109.
31. Norton D. Migraine and photic stimulation: Report on a survey of migraineurs using flickering light therapy. *Complement Ther Nurs Midwifery* 2000;6:138–142.
32. Pryse-Phillips WE, Dodick DW, Edmeads JG, et al. Guidelines for the non-pharmacological management of migraine in clinical practice. Canadian Headache Society. *Can Med Assoc J* 1998;159(1): 47–54.
33. Goslin RE, Gray RN, McCrory DC, et al. Behavioral and physical treatments for migraine headache. Technical review 2. February 1999. Prepared for Agency for Health Care Policy and Research, Contract No. 290-94-2025. Available at: www.clinpol.mc.duke.edu./Pubs/Publications/Behavioral_Manuscript.pdf. Accessed August 2007.
34. Holroyd KA, Penzien DB. Pharmacological versus non-pharmacological prophylaxis of recurrent migraine headache: A meta-analytic review of clinical trials. *Pain* 1990;42:1–13.
35. Diamond ML, Wenzel RG, Nissan. Optimizing migraine therapy: Evidence-based and patient-centered care. *Expert Rev Neurother* 2006;6(6):911–919.
36. Silberstein SD, for the U.S. Headache Consortium. Practice Parameter: Evidence-Based Guidelines for Migraine Headache (An Evidence-Based Review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000; 55:754–762.
37. Educational Resources and Headache Diaries, National Headache Foundation. Available at: www.headaches.org. Accessed August 2007.
38. Weitzel KW. Thomas ML, Small RE. Migraine: A comprehensive review of new treatment options. *Pharmacotherapy* 1999;19(8): 957–973.
39. Diamond S, Bigal ME, Silberstein S. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: Results from the American Migraine Prevalence and Prevention study. *Headache* 2007;47(3):355–363.
40. Wenzel RG, Lipton RB, Diamond ML, et al. Migraine therapy: A survey of pharmacists' knowledge, attitudes, and practice patterns. *Headache* 2005;45:47–52.
41. King DS, Herndon KC. Headache disorders. *In:* DiPiro JT, Talbert RL, Yee GC, Matzke GR, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach*. 6th ed. Norwalk, CT: Appleton & Lange; 2005:1105–1121.
42. Alldredge BK. Neurologic disorders: headache. *In:* Koda-Kimble MA, Young YL, eds. *Applied Therapeutics: The Clinical Use of Drugs,* 8th ed. Baltimore: Lippincott Williams & Wilkins; 2005:52-1–52-27.
43. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med* 2002;112:135–140.
44. Lipton RB, Stewart WF. Acute migraine therapy: Do doctors understand what migraine patients want from therapy? *Headache* 1999; 39(Suppl 2):S20–S26.
45. Malik SN, Hopkins M, Young W, Silberstein SD. Acute migraine treatment: Patterns of use and satisfaction in a clincal population. *Headache* 2006;46:773–780.
46. Remington TL. Headache. *In:* Berardi RR, McDermott JH, Newton GD, et al., eds. *Handbook of Nonprescription Drugs*, 14th ed. New York: McGraw-Hill; 2006:69–90.
47. Wenzel RG, Sarvis CA, Krause ML. Over-the-counter drugs for acute migraine attacks: Literature review and recommendations. *Pharmacotherapy* 2003;23(4):494–505.
48. Lipton RB, Baggish JS, Stewart WF, et al. Efficacy and safety of acetaminophen in the nonprescription treatment of migraine: Results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med* 2000;160:3486–3492.
49. Larson BH, Christiansen LV, Andersen B, et al. Randomized double-blind comparison of tolfenamic acid and paracetamol in migraine. *Acta Neurol Scand* 1990;81(5):464–467.
50. Hamalainen ML, Hoppu K, Valkeila E, et al. Ibuprofen or acetaminophen for the acute treatment of migraine in children: A double-

blind, randomized, placebo-controlled, crossover study. *Neurology* 1997;48(1):103–107.
51. Lipton, RB, Goldstein J, Baggish JS, et al. Aspirin is efficacious for the treatment of acute migraine. *Headache* 2005;45(4):283–292.
52. Diener HC, Lampl C, Reimnitz P, et al. Aspirin in the treatment of acute migraine attacks. *Exp Rev Neurother* 2006;6(4):563–573.
53. MacGregor EA, Dowson A, Davies PT. Mouth-dispersible aspirin in the treatment of migraine. *Headache* 2002;42(4):249–255.
54. Lange R, Schwarz JA, Hohn M. Acetylsalicylic acid effervescent 1000 mg in acute migraine attacks. *Cephalalgia* 200;20:663–667.
55. Diener HC, Bussone G, de Liano H, et al. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan, and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004;24(11): 947–954.
56. Diener HC, Eikermann A, Gessner U, et al. Efficacy of 1000 mg effervescent acetylsalicylic acid and sumatriptan in treating migraine symptoms. *Eur Neurol* 2004;52:50–56.
57. Lipton RB, Stewart WF, Ryan RE, et al. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain: Three double-blind, randomized, placebo-controlled trials. *Arch Neurol* 1998;55:210–217.
58. Goldstein J, Hoffman HD, Armellino JJ, et al. Treatment of severe, disabling migraine in an over-the-counter population of migraine sufferers: Results from three randomized, placebo-controlled studies of the combination of acetaminophen, aspirin, and caffeine. *Cephalalgia* 1999;19:684–691.
59. Silberstein SD, Armellino JJ, Hoffman HD, et al. Treatment of menstruation-associated migraine with the non-prescription combination of acetaminophen, aspirin, and caffeine: Results from three randomized, placebo-controlled studies. *Clin Ther* 1999;21(3):475–491.
60. Goldstein J, Silberstein SD, Saper JR, et al. Acetaminophen, aspirin and caffeine in combination versus ibuprofen for acute migraine: Results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* 2006;6(3): 444–453.
61. Goldstein J, Silberstein SD, Saper JR, et al. Acetaminophen, aspirin, and caffeine versus sumatriptan succinate in the early treatment of migraine: Results from the ASSET trial. *Headache* 2005;45: 973–982.
62. Diener HC, Katasarva Z. Analgesic/abortive overuse and misuse in chronic daily headache. *Curr Pain Headache Rep* 2001;5:545–550.
63. Mathew NT, Kurman R, Perez F. Drug-induced refractory headache: Clinical features and management. *Headache* 1990;13:634–638.
64. Kellstein DE, Lipton RB, Geetha R, et al. Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: A randomized, double blind, placebo-controlled, dose-ranging study. *Cephalalgia* 2000;20:233–243.
65. Codispoti JR, Prior MJ, Fu M, et al. Efficacy of nonprescription doses of ibuprofen for treating migraine headache: A randomized controlled trial. *Headache* 2001;41:665–679.
66. Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. *Cephalalgia* 1992;12(3):169–171.
67. Lewis DW, Kellstein D, Dahl G. Children's ibuprofen suspension for the acute treatment of pediatric migraine. *Headache* 2002;42(8): 780–786.
68. Andersson PG, Hinge HH, Johansen O, et al. Double-blind study of naproxen vs. placebo in the treatment of acute migraine attacks. *Cephalalgia* 1989;9(1):29–32.
69. Johnson ES, Ratcliffe DM, Wilkinson M. Naproxen sodium in the treatment of migraine. *Cephalalgia* 1985;5(1)5–10.
70. Nestvold K, Kloster R, Partinen M, et al. Treatment of acute migraine attack: Naproxen and placebo compared. *Cephalalgia* 1985;5(2):115–119.
71. Massiou H, Serrurier D, Lasserre O, et al. Effectiveness of oral diclofenac in the acute treatment of common migraine attacks: A double-blind study versus placebo. *Cephalalgia* 1991;11:59–63.
72. Karachalios GN, Fotiadou A, Chrisikos N, et al. Treatment of acute migraine attack with diclofenac sodium: A double-blind study. *Headache* 1992;32:98–100.
73. Dahlof C, Bjorkman R. Diclofenac-K (50 mg and 100 mg) and placebo in the acute treatment of migraine. *Cephalalgia* 1993;13: 117–123.
74. Dib M, Massiou H, Weber M, et al. Efficacy of oral ketoprofen in acute migraine. *Neurology* 2002;58:1660–1665.
75. Harden RN, Carter TD, Gilman CS, et al. Ketorolac in acute headache management. *Headache* 1991;31:463–464.
76. Nebe J, Heier M, Diener HC. Low-dose ibuprofen in self-medication of mild to moderate headache: A comparison with acetylsalicylic acid and placebo. *Cephalalgia* 1995;15:31–35.
77. Treves TA, Streiffler M, Korczyn AD. Naproxen sodium versus ergotamine tartrate in the treatment of acute migraine attacks. *Headache* 1992;32(6):280–282.
78. Smith TR, Sunshine A, Stark SR, et al. Sumatriptan and naproxen for the acute treatment of migraine. *Headache* 2005;45(8):983–991.
79. Stronks DL, Tulen JH, Bussmann HB, et al. Effects of naratriptan versus naproxen on daily functioning in the acute treatment of migraine: A randomized, double-blind, double-dummy, crossover study. *Headache* 2003;43(8):845–852.
80. Evers S, Rahmann A, Kraemer C, et al. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. *Neurology* 2006;67:497–499.
81. Pradalier A, Rancurel G, Dordain G, et al. Acute migraine attack therapy: Comparison of naproxen sodium and ergotamine tartrate compound. *Cephalalgia* 1985;5:107–113.
82. Sargent JD, Baumel B, Peters K, et al. Aborting a migraine attack: Naproxen sodium vs ergotamine plus caffeine. *Headache* 1988;28: 263–266.
83. Diclofenac-K and the Sumatriptan Migraine Study Group. Acute treatment of migraine attacks: Efficacy and safety of a nonsteroidal anti-inflammatory drug, diclofenac-potassium, in comparison with oral sumatriptan and placebo. *Cephalalgia* 1999;19:232–240.
84. Winner P, Cady RK, Ruoff GE, et al. Twelve-month tolerability and safety of sumatriptan and naproxen sodium for the treatment of acute migraine. *Mayo Clin Proc* 2007;82(1):61–68.
85. Peroutka S, Lyon JA, Swarbrick J, et al. Efficacy of diclofenac sodium softgel 100 mg with or without caffeine 100 mg in migraine without aura: A randomized, double-blind, crossover study. *Headache* 2004;44:136–141.
86. Tfelt-Hansen P, Olesen J. Effervescent metoclopramide and aspirin (Migravess) versus effervescent aspirin or placebo for migraine attacks: A double blind study. *Cephalalgia* 1984;4:107–111.
87. Charney DS, Mihic SJ, Harris RA. Hypnotics and sedatives; ethanol. *In:* Goodman Gilman A, Rall TW, Hardman JG, Limbird LE, eds. *The Pharmacological Basis of Therapeutics,*10th ed. New York: McGraw-Hill; 1990:348–382.
88. Silberstein SD, McCrory DC. Butalbital in the treatment of headaches: History, pharmacology, and efficacy. *Headache* 2001;41: 953–967.
89. Sellers EM, Hoornweg K, Busto UE, et al. Risk of drug dependence and abuse posed by barbiturate-containing analgesics. *Can J Clin Pharmacol* 1999;6:18–35.
90. McLean W, Boucher EA, Brennan M, et al. Is there an indication for the use of barbiturate-containing analgesic agents in the treatment of pain? Guidelines for their safe use and withdrawal management. *Can J Clin Pharmacol*. 2000;7(4):191–197.
91. Matchar DB, Young WB, Rosenberg JH, et al. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacological management of acute attacks. Available at: www.aan.com/public/practiceguidelines/03.pdf/. Accessed August 2007.
92. Capobianco DJ, Swanson JW, Dodick DW. Medication-induced (analgesic rebound) headache: Historical aspects and initial descriptions of the North American experience. *Headache* 2001;41: 500–502.
93. Mathew NT. Transformed migraine, analgesic rebound, and other chronic daily headaches. *Neurol Clin* 1997;15(1):167–186.
94. Panconesi A, Anselmi B, Franchi G. Increased adverse effects of opiates in migraine patients. *Cephalalgia* 1995;15(2):159–160.
95. Boureau F, Joubert JM, Lasserre V, et al. Double-blind comparison of an acetaminophen 400 mg-codeine 25 mg combination versus aspirin 1000 mg and placebo in acute migraine attack. *Cephalalgia* 1994;14:156–161.
96. Adam EI. A treatment for the acute migraine attack. *J Int Med Res* 1987;15:71–75.
97. Carasso RI, Yehuda S. The prevention and treatment of migraine with an analgesic combination. *Br J Clin Pract* 1984;38:25–27.

98. Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. *Ann Emerg Med* 1989;18(4):361–365.
99. Gallagher MR. Emergency treatment of intractable migraine. *Headache* 1985;26:74–75.
100. Fisher MA, Glass S. Butorphanol (Stadol): A study in problems of current drug information and control. *Headache* 1997;48:1156–1160.
101. Hoffert MJ, Couch JR, Diamond S, et al. Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995;35:65–69.
102. Biondi DM. Opioid resistance in chronic daily headache: A synthesis of ideas from the bench and bedside. *Curr Pain Headache Rep* 2003;7(1):67–75.
103. Edmeads J. Analgesic-induced headaches: An unrecognized epidemic. *Headache* 1990:614.
104. Diamond S, Medina JL, Isometheptene: A non-ergot drug in the treatment of migraine. *Headache* 1975;15:211–213.
105. Yuill GM, Swinburn WR, Liversedge LA. A double-blind cross-over trial of isometheptene mucate compound and ergotamine in migraine. *Br J Clin Pract* 1972;26:76–79.
106. Diamond S. Treatment of migraine with isometheptene, acetaminophen, and dichloralphenazone combination: A double-blind, crossover trial. *Headache* 1976;15:282–287.
107. Freitag FG, Cady R, DiSerio F, et al. Comparative study of a combination of isometheptene mucate, dichloralphenazone with acetaminophen, and sumatriptan succinate in the treatment of migraine. *Headache* 2001;41(4):391–398.
108. Bigal ME, Rapoport AM, Sheftell FD, et al. Transforming migraine and medication overuse in a tertiary headache centre: Clinical characteristics and treatment. *Cephalalgia* 2004;24(6):4483–4490.
109. Micieli G, Manzoni GC, Granella F, et al. Clinical and epidemiological observations on drug abuse in headache patients. *In:* Diener HC, Wilkinson M, eds. *Drug-Induced Headache*. Heidelberg, Germany: Springer-Verlag; 1988:20–28.
110. Ferrari A, Savino G, Gallesi D, et al. Effects of overuse of the antimigraine combination of indomethacin, prochlorperazine and caffeine on the disposition of its components in chronic headache patients. *Pharmacol Res* 2006;54:142–149.
111. Paemeleire K, Crevits L, Goadsby PJ, et al. Practical management of medication-overuse headache. *Acta Neurol Belg* 2006;106(2):43–51.
112. Freitag FG, Lake A, Lipton R, et al. Inpatient treatment of headaches: An evidence-based assessment. *Headache* 2004;44:342–360.
113. Raskin NH. Repetitive intravenous dihydroergotamine as therapy for intractable migraine. *Neurology* 1986;36:995–997.
114. Smith RS. Low-dose tizanidine with nonsteroidal anti-inflammatory drugs for detoxification from analgesic rebound headache. *Headache* 2002;42:175–177.
115. Zed PJ, Loewen PS, Robinson G. Medication-induced headache: Overview and systematic review of therapeutic approaches. *Ann Pharmacother* 1999;33:61–72.
116. Humphrey PP, Feniuk W, Perren MJ et al. Serotonin and migraine. *Ann NY Acad Sci* 1990;600:587–598.
117. Hoyer D, Clarke DE, Fozard JR, et al. International Union of Pharmacology classification of receptors for 5-hydroxytriptamine (serotonin). *Pharmacol Rev* 1994;46:157–203.
118. Hartig PR, Hoyer D, Humphrey PP, et al. Alignment of receptor nomenclature with the human genome: Classification of 5-HT_{IB} and 5-HT_{1D} receptor subtypes. *Trends Pharmacol Sci* 1996;17: 103–105.
119. Goldstein DJ, Roon KI, Offen WW, et al. Selective serotonin 1F (5-HT_{1F}) receptor agonist LY334370 for acute migraine: A randomized controlled trial. *Lancet* 2001;358:1230–1234.
120. Peroutka SJ. Developments in 5-hydroxytriptamine receptor pharmacology in migraine. *Neurol Clin* 1990;8:829–839.
121. Siberstein SD. The pharmacology of ergotamine and dihydroergotamine. *Headache* 1997;36(Suppl 1):S15–S25.
122. Siberstein SD. Serotonin (5-HT) and migraine. *Headache* 1994;34:408–417.
123. Peroutka SJ. 5-Hydroxytriptamine receptor subtypes and the pharmacology of migraine. *Neurology* 1993;43(Suppl 3):S34–S38.
124. Borne RF. Serotonin: the neurotransmitter for the 90's. *Drug Top* 1994;10:108.
125. Deliganis AV, Peroutka SJ. 5-Hydroxytriptamine$_{1D}$ receptor agonism predicts antimigraine efficacy. *Headache* 1991;31(4):228–231.
126. Buzzi MG, Moskowitz MA. Evidence for 5-$HT_{1B/1D}$ receptors mediating the antimigraine effect of sumatriptan and dihydroergotamine. *Cephalalgia* 1991;11(4):165–168.
127. Scott AK. Dihydroergotamine: A review of its use in the treatment of migraine and other headaches. *Clin Neuropharmacol* 1992;15(4):289–296.
128. Goldstein J. Ergot pharmacology and alternative delivery systems for ergotamine derivatives. *Neurology* 1992;42(Suppl 2):45–46.
129. Bigal ME, Tepper SJ. Ergotamine and dihydroergotamine: A review. *Curr Pain Headache Rep* 2003;7(1):55–62.
130. Goadsby PJ, Edvinsson L. The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 1993;33:48–56.
131. Ward TN, Scott G. Dihydroergotamine suppositories in a headache clinic. *Headache* 1991;31(7):465–466.
132. Neuman M, Demarez JP, Harmey JL, et al. Prevention of migraine attacks through the use of dihydroergotamine. *Int J Clin Pharmacol Res* 1986;VI(1):11–13.
133. Young WB. Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine: Current perspectives. *Headache* 1997;37(Suppl 1):S42–S45.
134. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. *Headache* 1986;26:168–171.
135. Carleton SC, Shesser RF, Pietrzak MP, et al. Double-blind, multicenter trial to compare the efficacy of intramuscular dihydroergotamine plus hydroxyzine versus intramuscular meperidine plus hydroxyzine for the emergency treatment of acute migraine headaches. *Am Emerg Med* 1998;32:129–138.
136. Winner P, Ricalde O, Le Force B, et al. A double-blind study of subcutaneous dihydroergotamine vs. subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol* 1996;53:180–184.
137. Colman I, Brown MD, Innes GD, et al. Parenteral dihydroergotamine for acute migraine headaches: A systemic review of the literature. *Ann Emerg Med* 2005;45(4):393–401.
138. Gallagher RM. Acute treatment of migraine with dihydroergotamine nasal spray. *Arch Neuro*l 1996;53:1285–1291.
139. Ziegler D, Ford R, Kriegler J, et al. Dihydroergotamine nasal spray for the acute treatment of migraine. *Neurology* 1994;44:447–453.
140. Dihydroergotamine Nasal Spray Multicenter Investigators. Efficacy, safety, and tolerability of dihydroergotamine nasal spray as monotherapy in the treatment of acute migraine. *Headache* 1995;35:177–184.
141. Touchon J, Bertin L, Pilgrim AJ, et al. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology* 1996;47:361–365.
142. Migranal (dihydroergotamine), package insert. East Hanover, NJ: Novartis; December 2001.
143. Schulman EA, Rosenberg SB. Claudication: An unusual side effect of DHE administration. *Headache* 1991;31(4):237–239.
144. Peters GA, Horton BT. Headache with special reference to the excessive use of ergotamine preparations and withdrawal effects. *Mayo Clin Proc* 1951;26:153–161.
145. Saper J. Ergotamine tartrate addiction. *Mich Pharm* 1986;4–8.
146. Saper J. Ergotamine dependency: A review. *Headache* 1987;27:435–438.
147. Saper J, Jones JM. Ergotamine tartrate dependency: Features and possible mechanisms. *Clin Neuropharmacol* 1986;9(3):244–256.
148. Imitrex (sumatriptan), package insert. Research Triangle Park, NC: GlaxoSmithKline; 2006.
149. Zomig, ZMT, Nasal Spray (zolmitriptan), package insert. Wilmington, DE: AstraZeneca; 2006.
150. Amerge (naratriptan), package insert. Research Triangle Park, NC: GlaxoSmithKline; 2006.
151. Maxalt, Maxalt-MLT (rizatriptan), package insert. Whitehouse Station, NJ: Merck & Co.; 2007.
152. Axert (almotriptan), package insert. Raritan, NJ: Ortho-McNeil; 2006.
153 Frova (frovatriptan), package insert. Chadds Ford, PA: Endo; 2005.
154. Relpax (eletriptan), package insert. New York: Pfizer; 2006.
155. Burstein R, Jakubowski M. Analgesic triptan action in an animal model of intracranial pain. *Ann Neurol* 2004;55:27–36.
156. Coulter DM, Passier JL, Clark DW, et al. Activation of pain by suma-

triptan. *Headache* 2003;43(9):994–999.
157. Tepper SJ, Rapoport AM, Sheftell FD. Mechanisms of action of the 5-$HT_{1B/1D}$ receptor agonists. *Arch Neurol* 2002;59(7):1084–1088.
158. Durham P, Russo A. New insights into the molecular actions of serotonergic antimigraine drugs. *Pharmacol Ther* 2002;94(1–2):77–92.
159. Buzzi MG, Moskowitz MA. The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater. *Br J Pharmacol* 1990;99:202–206.
160. Jansen I, Edvinsson L, Mortensen A, et al. Sumatriptan is a potent vasoconstrictor of human dural arteries via a 5-HT_1 like receptor. *Cephalalgia* 1992;12:202–205.
161. Humphrey A, Goadsby PJ. The mode of action of sumatriptan is vascular? A debate. *Cephalalgia* 1994;14:401–410.
162. Fullerton T, Gengo FM. Sumatriptan: A selective 5-hydroxytriptamine receptor agonist for the acute treatment of migraine. *Ann Pharmacother* 1992;26:800–807.
163. Ryan RE. Patient treatment preferences and the 5-$HT_{1B/1D}$ agonists. *Arch Intern Med* 2001;161:2545–2553.
164. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: A comparative review of pharmacology, pharmacokinetics, and efficacy. *Drugs* 2000;50:1259–1287.
165. Gobel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in recurrence-prone migraine patients. *Clin Ther* 2000; 22:981–989.
166. Dixon R, French S, Kemp J, et al. Effect of hepatic impairment on the pharmacokinetics of zolmitriptan. *J Clin Pharmacol* 1998;38: 694–701.
167. Yu DK. The contribution of P-glycoprotein to pharmacokinetic drug–drug interactions. *J Clin Pharmacol* 1999;39:1203–1211.
168. Pascual J, Munoz P. Correlation between lipophilicity and triptan outcomes. *Headache* 2005;45(1):3–6.
169. Ferrari MD, Roon KI Lipton RB, et al. Oral triptans in acute migraine treatment: A meta-analysis of 53 trials. *Lancet* 2001;358:1668–1675.
170. Dahlof CG, Pascual J, Dodick DW, et al. Efficacy, speed of action, and tolerability of almotriptan in the acute treatment of migraine: Pooled individual patient data from four randomized, double-blind, placebo-controlled clinical trials. *Cephalalgia* 2006;26(4):400–408.
171. Winner P, Linder SL, Lipton RB, et al. Eletriptan for the acute treatment of migraine in adolescents: Results of a double-blind, placebo-controlled trial. *Headache* 2007;47(4):511–518.
172. Poolsup N, Leelasangaluk V, Jittangtrong J, et al. Efficacy and tolerability of frovatriptan in acute migraine treatment: Systemic review of randomized controlled trials. *J Clin Pharm Ther* 2005;30(6): 521–532.
173. Ahonen K, Hamalainen ML, Eerola M, et al. A randomized trial of rizatriptan in migraine attacks in children. *Neurology* 2006;67(7): 1135–1140.
174. Tepper SJ, Cady R, Dodick D, et al. Oral sumatriptan for the acute treatment of probable migraine: First randomized, controlled trial. *Headache* 2006;46(1):115–124.
175. Goadsby PJ, Massiou H, Pascual J, et al. Almotriptan and zolmitriptan in the acute treatment of migraine. *Acta Neurol Scand* 2007; 115(1):34–40.
176. Mandema JW, Cox E, Alderman J, et al. Therapeutic benefit of eletriptan compared to sumatriptan for the acute relief of migraine pain. *Cephalagia* 2005;25(9):715–725.
177. Diener HC, Gendolla A, Gebert I, et al. Almotriptan in migraine patients who respond poorly to oral sumatriptan: A double-blind, randomized trial. *Headache* 2005;45(7):874–882.
178. Rapoport AM, Tepper SJ, Sheftell FD, et al. Which triptan for which patient? *Neurol Sci* 2006;27:S123–S129.
179. Goldstein J, Tiseo PT, Albert KS, et al. Eletriptan in migraine patients reporting unsatisfactory response to rizatriptan. *Headache* 2006; 46(7):1142–1150.
180. Diener HC. Efficacy of almotriptan 12.5 mg in achieving migraine-related composite endpoints: A double-blind, randomized, placebo-controlled study in patients with a previous poor response to sumatriptan 50 mg. *Curr Med Res Opin* 2005;21(10):1603–1610.
181. Dahlof CG. Infrequent or non-response to oral sumatriptan does not predict response to other triptans: Review of four trials. *Cephalalgia* 2006;26(2):98–106.
182. Lainez MJ, Evers S, Kinge E, et al. Preference for rizatriptan 10-mg wafer vs. eletriptan 40-mg tablet for acute treatment of migraine. *Cephalalgia* 2006;26(3):246–256.
183. Diez FI, Straube A, Zanchin G. Patient preference in migraine therapy: A randomized, open-label, crossover clinical trial of acute treatment of migraine with oral almotriptan and rizatriptan. *J Neurol* 2007;254(2):242–249.
184. Evers S, Rahmann A, Kraemer C, et al. Treatment of childhood migraine attacks with oral zolmitriptan and ibuprofen. *Neurology* 2006;67(3):497–499.
185. Friedman BW, Corbo J, Lipton RB, et al. A trial of metoclopramide vs. sumatriptan for the emergency department treatment of migraines. *Neurology* 2005;64(3):463–468.
186. Friedman BW, Hochberg M, Esses D, et al. A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines. *Headache* 2006;46(6):934–941.
187. Martin VT, Loder E, Taylor K, et al. Eletriptan treatment of migraine in patients switching from barbiturate-containing analgesics: Results from a multiple attack study. *Cephalalgia* 2005;25(9):726–734.
188. Pascual J, Garcia-Monco C, Roig C, et al. Rizatriptan 10-mg wafer versus usual non-triptan therapy for migraine: Analysis of return to function and patient preference. *Headache* 2005;45(9):1140–1150.
189. Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: A randomized trial. *JAMA* 2007; 297(13):1443–1454.
190. Dahlof C. Sumatriptan nasal spray in the acute treatment of migraine: A review of clinical studies. *Cephalalgia* 1999;19:769–778.
191. Ensink FB. Subcutaneous sumatriptan in the acute treatment of migraine. *J Neurol* 1991;238:S66–S69.
192. Jamieson DG. The safety of triptans in the treatment of patients with migraine. *Am J Med* 2002;112:135–140.
193. Dodick D, Lipton RB, Martin V, et al. Consensus Statement: Cardiovascular Safety Profile of Triptans (5-HT Agonists) in the Acute Treatment of Migraine. *Headache* 2004;44(5):414–425.
194. Maassen VanDen Brink A, Reekers M, Bax WA, et al. Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation* 1998;98:25–30.
195. Laine K, Raasakka T, Mantynen J, et al. Fatal cardiac arrhythmia after oral sumatriptan. *Headache* 1999;39:511–512.
196. Wammes-van der Heijden EA, Rahimtoola H, Leufkens HG, et al. Risk of ischemic complications related to the intensity of triptan and ergotamine use. *Neurology* 2006;67(7):1128–1134.
197. Pacheco-Coronado R, McMullan PW, Galbut BH, et al. Myocardial infarction after taking zolmitriptan. *Yale J Biol Med* 2005;78(3): 147–150.
198. Arora A, Arora S. Spontaneous splenic infarction associated with sumatriptan use. *J Headache Pain* 2006;7(4):214–216.
199. Fulton JA, Kahn J, Nelson LS, et al. Renal infarction during the use of rizatriptan and zolmitriptan: Two case reports. *Clin Toxicol* 2006; 44(2):177–180.
200. Repaka A, Wenger J, Sitaraman SV. A case of sumatriptan-induced intestinal ischemia. *J Gastroenterol* 2006;41(2):177–178.
201. Tepper SJ. Safety and rational use of the triptans. *Med Clin North Am* 2001:85(4):959–970.
202. Martin VT, Goldstein JA. Evaluating the safety and tolerability profile of acute treatments for migraine. *Am J Med* 2005;228(Suppl 1):36S–44S.
203. Hilaire ML, Cross LB, Eichner SF. Treatment of migraine headaches with sumatriptan in pregnancy. *Ann Pharmacother* 2004;38(10): 1726–1730.
204. Gardner DM, Lynd LD. Sumatriptan contraindications and serotonin syndrome. *Ann Pharmacother* 1998;32:33–38.
205. Shapiro RE, Tepper SJ, et al. The serotonin syndrome, triptans and the potential for drug–drug interactions. *Headache* 2007;47:266–269.
206. Wooltorton E. Triptan migraine treatment and antidepressants: Risk of serotonin syndrome. *Can Med Assoc J* 2006;175(8):874.
207. Eadie M. Clinically significant drug interactions with agents specific for migraine attacks. *CNS Drugs* 2001;15(2):105–118.
208. Goldberg MR, Lowry RC, Musson DG, et al. Lack of pharmacokinetic and pharmacodynamic interaction between rizatriptan and paroxetine. *J Clin Pharmacol* 1999;39:192–199.
209. Michalets EL. Update: Clinically significant cytochrome P-450 drug interactions. *Pharmacotherapy* 1998;18(1):84–112.
210. Goldberg MR, Sciberras D, De Smet M, et al. Influence of beta-adrenoceptor antagonists on the pharmacokinetics of rizatriptan, a

5-HT$_{1b/1d}$ agonist: Differential effects of propranolol, nadolol, and metoprolol. *J Clin Pharmacol* 2001;52:69–76.
211. Cutrer FM, Goadsby PJ, Ferrari MD, et al. Priorities for triptan treatment attributes and the implications for selecting an oral triptan for acute migraine: A study of U.S. primary care physicians. *Clin Ther* 2004;26(9):1533–1545.
212. Dahlof CG. Non-oral formulations of triptans and their use in acute migraine. *Curr Pain Headache* 2005;9(3):206–212.
213. Diamond S, Freitag FG, Feoktistov A, et al. Sumatriptan 6 mg subcutaneous as an effective migraine treatment in patients with cutaneous allodynia who historically fail to respond to oral triptans. *Headache Pain* 2007;8(1):13–18.
214. Winner P, Adelman J, Aurora S, et al. Efficacy and tolerability of sumatriptan injection for the treatment of morning migraine: Two multicenter, prospective, randomized, double-blind, controlled studies in adults. *Clin Ther* 2006;28(10):1582–1591.
215. Winner P, Rothner AD, Wooten JD, et al. Sumatriptan nasal spray in adolescent migraineurs: A randomized, double-blind, placebo-controlled, acute study. *Headache* 2006;46(2):212–222.
216. Goadsby PJ, Yates R. Zolmitriptan intranasal: A review of the pharmacokinetics and clinical efficacy. *Headache* 2006;46(1):138–149.
217. Dowson AJ, MacGregor EA, Purdy RA, et al. Zolmitriptan orally disintegrating tablet is effective in the acute treatment of migraine. *Cephalalgia* 2002;22(2):101–106.
218. Dodick DW, Silberstein S, Daholf CG. Is there a preferred triptan? (Editorial) *Headache* 2002;42:1–7.
219. Adelman JU, Lipton RB, Ferrari MD, et al. Comparison of rizatriptan and other triptans on stringent measures of efficacy. *Neurology* 2001;57:1377–1383.
220. Dowson AJ, Mathew NT, Pascual J. Review of clinical trials using acute intervention with oral triptans for migraine management. *Int J Clin Pract* 2007;60(6):698–706.
221. Sullivan JT, Preston KL, Testa MP, et al. Psychoactivity and abuse potential of sumatriptan. *Clin Pharmacol Ther* 1992;52(6):635–642.
222. Katsarava Z, Fritsche G, Muessig M, et al. Clinical features of withdrawal headache following overuse of triptans and other headache drugs. *Neurology* 2001;57:1694–1698.
223. Jones J, Sklar D, Dougherty J, et al. Randomized double-blind trial of intravenous prochlorperazine for the treatment of acute headache. *JAMA* 1989;261(8):1174–1176.
224. Kabbouche MA, Vockell AL, LeCates SL, et al. Tolerability and effectiveness of prochlorperazine for intractable migraine in children. *Pediatrics* 2001;107(4):E62 and online.
225. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995;26:541–567.
226. Jones J, Pack S, Chun E. Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of migraine headache. *Ann Emerg Med* 1995;26:541–546.
227. Seim MB, March JA, Dunn KA. Intravenous ketorolac vs. intravenous prochlorperazine for the treatment of migraine headaches. *Acad Emerg Med* 1998;5(6):573–576.
228. Jones EB, Gonzalez ER, Boggs JG, et al. Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med* 1994;24:237–241.
229. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: A randomized controlled trial. *J Emerg Med* 2002;23(2):141–148.
230. Cameron JD, Lane PL, Speechley M. Intravenous chlorpromazine vs. intravenous metoclopramide in acute migraine headache. *Acad Emerg Med* 1995;2(7):597–602.
231. Shrestha M, Singh R, Moreden JE, et al. Ketorolac vs. chlorpromazine in the treatment of acute migraine without aura: A prospective, randomized, double-blind trial. *Arch Intern Med* 1996;156(15):1725–1728.
232. Morgenstern LB, Huber JC, Luna-Gonzales H, et al. Headache in the emergency department. *Headache* 2001;41:537–541.
233. Wang SJ, Silberstein SD, Young WB, et al. Droperidol treatment of status migrainous and refractory migraine. *Headache* 1997;37(6):377–382.
234. Richman PB, Allegra J, Eskin B, et al. A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headaches. *Am J Emerg Med* 2002;20:39–42.
235. Richman P, Reischel U, Ostrow A, et al. Droperidol: A novel therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1999;17:398–400.
236. Fisher H. A new approach to emergency department therapy of migraine headaches with intravenous haloperidol: A case series. *J Emerg Med* 1995;13(1):119–122.
237. Colman I, Brown MD, Innes GD, et al. Parenteral metoclopramide for acute migraine: Meta-analysis of randomised controlled trials. *BMJ* 2004;329(7479):1369–1373.
238. Klapper JA, Stanton JS. Ketorolac versus DHE and metoclopramide in the treatment of migraine headaches. *Headache* 1991;31(8):523–524.
239. Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. *Headache* 2003;43(7):729–733.
240. Waberzinek G, Markova J, Mastik J. Safety and efficacy of intravenous sodium valproate in the treatment of acute migraine. *Neuro Endocrinol Lett* 2007;28(1):59–64.
241. Reiter PD, Nickisch J, Merritt G. Efficacy and tolerability of intravenous valproic acid in acute adolescent migraine. *Headache* 2005;45(7):899–903.
242. Norton J. Use of valproate in status migraine. *Headache* 2000;40:755–757.
243. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. *Headache* 2001;41:976–980.
244. Mathew NT, Kailasam J. Repetitive intravenous administration of valproate sodium in intractable migraine: Comparison with intravenous dihydroergotamine (DHE) (Abstract). *Cephalalgia* 2000;20:351.
245. Goldner JA, Levitt LP. Treatment of complicated migraine with sublingual nifedipine. *Headache* 1987;27:484–486.
246. Yu W, Horowitz SH. Familial hemiplegic migraine and its abortive therapy with intravenous verapamil. *Neurology* 2001;57:1732.
247. Engindeniz Z, Demircan C, Karli N, et al. Intramuscular tramadol vs diclofenac sodium for the treatment of acute migraine attacks in emergency department: A prospective randomised, double-blind study. *J Headache Pain* 2005;6:143–148.
248. Cady RK, Schreiber CP, Beach ME, et al. Gelstat migraine (sublingually administered feverfew and ginger compound) for acute treatment of migraine when administered during the mild phase. *Med Sci Monit* 2005;11(9):165–169.
249. Klapper J, Stanton J. The emergency treatment of acute migraine headache: A comparison of intravenous dihydroergotamine, dexamethasone, and placebo. *Cephalalgia* 1991;11(Suppl 11):159–160.
250. Corbo J, Esses D, Bijur PE, et al. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. *Ann Emerg Med* 2001;38:621–627.
251. Ramadan NM, Silberstein SD, Freitag FG, et al. Evidence-based guidelines for migraine headache in the primary care setting: Pharmacological management for prevention of migraine. U.S. Headache Consortium. Available at: www/aan.com/professional/practice. Accessed August 2007.
252. McCory DC, Matchar DB, Rosenberg JH, et al. Evidence-based guidelines for migraine headache: Overview of program description and methodology. Available at: www.aan.com/public/practice guidelines/01.pdf. Accessed August 2007. ■

Conflict of Interest (COI) Statement

Dr. DeMaagd has no relationships to disclose. This article contains discussions of off-label use. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.

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

CME Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Jefferson Medical College and MediMedia USA, Inc.

Thomas Jefferson University | Jefferson Medical College

Jefferson Medical College of Thomas Jefferson University, as a member of the Consortium for Academic Continuing Medical Education, is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. All faculty/authors participating in continuing medical education activities sponsored by Jefferson Medical College are expected to disclose to the activity audience any real or apparent conflict(s) of interest related to the content of their article(s). Full disclosure of these relationships appears on the last page of the article.

Continuing Medical Education Credit

This CME activity is designed to assist physicians and other health care professionals who are P&T committee members in making formulary decisions. Its goal is to increase participants' ability to recognize and treat important medical problems.

Jefferson Medical College designates this continuing medical education activity for a maximum of one Category 1 credit toward the Physician's Recognition Award (PRA) of the American Medical Association. Each physician should claim only those credits that he/she actually spent in the educational activity.

This credit is available for the period of one year from the date of publication.

Although forms will be processed when received, certificates for CME credits will be issued every six months, in February and August. Interim requests for certificates can be made by contacting the Jefferson Office of Continuing Medical Education at (215) 955-6992 or by going online to http://jeffline.tju.edu/jeffcme/.

Continuing Pharmacy Education Credit

The Department of Health Policy, Thomas Jefferson University Hospital, is approved by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education and complies with the Criteria for Quality for continuing pharmacy education programming. This program (079-000-08-017-H01-P) is acceptable for 1.0 hour of continuing education credit (0.1 CEUs) in states that recognize ACPE-approved providers. Statements of Credit indicating hours/CEUs will be mailed within six to eight weeks to participants who completed this activity and submitted a completed evaluation with payment.

How to Apply for CE Credit

1. Each CE article is prefaced by learning objectives for participants to use to determine whether the article relates to their individual learning needs.
2. Read the article carefully, paying particular attention to the tables and other illustrative materials.
3. Complete the questions and fill in the answers on the evaluation form on the next page.
4. Complete the CE Registration and Evaluation Form. Type or print your full name and address in the space provided, and evaluate the activity as requested. In order for the form to be processed, all information must be complete and legible.
5. Payment of $10 per exam is required for processing and maintenance of records. Make checks payable to P&T®. This processing fee is non-refundable.
6. Send the completed form, answer sheet, and $10 payment to:
   Department of Health Policy
   Thomas Jefferson University
   Attn: Continuing Education Credit
   1015 Walnut Street, Suite 115
   Philadelphia, PA 19107
7. Be sure to mail the Registration, Evaluation Form, and $10 payment within one year of the date of publication. After that date, this article will no longer be designated for credit and forms cannot be processed.

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

CE Evaluation: Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

Multiple Choice

Select the one correct answer.

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 haloperidol.
    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

Pharmacy and Therapeutics P&T
A Peer-Reviewed Journal for Managed Care and Hospital Formulary Management

Registration

Name: _____ Degree: _____

Street address: _____ Last 4 Digits of Social Security No. (Web ID): _____

City: _____ State: _____ Zip: _____ Telephone: _____

E-mail Address: _____ Check one: ☐ Physician ☐ Pharmacist ☐ Other

Time needed to complete this CE activity in hours: ☐ 0.5 hr ☐ 1 hr ☐ 1.5 hr ☐ 2 hr ☐ Other _____

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:	Very High	High	Moderate	Low	Very Low
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
   - ☐ Discuss with industry representative(s)
   - ☐ Other _____
   - ☐ Consult the literature
   - ☐ Participate in another educational activity
   - ☐ None

Send the completed form and $10 payment (make checks payable to P&T***) to:*** Department of Health Policy, Thomas Jefferson University, Attn: Continuing Education Credit, 1015 Walnut Street, Suite 115, Philadelphia, PA 19107.