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The Practical Guide for Emergency Physicians

Emergency Medicine Reports™

Volume 20, Number 23 **November 8, 1999**

Migraine headaches were first described more than 4,000 years ago.[15] Aretaeus of Cappadocia gave them the name "hemicrania"[15] (or "heterocrania") in 100 AD, and the current term "migraine" was introduced by Galen 50 years thereafter.[19] They have been described as "a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency, and duration. Attacks typically are unilateral and frequently are associated with anorexia, nausea, and/or vomiting. In some cases they are preceded by or associated with neurologic or mood disturbances."[15]

While a "unified theory" of the pathophysiology of migraine has not yet been fully elucidated, some recent findings have produced a new model for the development of migraine headaches. Recent modalities for the acute management of migraines have, therefore, also changed to some extent. While many of the medications currently used for emergency treatment of migraine have been available for many years, there has been a shift in recommendations regarding use of these abortive medications. Moreover, several new agents have been developed in the last decade for acute migraine therapy. Finally, narcotics are not considered agents of choice for management of severe headaches, due to the risks associated with tolerance and dependence.[19]

With these clinical issues in focus, this review will discuss recent theories of migraine pathophysiology and diagnosis, and will review currently available therapeutic options for emergency department management of migraine headache.

— The Editor

Migraine Headache: Evidence-Based Treatment Guidelines for Emergency Management

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Epidemiology

Headache is the ninth most common chief complaint for which patients visit a physician in the United States;[19] about 40% of Americans suffer from "severe" headaches,[19,20] while 64% suffer "bothersome" headaches at least occasionally.[19] Ten percent of Americans see a doctor episodically for headache relief.[19,20] It is estimated that migraine headaches alone affect approximately 23 million Americans, or about 12% of the population.[20] These estimates vary, with some sources estimating the incidence of migraine at between 5-10%[19] and 15-20%[15] of the population. Up to 90% of the headaches evaluated in emergency and outpatient departments and by primary care physicians are thought to be due to muscle contraction or migraine.[19]

There is a significant female predominance among migraine sufferers, with about a 4:1 female to male ratio. There is often a definite relationship between migraine headache frequency and menses; this frequency sometimes decreases (or increases) during pregnancy and after menopause. Migraine headaches often begin in childhood, but they may also be noted first during or

after puberty. It is unusual for migraine headaches to start after age 40.[19]

Classification

The once accepted definition of "vascular headaches of the migraine type" was generated by the Ad Hoc Committee on Classification of Headache of the National Institute of Neurologic Disease and Blindness in 1962.[19] It was supplanted in 1988 by the International Headache Society (IHS) criteria, which are more specific and, therefore, ensure consistency in the diagnosis of migraine headaches.[20]

The IHS criteria for diagnosis and classification of migraine headaches are presented in Table 1. Common migraines, which account for 80% of all migraine headaches, may have vague prodromes of varying duration; visual changes generally are not associated with common migraines. Photophobia, sonophobia, anorexia, nausea, vomiting, and malaise are frequent findings.

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by American Health Consultants, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Publisher: Brenda Mooney
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Managing Editor: Valerie Loner
Associate Managing Editor: Suzanne Zunic
Marketing Manager: Schandale Kornegay

GST Registration No.: R128870672

Periodical postage paid at Atlanta, GA. **POSTMASTER:** Send address changes to ***Emergency Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $21. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $287 each; 10 or more additional copies, $255 each.

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Classic migraine, which accounts for 12% of migraine headaches, has a sharply defined prodromal phase, lasting up to one hour prior to the onset of the headache. The most common auras are characterized by temporary, scintillating scotomas or homonymous hemianopsia progressing from the central visual fields to the periphery. Other aura symptoms are listed in Table 1 in the section on IHS criteria for migraine with aura. As with common migraines, classic migraine also is associated with nausea, vomiting, photophobia, and/or sonophobia.[19,20]

Several other migraine variants have been described in the medical literature, although specific inclusion criteria and classification scales have not been developed for their diagnosis. Hemiplegic migraine is manifested by hemiparesis ranging from mild weakness to full hemiplegia. This may persist for some time after resolution of the headache pain. Unless the patient has a history of similar migraines, this is strictly a diagnosis of exclusion, and CT scanning may be necessary to rule out an intracranial process.[10,19]

Ophthalmoplegic migraine is a rare variant usually seen in young adults. The headache pain, which tends to be less intense than a classic migraine, is associated with ipsilateral ophthalmoplegia including extraocular paralysis (usually involving CN III), ptosis, ocular muscle weakness, and occasionally pupillary changes. The Tolosa-Hunt syndrome is a periarteritis of the carotid siphon, which may simulate an ophthalmoplegic migraine. Steady retroorbital pain, oculomotor paralysis, and variable involvement of visual function are suggestive symptoms, which may persist for days to weeks. As with hemiplegic migraine, this is a diagnosis of exclusion, as the differential diagnosis includes carotid artery aneurysm.[10,19]

Basilar artery migraine (or vertebrobasilar migraine) may include severe headache and paroxysmal neurologic deficits, as well as associated symptoms such as vertigo, dysarthria, ataxia, paresthesias, and visual changes. These symptoms should precede the headache and persist only for the duration of the headache, usually from six to eight hours. Basilar artery migraine is most common among females in their teens and 20s. Neuroradiologic scanning may be necessary to exclude posterior fossa tumors, thrombosis of the vertebral/basilar system, and cerebellar hemorrhage or infarct.[10,19]

Status migrainosus refers to any migraine headache persisting for longer than 24 hours. This classification has clinical importance in that headache management may be more difficult in this population, and sequelae such as dehydration are more likely to be present.

Migraine equivalent refers to a condition in which a migraine sufferer experiences autonomic nervous system effects resulting in tachycardia, edema, vertigo, chest pain, thoracic, and abdominal pain, or pelvic pain with little or no headache. Only about 10% of migraineurs suffer this type of migraine variant.[19]

Cluster headaches are sometimes classified as migraine variants, since they are considered to be vascular in origin. They account for between 2% and 9% of migraine headaches. Cluster headaches are characterized by unilateral, excruciating facial pain that rarely lasts for more than two hours. Sufferers may also experience ipsilateral nasal congestion, lacrimation, and conjunctival injection. Attacks occur several times a day for weeks to months with pain-free intervals. They often follow ingestion of alcohol, nitroglycerin, or histamine-containing compounds, or

Table 1. IHS Criteria (1988)

MIGRAINE WITHOUT AURA (COMMON MIGRAINE)

A. Duration 4-72 hours
B. Two or more of the following:
   1. Unilateral location
   2. Pulsating quality
   3. Moderate to severe intensity
   4. Aggravated by routine physical activity
C. At least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia
D. Five or more attacks fitting the above criteria
E. Exclusion of secondary cause of headache

MIGRAINE WITH AURA (CLASSIC MIGRAINE)

A. At least three of the following:
   1. One or more fully reversible aura symptoms indicating brain dysfunction
   2. One aura symptom developing in at least 4 minutes, or two or more symptoms in succession
   3. No aura symptom lasting over one hour
   4. Headache follows aura within one hour
B. At least two attacks fitting the above criteria
C. Exclusion of secondary cause of headache

AURAS[10,19]

- Positive scotomas (arc of scintillating lights in a herring-bone-like pattern)
- Negative scotomas (blind spots)
- Teichopsia/fortification spectra (luminous appearance before the eyes)
- Photopsia (flashing lights)
- Homonymous visual disturbance
- Unilateral paresthesias/numbness
- Unilateral weakness
- Aphasia/unclassifiable speech difficulty
- Visual or auditory hallucinations
- Diplopia
- Ataxia
- Vertigo
- Syncope
- Hyperosmia

they may be related to stress, climate changes, or allergies. This migraine variant predominates in the male population, usually beginning in mid-adult life.[19]

Clinical Pathophysiology

Multiple physiologic mechanisms for migraine headache have been postulated, some of which may play a role in the clinical pain syndrome of this condition. While all *extracranial* structures are pain-sensitive, the majority of the *intracranial* compartment is insensate. However, the venous sinuses and major arteries at the base of the brain do sense pain, while smaller, intraparenchymal arteries lack pain sensation. The dura mater covering the base of the brain and the dural arteries are somewhat pain-sensitive. The remainder of the intracranial cavity is insensate.

Headache may be produced due to traction, distention, or inflammation of the pain-sensate areas of the head and neck. For example, muscular tension headaches are due to contraction of the extracranial muscles of the neck and scalp. Traction headaches are the result of stress applied on intracranial structures due to mass effect (tumor, intracranial bleed, etc.). In contrast, vascular headaches are secondary to dilatation and distention of the pain-sensitive, intracranial vascular structures. The resulting pain is usually throbbing in nature, fluctuating with the patient's heartbeat. Migraine falls into this category, as do hypertensive headaches and vasodilator headaches (as seen with certain toxins and drugs, such as nitroglycerin). Inflammatory headaches result from inflammation of the peripheral nerves of the head and neck and/or of the basal meninges.

While migraine is primarily a vascular dilatory problem, it may also have a significant inflammatory component.[19] Accordingly, migraine syndromes have long been thought to result from dysfunction of the central autonomic nervous system. This theory (Wolff's vascular theory) postulates that migraines begin with a phase of intracranial arterial vasoconstriction, which is followed by ischemic changes in the corresponding vascular distribution in the brain, which leads to prodromal symptoms. This is followed by a vasodilatation phase, involving primarily those of the extracranial arteries, which causes the characteristic headache of migraine. A "steal syndrome," in which blood is shunted away from cortical areas and into vasodilated extracranial arteries, produces some of the signs and symptoms of migraine. Neuroactive substances released as the migraine develops may produce some of the other symptoms of the headache.[19]

A more current theory of migraine pathogenesis focuses on central serotonergic transmission abnormalities, trigeminovascular neuronal transmission dysfunction, vascular structures, and neurogenic inflammation. Platelet aggregation precipitated by release of vasoactive substances and prostaglandin synthesis also may be involved in the genesis of migraine headache. In this model, activation of the trigeminovascular system induces vasodilatation and neurogenic inflammation.[20] Several recent therapies (i.e., the "triptans") have been developed based on the concept of modulating this system through stimulation of serotonin receptors. A recent review suggests that, in addition to serotonin and neuropeptides, dopamine plays a significant role in the pathophysiology of migraine headaches.[29]

Dopaminergic stimulation (with apomorphine) can induce migraine symptoms and does so more in migraineurs than in a control group (86% of migraineurs developed headache, 0% of controls did). This strongly suggests dopaminergic hypersensitivity as a possible etiology of migraine. The presence of nausea and vomiting as concomitant symptoms in migraine also suggest a dopamine-related etiology, inasmuch as dopamine receptors modulate central emetic centers in the chemotrigger receptor zone. Neuroendocrinologic studies have also demonstrated dopaminergic receptor supersensitivity in migraineurs. Finally, dopamine antagonists (prochlorperazine, haloperidol, chlorpromazine, and metoclopramide) that have long been used empirically for treatment of migraine headaches and their associated symptoms have been successful even as single-agent therapies.

Table 2. Differential Diagnosis of Migraine Headache

NONMIGRAINOUS VASCULAR HEADACHE
Fever
Hypoxia/hypercarbia
Carbon monoxide poisoning
Hypertensive headache
Anemia
Altitude headache
Stroke
Effort/coital headache
Hypoglycemia
Hypothyroidism/hyperthyroidism
Hypoadrenalism
Menopausal hormone cessation
TRACTION HEADACHE
Tumor
Arteriovenous malformation
Cerebral aneurysm/subarachnoid hemorrhage
Pseudotumor cerebri
Brain abscess
Subdural hematoma/epidural hematoma
Postspinal puncture headache
INFLAMMATORY HEADACHE
Temporal arteritis
INFECTIOUS CAUSES
Meningitis
Encephalitis
Abscess (brain, dental)
Sinus headache
MISCELLANEOUS
Trigeminal neuralgia
Glaucoma
Temporomandibular joint (TMJ) syndrome
Post-traumatic (post-concussive) headache
Ventricular shunt headache
Cervical headache (rheumatoid arthritis, spondylosis, trauma)
Postictal headache
Muscle contraction headache

Dopamine activity appears to be a key component of migraine. Some experts consider it to be the "endogenous protagonist in the pathophysiology of the disorder." Serotonin, on the other hand, is viewed as an "endogenous antagonist," since drugs that stimulate serotonin receptors can relieve symptoms of migraine.[29] A unified theory of migraine headache pathophysiology has yet to be developed. Multitudinous therapeutic options available for this disorder, suggesting that at least some of the theories play a significant role in migraine pathogenesis.

Clinical Features

The diagnosis of migraine headache is based on 1) a history consistent with the IHS criteria definition of migraine; and 2) ruling out other organic causes of severe headache. For all practical purposes, then, it is a diagnosis of exclusion. Unfortunately, there are no consistent physical, laboratory, or radiographic findings associated with migraine headache that confirm this diagnosis, although ancillary testing may be indicated in order to rule out other possible causes of head pain.

History. A history in the headache patient should identify the quality, location, temporal factors (speed of onset, timing of maximal intensity, duration, frequency), mitigating factors, prodromal symptoms, associated symptoms, as well as other historical features (medical history, family history, occupational history) that may have diagnostic implications. Although a complete analysis of the differential diagnostic implications of various headache syndromes is beyond the scope of this chapter, it should be emphasized that the typical migraine headache can be described as: unilateral (location); throbbing/pulsatile (quality); gradually progressive in onset, and variably associated with prodromal symptoms; usually accompanied by nausea, vomiting, photophobia, and/or phonophobia; and most commonly is encountered in patients with a prior history and/or family history of similar headaches. The intensity of headache is not as important as is the entire constellation and evolution of symptoms for distinguishing migraine from more serious causes of head pain.[19]

Certain features of headache should prompt a search for more serious non-migraine etiologies. These include: 1) first-time headache, or worst headache ever (especially if acute in onset with noted neurological deficit); 2) change in character or quality of usual headache; 3) progressively worsening pain over days to weeks with subacute onset; 4) fever, nausea, and vomiting without signs of systemic illness; 5) neck stiffness; 6) or no evident etiology after careful history-taking.[20]

A complete history should also address the patient's prior response to migraine therapies. Most migraine patients presenting to the emergency department are quite knowledgeable about their condition. They usually are familiar with their symptoms and can identify medications that have helped them obtain relief in the past.[33] Because there is currently no "optimal" therapy for migraine headaches—patient response can be variable—the clinician should determine which classes of therapeutic agents have worked for a patient in the past in order to guide current therapy.

Physical Examination. As emphasized, physical examination of the migraine patient is aimed at ruling out more dangerous etiologies of headache. As a general rule, most life-threatening causes of headache have demonstrable physical findings,[19] although this is not always the case, and vital signs should be noted in any patient complaining of headache; fever may suggest meningitis, encephalitis, brain abscess, or sinus infection. Severe hypertension may cause head pain, and may predispose to stroke or intracerebral hemorrhage. Respiratory rate may be elevated in patients with hypoxia, hypercarbia, CO or CN poisoning, or anemia as the cause of headache.

Palpation of the scalp, sinuses, neck muscles, oral cavity (teeth and gums), temporomandibular joints, and temporal arteries may reveal other sources of pain. Trigeminal neuralgia may be discovered by tapping over the root of cranial nerve V. The ocular examination may reveal iritis or glaucoma; papilledema should prompt a search for causes of increased intracranial pressure. Retinal hemorrhages may be seen in subarachnoid hemorrhage or hypertensive crisis. Pupillary changes may indicate an

intracranial process. Ear examination for otitis media or otitis externa is also important. Meningismus, especially flexion rigidity, suggests meningeal irritation, possibly due to meningitis.

The importance of the neurological examination cannot be overstated. Any patient presenting for headache should undergo careful motor and sensory exams, cranial nerve testing, mental status assessment, and some cerebellar evaluation (gait, tandem walk, finger-to-nose). Abnormalities in any of these evaluations should prompt an intensive search for organic intracranial lesions.

Laboratory Examination. Laboratory and other ancillary studies are reserved for confirming suspected causes of headache other than those caused by migraine. CT scanning is useful for excluding vascular or space-occupying lesions. It is recommended for patients who present with a recent change in headache pattern, seizures, or focal neurological symptoms or signs.[30] Lumbar puncture may be necessary if subarachnoid hemorrhage or an infectious source of headache (meningitis, encephalitis) is suspected. Other tests may include ESR (for temporal arteritis), hemoglobin (for anemia), ABG (for hypoxia/hypercarbia), glucose, WBC, and CO level (or other toxins). If no significant historical or physical exam findings suggest other possible etiologies of headache, and if the headache description is typical of migraine, no laboratory or other testing is required.

It is also important to note that response to therapy is *not* diagnostic of migraine. There are several case reports in the literature of patients with secondary headaches that responded transiently to symptomatic therapies such as DHE and sumatriptan.[42]

Differential Diagnosis. The differential diagnosis of migraine headaches is broad.[19] *(See Table 2.)* The key to migraine diagnosis lies in ruling out these other possible causes of head pain (in a patient with an otherwise consistent history and description of current headache quality and associated symptoms).

Management

There is no ideal, universally consistent and successful therapy for all migraine sufferers. The wide variety of therapeutic agents used for treatment of migraine headaches supports this contention. *(See Table 3.)* Nevertheless, there are a number of agents available for migraine treatment which have a high rate of success in a large percentage of patients; some of these medications have significant adverse side effects and should not be used in certain populations. Some therapies (particularly opioids) have the potential to induce dependence, and should not be prescribed casually. Other agents have a safer treatment profile, but may be less than ideally effective in eliminating migraine headaches. One way to determine the agent of choice for a particular migraine sufferer is to ask what has worked for them in the past. For those patients who do not know what therapies have been effective or have not received prior medical therapy for migraine, there are several options, all of which have a large number of proponents as well as detractors.

Analgesics. First-line therapy for migraine patients who experience a mild headache or prodrome is an analgesic such as aspirin, acetaminophen, or a NSAID (e.g., naproxen sodium, ibuprofen). These medications are more likely to be effective early in the attack[17] and, therefore, are unlikely to relieve head pain serious enough to bring a patient to the emergency department. In one study, only 44% of patients reported that they obtained relief from aspirin or acetaminophen, while 25% occasionally reported relief with these agents.[24] Intestinal absorption of drugs may be impaired in patients experiencing migraine, and these agents may not be adequately absorbed to be efficacious. Concomitant administration of an antiemetic improves absorption and makes other agents more effective.

This is not meant to suggest that aspirin and NSAIDs do not play a role in migraine treatment. Aspirin, ibuprofen, and naproxen have all proven more effective than placebo in alleviating mild attacks in randomized, controlled trials.[30] One review suggests that, in combination with metoclopramide (10 mg), 900 mg aspirin is as effective as oral sumatriptan, and causes fewer side effects. Acetaminophen has not been demonstrated to be effective as single-agent migraine therapy,[30] although it can be helpful in combinations such as Excedrin Migraine (with aspirin and caffeine) or acetaminophen/codeine preparations. Other combination therapies will be discussed in subsequent sections of this review.

The most common side effects of aspirin and NSAIDs are gastrointestinal upset and renal impairment,[17,30] and their use should be avoided in the elderly and those with known renal disease or GI bleeding problems. Patients who overuse analgesics are more likely to develop rebound headaches and chronic daily headache, and should be warned against frequent use of symptomatic treatments.[30]

One NSAID that has received unique attention in migraine treatment research is ketorolac (Toradol). Intramuscular (IM) ketorolac (60 mg) provides acceptable or complete pain relief in about 60% of migraine patients.[17] The IM route produces less GI upset than oral administration, and more rapid absorption.[27] It should be stressed that studies have produced mixed results regarding the efficacy of ketorolac. One randomized, double-blind, prospective trial compared the effectiveness of 60 mg of ketorolac to that of 100 mg of meperidine plus 50 mg of hydroxyzine, both given intramuscularly. In this study, 60% of the ketorolac group and 56% of the meperidine/hydroxyzine group had complete or significant relief of their headache pain at 60 minutes, and the ketorolac group experienced fewer side effects.[11] Another trial compared ketorolac 60 mg IM to meperidine 75 mg and promethazine 25 mg IM, and found no statistically significant difference between the two groups with regard to headache or nausea reduction.[9] Another study suggested that ketorolac is less effective than meperidine in the treatment of severe migraine, but only 30 mg of IM ketorolac was used (compared to 75 mg of meperidine). Clearly, the lack of efficacy may have been due to subtherapeutic ketorolac dosing.[26] Comparisons of ketorolac to the phenothiazines have also resulted in mixed results. Ketorolac 60 mg IM compared favorably with chlorpromazine 25 mg IV.[35] Ketorolac 30 mg IV, however, was less effective than prochlorperazine 10 mg IV in another prospective double-blind comparison.[34] Once again, the dosing of ketorolac may have been an issue in this study. Overall, the clinical studies supporting the efficacy of ketorolac are substantial.

Interestingly, it has been suggested that migraine patients "either respond to ketorolac or they do not." In one trial, 74% of patients treated with ketorolac 60 mg IM had a significant reduction in their headache pain within 30-60 minutes, and this effect lasted at least six hours. Ketorolac reaches peak blood levels 45 minutes after IM administration, and its half-life is about six hours. In those individuals whose headache responds to ketorolac, nausea and photophobia are also reduced or elimi-

Table 3. Emergency Department Therapy for Migraine

	Medication Name: Generic (Trade)	Dosage/Route of Administration	Comments/Side Effects/ Precautions
FIRST LINE	Prochlorperazine (Compazine)	5-10 mg IV	10 mg IM or 25 mg PR not as effective; Extrapyramidal side effects (dystonia/akathisia), sedation, orthostasis
	Metoclopramide (Reglan)	10 mg IV	IM route not effective as single agent; Less effective than prochlorperazine; Same side effects, but less common
	Ketorolac (Toradol)	30-60 mg IM	Good choice if no IV access; Risk of GI upset, renal impairment; GI upset worse with PO administration; Avoid use in elderly, known renal disease, hypertension, or GI bleeding problems
	Chlorpromazine (Thorazine)	25 mg IM	High risk of orthostatic hypotension; Always pre-treat with 5 cc/kg IV normal saline bolus; Extrapyramidal side effects and sedation are more common than with other antiemetics
	Sumatriptan (Imitrex)	6 mg SQ 25 mg PO	Not to be used within 24 hours of ergots; Contraindications: hypertension, coronary artery disease, other vascular insufficiency; Side effects: injection site discomfort, pressure or tightness in chest or throat, dizziness, vertigo; High rate of headache recurrence
SECOND LINE	Dihydroergotamine (DHE)	1 mg IV/IM	Tends to worsen GI symptoms; use only with concomitant antiemetic; Cannot be used if sumatriptan has already been taken during current attack; Contraindications: coronary artery disease, uncontrolled hypertension, pregnancy; Side effects: transient worsening of headache, chest tightness, hypertension, claudication
	Isometheptene (Midrin)	2 capsules PO	Consider for refractory headache if DHE and sumatriptan are contraindicated
THIRD LINE	Meperidine (Demerol) Stadol (Butorphanol)	50-100 mg IV/IM 2 mg IM	Opioids less efficacious than other treatment modalities; Higher relapse rate; Risk of addiction; Side effects: sedation, dysphoria, psychomimetic effects, respiratory depression; Last resort rather than withholding therapy
	Steroids	Multiple regimens	Only for status migrainosus, severe refractory headaches; Risks: GI bleeding, infection, cataracts, aseptic necrosis, memory disturbances; Consider antacids, H2-blockers for GI protection

nated. Those patients with no response after one hour are unlikely to have any additional relief of their head pain.[8] Home administration of IM ketorolac has been studied in an attempt to reduce emergency department usage; of note is that 87% of patients reported sufficient relief to avoid an emergency department visit; in this study, rectal antinauseants were offered to patients whose symptoms necessitated such therapy.[39]

Phenothiazines/Antiemetics. Significant attention has been directed toward evaluating the role of phenothiazines in migraine treatment. While prochlorperazine, chlorpromazine, metoclopramide, and other phenothiazine derivatives have long been used for managing the nausea that accompanies many migraine attacks, only recently have these agents been recognized as single-agent therapeutic modalities for migraine headache. At present, the efficacy of the phenothiazines is thought to be due to their modulation of dopaminergic transmission.[29] The phenothiazines should be considered for migraineurs with known or suspected coronary artery disease, since other

agents known to be effective in migraine may be associated with serious side effects in the setting of coronary heart disease.

Prochlorperazine can be considered a first-line agent for management of migraine headaches. Because most patients who access the emergency department with a migraine headache have already tried NSAIDs or mild narcotics without adequate relief, an intravenous antiemetic may be an effective initial ED therapy.[27] Prochlorperazine is a potent dopamine receptor antagonist and has been proven as an effective, single-agent treatment for migraine. In one prospective, randomized, double-blind trial, prochlorperazine 10 mg IV provided complete relief in 74% and partial relief in 14% of patients within 60 minutes of administration (mean of 21 minutes).[24,29] No significant side effects were noted, and no patient returned to the emergency department within 48 hours.[24] Another study reported that prochlorperazine 10 mg IV was effective in 82% of patients within 30 minutes; there were no recurrences of headache within 24 hours and two dystonic reactions among the 22 patients studied.[29] It should be noted that when prochlorperazine is administered by a route other than the intravenous route, it is not as consistently efficacious. However, one placebo-controlled study of rectal (25 mg) prochlorperazine demonstrated efficacy (at least 50% reduction in pain intensity) at 120 minutes in all patients. It is important to note that 50% of the control patients in this study had relief from placebo, and that no significant difference between study and control patients was seen at 30 or 60 minutes.[21]

Two studies have compared prochlorperazine with another phenothiazine-related compound, metoclopramide. The first trail compared 10 mg of IV prochlorperazine, 10 mg of IV metoclopramide, and placebo. Prochlorperazine achieved patient satisfaction and at least 50% reduction in headache in 82% of patients, in contrast to 48% of metoclopramide patients and 29% of placebo patients. Nausea reduction was also more pronounced with prochlorperazine, and headache recurrence was less common in the prochlorperazine group.[7] The second study compared 10 mg of IM prochlorperazine, 10 mg of IM metoclopramide, and placebo. Prochlorperazine produced significant headache reduction in 67% of patients, metoclopramide in 34%, and placebo in 16%. Thirty-two percent of patients who received prochlorperazine had complete headache relief vs. 14% of the metoclopramide group and 7% of the placebo group. Nausea was completely relieved in 74% of subjects with prochlorperazine, 52% with metoclopramide, and 13% with placebo.[22] No significant difference was found between the two agents in terms of adverse effects. In summary, current studies suggest prochlorperazine is significantly more effective than metoclopramide; however, prochlorperazine administered by intramuscular route did not achieve complete headache relief in a sufficient percentage of patients to justify IM prochlorperazine as an appropriate choice for single-agent therapy.[22]

Single-agent therapy with metoclopramide has met with mixed reviews.[15,24,29] This agent is commonly used in Europe as an adjunctive agent to improve oral absorption of other analgesics. It has been shown to have a beneficial effect as a *prophylactic* agent for migraine patients. It is only moderately effective for acute migraine therapy as a single agent, however, because it has less affinity for dopamine receptors than other phenothiazines.[29] *Intramuscular* metoclopramide, in fact, is no more effective than placebo for pain reduction, although IV metoclopramide has provided adequate relief for ED discharge in 67% of patients (vs 19% with placebo).[24] Other studies have found IV metoclopramide efficacious in treatment of both the pain and nausea of migraine, independent of the concomitant use of other medications.[15] One comparative study evaluating IV metoclopramide and IV chlorpromazine found the two to be equally efficacious for migraine treatment.[4]

Intravenous chlorpromazine is reportedly 89-94% effective for emergency department treatment of migraine.[24-29,38] Intramuscular chlorpromazine has also relieved both headache and nausea in 96% of patients in the ED setting. However, 18% of patients treated with IM chlorpromazine developed orthostatic hypotension.[24,29,38] Consequently, some authorities recommend that patients who receive chlorpromazine should be *pretreated* with a bolus of normal saline (5mL/kg).[30] Several other studies have shown chlorpromazine to be effective for treatment of migraine headache, but this agent does not appear to produce relief in as high a percentage of patients as prochlorperazine, and it is more commonly associated with side effects.[24] In one study, about 32% of patients indicated they would not be willing to take chlorpromazine again for future treatment of migraine.[38]

Other phenothiazines and related compounds have been evaluated in Canadian migraine headache studies. For example, methotrimeprazine was found to be comparable to meperidine with dimenhydrinate for treating severe migraines.[36] Granisetron, a selective serotonin antagonist with potent antiemetic properties, was not significantly different from placebo in relieving migraine headaches.[32] Neither of these medications is currently available in the United States.

Although haloperidol is a butyrophenone, as opposed to a phenothiazine, its mode of action is the same as the phenothiazines, and it is therefore discussed in this section. Haloperidol is a potent dopamine receptor antagonist with antiemetic activity. One case series has studied relief of migraine headache with intravenous haloperidol (5 mg). All six patients achieved complete or substantial headache relief within 65 minutes, with minimal or nonexistent side effects.[16] Haldol may be of use in the treatment of migraine headaches, though this small study is insufficient to allow its recommendation as a first-line therapeutic agent.

Side effects of the phenothiazines (and butyrophenones) include extrapyramidal reactions such as dystonia and akathisia.[17] Sedation and orthostasis are also significant risks, and may limit the use of these agents in patients with poor cardiac function and in the elderly.[27]

Ergots. Ergotamine compounds have been used for decades as an *abortive* agent for migraine attacks. Once a migraine headache has ensued, there is no role for ergotamine. Its mechanism of action is vasoconstriction, which counteracts the dilatation of extracranial arteries and arterioles. In order to prevent rebound headaches, ergotamine should not be used more often than every five days. It also *cannot* be used concomitantly with sumatriptan, so ergotamine should not be administered if the patient has already taken sumatriptan during the current attack. Due to severe side effects, parenteral ergotamine is no longer available in the United States. However, sublingual ergotamine (Ergostat) and oral or rectal ergotamine/caffeine combinations (Cafergot, Wigraine) are still available.[10] Rectal administration results in higher blood levels than oral administration. A high rate of side effects and rebound headaches makes this a less than optimal therapy for most patients.[24]

For parenteral therapy, dihydroergotamine (DHE) can be given by the IV or IM route, and it is often given concomitantly with an antiemetic to manage the nausea of migraine as well as the GI upset induced by DHE.[10] DHE has less vasoconstrictive action than ergotamine and produces fewer rebound headaches and fewer side effects.[24,38] In a prospective, double-blind trial, patients received either 1 mg of DHE or 1.5 mg/kg of meperidine intramuscularly. Both agents were given concomitantly with hydroxyzine as an antiemetic. DHE compared favorably with meperidine (no statistically significant difference in outcomes) and it produced fewer CNS side effects, such as dizziness. Another trial compared DHE 1 mg IV plus metoclopramide 10 mg IV with both butorphanol and meperidine plus hydroxyzine. More than 90% reduction in headache was achieved for 38% of patients treated with DHE/metoclopramide compared with 16% treated with butorphanol.[24] Another study found IV DHE superior to IM meperidine, but it must be interpreted with caution because the two medications were given by different routes.[25] DHE has also been tried by both the intranasal and the subcutaneous routes, but with poor efficacy.[24,38] Home administration of DHE by the intramuscular and subcutaneous routes has also been studied as a way of avoiding an ED visit. Results have been promising, but application may be limited by patients' reluctance to inject themselves and by the high rate of side effects.[43]

Contraindications to the use of ergotamine/DHE include uncontrolled hypertension and coronary artery disease (due to risk of vasoconstriction)[27] and pregnancy (due to oxytocic effects).[10] Severe side effects, such as peripheral vascular insufficiency requiring prostaglandin infusion for limb salvage, have been reported after ergotamine use.[13] Other side effects include transient worsening of headache, chest tightness, hypertension, and claudication.[17] Gastrointestinal distress tends to worsen, rather than improve with DHE use. In fact, more than 25% of patients given DHE in one study said they would refuse the drug in the future, mostly due to the GI side effects that affected 58% of the study patients.[38] The decision to use ergots for migraine therapy should be made with caution, especially in patients at risk for vascular insufficiency.

Sumatriptan. The "triptans" represent the newest class of migraine therapeutic agents. Sumatriptan (Imitrex) was first introduced to the market in 1993 in injectable form, and later as a tablet and nasal spray. Three congeners have been subsequently introduced: zolmitriptan (Zomig), naratriptan (Amerge), and rizatriptan (Maxalt). From a practical, clinical perspective, none of these has supplanted sumatriptan. Moreover, none has proven as potent as parenteral sumatriptan, although some patients may have a particular preference among the "triptans." For the purposes of this review, only sumatriptan will be considered.

Sumatriptan's mechanism of action is vasoconstriction, which is mediated through serotonin, dopamine, and adrenergic receptor sites.[24] As mentioned above, it cannot be given concomitantly with (or within 24 hours of) ergots, due to a theoretical additive effect. At least one report has documented severe side effects from the combination of these two medications; renal papillary necrosis developed from renal ischemia after coadministration of sumatriptan, DHE, and ketorolac (all three of these agents probably contributed).[45] Like the ergots, sumatriptan is contraindicated in patients with known hypertension, coronary artery disease, or other vascular insufficiency. It does not worsen GI distress as do ergots. In fact, it tends to relieve headache and nausea,[27] as well as other associated symptoms of migraine.[10] Residual nausea, however, may necessitate addition of antiemetics for up to 25% of patients receiving sumatriptan.[38]

Rare, but potential life-threatening effects of sumatriptan include cardiac arrhythmia, including cardiac arrest and myocardial infarction, and stroke in the setting of occult coronary disease or atherosclerotic vascular disease. Relative contraindications to the use of sumatriptan include poorly controlled hypertension, history of diabetes mellitus, angina, or asthma.[46]

Side effects of administration of sumatriptan include local injection site symptoms (warmth, redness, tingling) and pressure or tightness in the throat or chest.[17] Dizziness and vertigo have also been reported.[1] Sumatriptan is associated with a 40% headache recurrence rate at 24 hours following administration.[17,24,27] One study found that of patients successfully treated with sumatriptan, 42% required rescue medication by eight hours after discharge, 61% by 24 hours postdischarge; only one-third of patients were pain free at the 24-hour follow-up.[38] Sumatriptan costs about $12 for a 25-mg tablet and about $40 for a single injection. Due to these limitations, sumatriptan has been recommended by some authorities as a second-line therapy for migraine patients who have failed to obtain relief after IV antiemetic administration.[27] Other experts, however, are sufficiently impressed with the drug's clinical efficacy, as well as evidence-based trials confirming its value in migraine treatment to position it as a first-line agent in appropriate patient subgroups.

Sumatriptan is effective if taken at any time during a migraine attack, but it should not be taken during the aura phase of a classical migraine, since at least one study has found it ineffective at this stage.[30] Sumatriptan administered by the intravenous route has been effective in 90% of cases in one study.[24] Orally, it provided significant relief for 70-80% of subjects within two hours of administration. Subcutaneous injection improved headache severity in 86-92% of patients at two hours, compared to 37% of placebo controls.[24] Another study of subcutaneous sumatriptan found that 6 mg resulted in complete or almost complete resolution of pain in 70-77% of patients within 60 minutes and 81-87% within two hours. Giving more than 6 mg initially, or repeat dosing later, did not provide any additional benefit.[17] Other authors have recommended repeat dosing at one hour if no relief has been obtained (up to 12 mg in 24 hours).[10] One clinical trial of subcutaneous sumatriptan in the ED found that 75% of patients obtained meaningful relief after 6 mg, vs. 35% with placebo. At discharge, a 100-mg tablet of oral sumatriptan was offered in case of headache return. Sixty-two percent of patients with mild or no pain at discharge took the oral form within 24 hours, and 65% of these patients obtained relief within two hours.[1]

The starting oral dose of sumatriptan is 25 mg, repeated in two hours if needed. This can be increased in 25 mg increments with subsequent dosing, up to a total of 200 mg in 24 hours. As is the case with ergots, a five-day hiatus is recommended between treatment days.[10]

Isometheptene. Isometheptene is a mild vasoconstrictor, and it is available in combination with acetaminophen and dichloralphenazone (a sedative metabolized to chloral hydrate) known as Midrin.[42] This is generally not considered a first-line agent, but it may be considered in patients with contraindications to ergots or sumatriptan, or if medication is still needed on the sec-

Table 4. Migraine Triggers[19]

- Nitrites (processed meats and foods, nitroglycerin)
- Tyramine (wine, sausages, some cheese)
- Tyrosine
- Phenylalanine
- Phenylethamine (cheese, chocolate)
- 1-octopamine (citrus fruits)
- Aspartame
- Monosodium glutamate
- Alcohol
- Tobacco
- Overuse of caffeine, or caffeine withdrawal
- Too much or too little sleep
- Fasting
- Physical activity, or relaxation following activity/stress
- Hot, humid weather, or change in weather
- Menstruation, or estrogen-containing oral contraceptives
- Minor head trauma

ond or third day of an attack.[10] Patients should take two tablets initially for optimal effect.[42]

Caffeine. Caffeine, a vasoconstrictor, is not a single-agent therapy for migraine, but it has been found helpful as an adjunct in combination medications. Preparations containing caffeine may have greater efficacy because caffeine acts as an analgesic, as well as promoting absorption across mucous membranes.[42] Fioricet and Fiorinal contain acetaminophen and aspirin, respectively, plus caffeine and butalbital. Excedrin contains aspirin, acetaminophen, and caffeine. Wigraine and Cafergot are comprised of ergotamine and caffeine.

Opioids. One of the factors fueling development of new treatment modalities and protocols for migraine is the concern that traditional therapy with opioid medications has the capacity to produce narcotic dependence in migraine sufferers if they require frequent treatment. A cross-sectional survey in 1993 determined that narcotics continue to be a common medication class used for migraine therapy; in fact, they were the most common choice in the study.[2] Many other studies cite the potential for abuse and addiction,[10,27,30] as well as lower efficacy and higher headache relapse rates[38] as reasons to avoid narcotic use for migraines, except as a last resort.[27,30]

As noted in previous sections of this review, many agents have been compared to meperidine to rate their efficacy, and most of them have proven superior. In a study of meperidine for migraine, 1.5 mg/kg of meperidine was given and repeat dosing was required in 43% of participants. Even after two injections, 63% of patients required further rescue medications before discharge, and 28% of patients had headache relapse within 24 hours.[5] Several other studies have confirmed poor results with narcotic injections.[11,36]

Some patients obtain relief from narcotic agents and fail with other therapies. If this is the case, the emergency physician should be willing to use narcotics rather than withholding treatment.[38] Nevertheless, narcotic agents remain a second-line therapy for use in treatment failures.[6]

Oral and transnasal opioids have been recommended for patients requiring narcotic medication for migraine treatment. A 1996 review introduced an oral narcotic protocol using oral meperidine or hydromorphone in combination with pretreatment phenothiazine and metoclopramide, as well as a sedative.[41] This approach was safe and cost-effective protocol, in that it reduced subsequent emergency visits. This approach is unlikely to be used in the emergency department setting.

Butorphanol (Stadol) is a mixed agonist-antagonist opioid analgesic available for parenteral administration as well as in a transnasal preparation for migraine.[10] One puff in one nostril is equipotent with 5 mg of morphine. It provides rapid pain relief, but causes sedation, dysphoria, and may produce rebound headaches if overused.[42] The adverse side effect profile of butorphanol is sufficiently problematic to categorize this agent as an undesirable choice for migraine treatment. A study of optimal butorphanol dosing and safety revealed that intramuscular injections of 2-3 mg provided significantly greater analgesia than a 1 mg injection, but no significant difference in efficacy was observed between the 2 mg and 3 mg doses. No major adverse effects occurred, although sedation, decrease in respiratory rate (of no clinical significance), and psychomimetic side effects (e.g., vivid dreams, hallucinations) were reported.[14] A study of transnasal butorphanol (TNB) use for migraine headaches in the emergency department found that 1 mg of TNB alone provided adequate relief in 60% of patients. Thirty-six percent reported side effects, although most were mild (drowsiness, dysphoria); 52% had some degree of headache recurrence within 48 hours.[28] As a result of these findings, butorphanol is not an ideal medication for migraine, although it can be used for patients with infrequent but severe migraine attacks for whom other treatments are either ineffective, inconvenient, or contraindicated.[30]

Lidocaine. Lidocaine nose drops have been recommended in one study as more effective than placebo in alleviating migraine headaches. One mg of 4% lidocaine may be instilled into the nostril ipsilateral to the head pain, with the head hyperextended 45 degrees and turned 30 degrees toward the headache side. Fifty percent of patients experience relief within minutes, but 50% of these headaches recur within one hour. This approach certainly is suboptimal for routine consideration.[42] On the other hand, about 80% of cluster headaches will resolve with 4% lidocaine (or cocaine hydrochloride[19]) administration into the sphenopalatine fossa. Lidocaine may, therefore, be considered in addition to 100% oxygen therapy for cluster headache.[20]

Corticosteroids. The use of corticosteroids in migraine is reserved for patients with a severe headache lasting more than 72 hours (status migrainosus). Chronic steroids should be reserved as a last resort for patients not responding to other measures, as they are less effective and more prone to side effects (hyperglycemia, hypertension, aseptic necrosis, GI bleeding, infection, cataracts, memory disturbances, etc.) than many other modalities.[42] Corticosteroids take several hours to produce clinical results, so additional medication for sleep may be given concomitantly. Antacids, H2-blockers, or other agents should also be considered for GI protection, and a sedating anti-emetic (hydroxyzine, prochlorperazine) may alleviate nausea, as well as insomnia caused by the corticosteroids.[42]

An emergency department study of corticosteroid use in migraine patients found that 72% of patients treated with meperidine 75-100 mg, promethazine 50 mg, and dexamethasone 8 mg reported significant relief. Only 37% of patients treated with

DHE 1 mg and meperidine 75-100 mg obtained relief, and only 29% of patients treated with meperidine 75-100 mg and promethazine 50 mg. While the groups are not strictly comparable, patients receiving corticosteroids had a superior outcome.[24]

Multiple dosing regimens for corticosteroids have been cited in the literature. Intravenous hydrocortisone 100 mg three times a day may be used, but should be considered only in patients admitted for their refractory headaches. Burst therapy with 10 mg of dexamethasone, repeated the next day if necessary, or a one-week tapering dose of prednisone (60 mg for 3 days, 40 mg for 2 days, 20 mg for 2 days) also may be considered.[42] Other authors have recommended either dexamethasone acetate, 16-mg long-acting preparation, or methylprednisolone acetate 80-mg IM injection, but they caution against repeating this therapy in less than three weeks.[10] A third source reports a dosing regimen of dexamethasone 8-20 mg IM or IV, or methylprednisolone sodium succinate 100-250 mg IV, either with or without added narcotic and antiemetic.[30]

Special Considerations

Special mention should be made of recommendations for migraine patients who are pregnant, and for pediatric patients. As mentioned above, the ergots are contraindicated in pregnancy due to oxytocic effects, and the triptans have unproven safety profiles in pregnant patients. Steroids and NSAIDs also have known adverse effects in pregnancy, and should be avoided. Therefore, for pregnant patients with mild to moderate symptoms, simple analgesics, such as acetaminophen, are recommended. Patients with severe headaches or those who fail therapy with analgesics should be given a trial of narcotic medication, a last resort in most other patient populations.[27]

For pediatric migraine, initial therapy consists of rest, removal of triggering factors *(See Table 4)*, and basic analgesics, such as acetaminophen 15-20 mg/kg. Some children may respond better to NSAIDs, and ibuprofen should therefore be considered. Aspirin should be avoided due to its association with Reye's syndrome. Second-line therapy includes addition of an antiemetic, such as promethazine, prochlorperazine, or metoclopramide. The antiemetics carry a higher risk of extrapyramidal side effects in children, however, and must be used with caution. Metoclopramide (0.1 mg/kg up to a maximum of 10 mg) has less propensity for causing these side effects, and therefore it is the antiemetic of choice in pediatric patients. For the rare child who does not respond to these measures, only IV DHE has been studied (in combination with metoclopramide) in children as young as 6 years. Because of associated side effects, however, this drug must be titrated carefully by a physician experienced in pediatric migraine treatment. Therefore, if headache is severe enough to mandate further abortive therapy beyond rest, reassurance, analgesics, and antiemetics, the emergency physician should consider consultation with a pediatric neurologist, or perhaps even admission for more intensive migraine therapy.[44]

Nonpharmacologic Therapy. Some nonpharmacologic adjuncts to migraine therapy have been found to be beneficial. Patient education should include a clear, definitive diagnosis of migraine once other causes of head pain have been ruled out. Reassurance that no other serious underlying etiology has been found can be an important component of initial therapy. Realistic goals of therapy should be addressed (the concept of control, rather than cure, of migraine). Recognition and avoidance of triggering factors is also important for prevention of future exacerbations, so patients should be educated about the common migraine triggers (See Table 4) and, perhaps, encouraged to keep a headache diary to be reviewed in follow-up with the primary physician. Other nonpharmacologic modalities that have been assessed and shown as possibly valuable include cold or pressure application to the head, reduction of activity and sensory input in a quiet or dark environment, and sleep. Less proven therapies include relaxation therapy/biofeedback, psychotherapy, hypnosis, transcutaneous electrical stimulation, acupuncture, chiropractic, and occipital or supraorbital nerve blockade.[31] These are outside of the scope of routine emergency department treatment, but may be offered to patients in the outpatient setting.[20]

Migraine Prophylaxis. Although it is unlikely that preventive medications will be prescribed by the emergency physician,[20] these agents are mentioned because migraine patients may already be using these therapies or they may ask about their role in migraine treatment when they present for acute headache control. Propranolol is probably the most common prophylactic medication used for migraine. This beta-blocker has been shown to decrease headache frequency by about 31%.[30] Metoprolol has been shown to reduce attack frequency by 28-33% in three separate trials.[19,20] Beta-blockers are contraindicated in asthmatics.[30] Amitryptiline and other tricyclic antidepressants have also been used, although only amitryptiline has been tested in double-blind, placebo-controlled trials. This agent may reduce the frequency of attacks up to 40%, and is the preferred preventive medication for patients with down mood or insomnia. Valproic acid has reduced the frequency of migraine attacks 39-43% below that of control groups, but it has been associated with birth defects and hepatotoxicity.[30] Valproate has recently been shown to be as effective as propranolol for the prophylaxis of migraine without aura.[47] Methysergide is the oldest of the preventives, but can induce an inflammatory fibrosis in the retroperitoneum, lungs, and heart valves. Discontinuing the medication for one month out of every 4-6 months of use can prevent this complication. Verapamil, aspirin, and NSAIDs have been shown to be effective prophylactic medications in selected groups of migraine sufferers. Magnesium, cyproheptadine, fluoxetine (and other selective serotonin reuptake inhibitors), riboflavin (vitamin B2), have all been suggested as preventive treatments for migraine, but definitive trials are lacking.

Disposition

The majority of patients with migraine headaches may be discharged from the emergency department after treatment and an appropriate observation period to ensure that adequate relief of headache and other symptoms has been achieved. It has been suggested that patients who leave the emergency department with residual headache have a much higher rate of headache persistence (61%) at 24 hours than the rate of headache recurrence in patients who leave the emergency department headache-free (31%), regardless of initial headache severity.[12] Therefore, it is prudent to observe patients and continue therapy until headache resolution, if possible. Obviously, this needs to be weighed against the reality of emergency department flow and resource availability.

Not all patients who still have residual headache after emergency department therapy require admission to the hospital. Nevertheless, some subgroups of patients may necessitate hospitalization for observation and continued therapy. Some indications

for hospital admission might include: headache and concomitant nausea/vomiting persisting for several days with signs of dehydration; headache complicated by overuse of therapeutic medications; chronic daily headache not responding to outpatient management; headache accompanied by other medical/surgical problem; intractable cluster headache; suspicion for possible organic disease (e.g., subarachnoid hemorrhage, tumor, meningitis); or interruption of ability to carry out activities of daily living.[19]

Conclusion

Migraine headaches afflict as many as 10-20% of the population and are disabling in at least one-half of these individuals. Recent developments have illuminated the importance of dopaminergic and serotonergic modulation as pathophysiologic mechanisms for migraine therapy. The importance of intravenous hydration in a migraine sufferer who has been vomiting is very important and should not be overlooked. The use of phenothiazines and related antinauseants as first-line therapy for migraine has developed from this knowledge. Triptans are also considered to be first-line agents.

The best initial agent for migraine is often the analgesic that has provided relief for the individual patient in the past. For those patients who cannot identify an appropriate analgesic that has predictably produced pain relief, an antiemetic is the best first-line choice. Prochlorperazine and metoclopramide are both highly effective and safe in most patients. DHE or sumatriptan may be added if pain relief is inadequate after 30 minutes. Intravenous chlorpromazine may be safely tried in the patient with an IV access, and ketorolac is a reasonable choice for patients without an IV access. In selected patients, narcotics may be used, but should be considered a last resort, except in pregnancy or when other agents are contraindicated.[27,38] As much as possible, patients should be treated in the emergency department until their headaches are completely resolved, as patients not obtaining complete relief in the emergency department have a higher rate of headache persistence or recurrence than do those who leave the ED with no pain.[12] Nonpharmacologic and prophylactic therapy may assist in the management of migraine sufferers, but are best left for the primary care physician or neurologist to manage in the outpatient arena.

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Physician CME Questions

73. Up to what percent of headaches evaluated in emergency departments and by primary care physicians are thought to be due to muscle contraction?
    A. 10%
    B. 30%
    C. 90%
    D. 50%

74. Frequent findings in the patient with common migraine include:
    A. photophobia.
    B. sonophobia.
    C. vomiting.
    D. anorexia.
    E. all of the above.

75. Headache pain in ophthalmoplegic migraine is associated with:
    A. ocular muscle weakness.
    B. ptosis.
    C. extraocular paralysis.
    D. pupillary changes.
    E. All of the above.

76. Migraine equivalent refers to a condition in which a migraine sufferer experiences autonomic nervous system effects resulting in:
    A. edema.
    B. chest pain.
    C. visual changes.
    D. intense headache pain.
    E. Both A and B are correct.

77. Cluster headaches are characterized by:
    A. unilateral, excruciating facial pain often lasting for days.
    B. lacrimation.
    C. ipsilateral nasal congestion.
    D. Both B and C are correct.

78. A history in the headache patient should include:
    A. location.
    B. mitigating factors.
    C. prodromal symptoms.
    D. quality.
    E. All of the above.

79. Sumatriptan's mechanism of action is vasoconstriction, which is mediated through which of the following receptor sites?
    A. Serotonin
    B. Dopamine
    C. Adrenergic
    D. All of the above.

80. What percent of cluster headaches will resolve with 4% lidocaine (or cocaine hydrochloride)?
    A. 5%
    B. 80%
    C. 20%
    D. 40%

In Future Issues: Thoracic Aneurysm