Treatment of Acute Migraine Headache

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Migraine headache is a common and potentially debilitating disorder often treated by family physicians. Before diagnosing migraine, serious intracranial pathology must be ruled out. Treating acute migraine is challenging because of substantial rates of nonresponse to medications and difficulty in predicting individual response to a specific agent or dose. Data comparing different drug classes are relatively scarce. Abortive therapy should be used as early as possible after the onset of symptoms. Effective first-line therapies for mild to moderate migraine are nonprescription nonsteroidal anti-inflammatory drugs and combination analgesics containing acetaminophen, aspirin, and caffeine. Triptans are first-line therapies for moderate to severe migraine, or mild to moderate migraine that has not responded to adequate doses of simple analgesics. Triptans should be avoided in patients with vascular disease, uncontrolled hypertension, or hemiplegic migraine. Intravenous antiemetics, with or without intravenous dihydroergotamine, are effective therapies in an emergency department setting. Dexamethasone may be a useful adjunct to standard therapy in preventing short-term headache recurrence. Intranasal lidocaine may also have a role in relief of acute migraine. Isometheptene-containing compounds and intranasal dihydroergotamine are also reasonable therapeutic options. Medications containing opiates or barbiturates should be avoided for acute migraine. During pregnancy, migraine may be treated with acetaminophen or nonsteroidal anti-inflammatory drugs (prior to third trimester), or opiates in refractory cases. Acetaminophen, ibuprofen, intranasal sumatriptan, and intranasal zolmitriptan seem to be effective in children and adolescents, although data in these age groups are limited. (*Am Fam Physician.* 2011;83(3):271-280. Copyright © 2011 American Academy of Family Physicians.)

ILLUSTRATION BY BERT OPPENHEIM

▶ **Patient information**: Handouts on this topic are available at http://familydoctor.org/127.xml and http://familydoctor.org/757.xml.

Migraine headache is one of the most common, yet potentially debilitating disorders encountered in primary care. Approximately 18 percent of women and 6 percent of men in the United States have migraine headaches, and 51 percent of these persons report reduced work or school productivity.[1] Patients typically describe recurrent headaches with similar symptoms, and approximately one-third describe an aura preceding the headache.[1] This article reviews treatment options for acute migraine headache.

Diagnosis

Table 1 lists International Headache Society diagnostic criteria for migraine with and without aura.[2] A thorough history and physical examination can help confirm the diagnosis of migraine and rule out emergent conditions. The mnemonic POUND is an evidence-based aid for migraine diagnosis[3]:

- Pulsatile quality of headache
- One-day duration (four to 72 hours)
- Unilateral location
- Nausea or vomiting
- Disabling intensity

In a primary care setting, the probability of migraine is 92 percent in patients who report at least four of the five POUND symptoms.[4] The probability decreases to 64 percent in patients with three of the symptoms, and 17 percent in patients with two or less symptoms.[4]

Table 2 outlines other serious causes of headache that must be considered in the differential diagnosis of migraine, such as temporal arteritis, cluster headache, and acute glaucoma.[3] Fever, meningismus, or altered mental status should prompt investigation for meningitis or subarachnoid

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Triptans are effective and safe for treatment of acute migraine.	A	8
Abortive therapy should be used as early as possible in the course of a migraine.	B	19
Combination analgesics containing aspirin, caffeine, and acetaminophen are an effective first-line abortive treatment for migraine.	A	7, 9
Ibuprofen at standard doses is effective for acute migraine treatment.	A	21
Intravenous metoclopramide (Reglan) is effective for acute migraine treatment.	B	11
Parenteral dexamethasone is useful as an adjunctive treatment in the emergency department to help prevent short-term headache recurrence.	A	12, 18
Opiates and barbiturate-containing compounds should not be routinely used for abortive treatment of migraine.	C	14, 34

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

hemorrhage. The U.S. Headache Consortium recommends considering neuroimaging in patients with an unexplained abnormal finding on neurologic examination and in patients with atypical headache features or headaches that do not fulfill the strict definition of migraine or other primary headache disorder.[5] The Consortium notes that neuroimaging generally is not indicated for patients with migraine and a normal neurologic examination.

In one study, age older than 50 years, sudden onset, and abnormal neurologic examination predicted serious intracranial pathology in adults presenting to an emergency department with nontraumatic headache; the presence of any one of these three features detected serious intracranial pathology with 98.6 percent sensitivity.[6]

General Treatment Principles

Several medications from different classes are available to treat acute migraine *(Table 3*[7-13]*)*. Because relatively few trials have directly compared the different medication classes

Table 1. International Headache Society Diagnostic Criteria for Migraine Headache With and Without Aura

Migraine without aura	**Migraine with aura**
Diagnostic criteria:	Recurrent disorder manifesting in headaches of reversible focal neurologic symptoms that usually develop gradually over five to 20 minutes and last for less than 60 minutes
Headache lasts four to 72 hours (untreated or unsuccessfully treated)	Headache with the features of migraine without aura usually follows the aura symptoms
Headache has at least two of the following:	Less commonly, headache lacks migrainous features or is completely absent
Aggravation by or causing avoidance of routine physical activity (e.g., walking, climbing stairs)	*Diagnostic criteria:*
Moderate or severe pain intensity	Aura consisting of at least one of the following, but no motor weakness:
Pulsating quality	Fully reversible dysphasic speech disturbance
Unilateral location	Sensory symptoms that are fully reversible, including positive features (pins and needles) and/or negative features (numbness)
During headache, at least one of the following:	Visual symptoms that are fully reversible, including positive features (flickering lights, spots, lines) and/or negative features (loss of vision)
Nausea and/or vomiting	At least two of the following:
Photophobia and phonophobia	Homonymous visual symptoms and/or unilateral sensory symptoms
Not attributed to another disorder	At least one aura symptom develops gradually over five minutes or different aura symptoms occur in succession over five minutes
History of at least five attacks fulfilling above criteria	Each symptom lasts at least five minutes, but no longer than 60 minutes
	Headache fulfilling criteria for migraine without aura begins during the aura or follows aura within 60 minutes
	Not attributed to another disorder
	History of at least two attacks fulfilling above criteria

Information from reference 2.

Table 2. Differential Diagnosis of Migraine Headache

Condition	*Characteristics*
Acute glaucoma	Associated with blurred vision, nausea, vomiting, and seeing halos around lights; ophthalmologic emergency
Acute or chronic subdural hematoma	Antecedent trauma; may have subacute onset; altered level of consciousness or neurologic deficit may be present
Acute severe hypertension	Marked blood pressure elevation (systolic > 210 mm Hg or diastolic > 120 mm Hg); may have confusion or irritability
Benign intracranial hypertension (pseudotumor cerebri)	Often abrupt onset; associated with nausea, vomiting, dizziness, blurred vision, and papilledema; may have cranial nerve V1 palsy; aggravated by coughing, straining, or changing position
Carbon monoxide poisoning	May be insidious or associated with dyspnea; occurs more commonly in colder months
Carotid dissection	Cause of stroke; can be spontaneous or follow minor trauma or sudden neck movement; unilateral headache or face pain; ipsilateral Horner syndrome
Cervical spondylosis	Worse with neck movement; posterior distribution; pain is neuralgic in character and sometimes referred to vertex or forehead; more common in older patients
Cluster headache	Uncommon; sudden onset; duration of minutes to hours; repeats over a course of weeks, then may disappear for months or years; unilateral lacrimation and nasal congestion; severe unilateral and periorbital pain; more common in men; patient is restless during episode
Encephalitis	Neurologic abnormalities, confusion, altered mental status or level of consciousness
Frontal sinusitis	Usually worse when lying down; nasal congestion; tenderness over affected sinus
Greater occipital neuralgia	Occipital location; tenderness at base of skull; pain is neuralgic in character and referred to vertex or forehead
Intracranial neoplasm	Worse on awakening; generally progressive; aggravated by coughing, straining, or changing position
Medication-induced headache	Chronic headache with few features of migraine; tends to occur daily; hormone therapy and hormonal contraceptives are frequent culprits; includes analgesic rebound
Meningitis	Fever; meningeal signs
Postconcussion syndrome	Antecedent head trauma; vertigo, lightheadedness; poor concentration and memory; lack of energy; irritability and anxiety
Subarachnoid hemorrhage	Explosive onset of severe headache; 10 percent preceded by sentinel headaches
Temporal arteritis	Almost exclusively in patients older than 50 years; associated with tenderness of scalp or temporal artery and jaw claudication; visual changes
Temporomandibular joint dysfunction	Pain generally involves the temporomandibular joint and temporal areas; associated with symptoms when chewing
Tension-type headache	Common; duration of 30 minutes to seven hours; typically bilateral; nonpulsating; mild to moderate intensity without limiting activity; no nausea or vomiting
Trigeminal neuralgia	Brief episodes of sharp, stabbing pain and trigeminal face distribution

Adapted with permission from Wilson JF. In the clinic. Migraine [published correction appears in Ann Intern Med. *2008;148(5):408].* Ann Intern Med. *2007;147(9):ITC11-4.*

available to treat acute migraine, definitive treatment algorithms cannot be developed. More than one-half of persons treat their migraine headaches with nonprescription medications, and patients often present to physicians after unsuccessfully trying multiple nonprescription therapies.[7] The U.S. Headache Consortium guidelines offer a general strategy based on expert consensus.[14] Nonsteroidal anti-inflammatory drugs (NSAIDs) or caffeine-containing combination analgesics may be first-line treatment for mild to moderate migraine, or severe migraine that has previously responded to these agents. Triptans are considered first-line abortive treatment of moderate to severe migraine, or mild attacks that have not responded to nonprescription medicines. Ergotamine-containing compounds may also be reasonable in this situation.[14] *Figure 1* provides a suggested algorithm for management of acute migraine headaches.[5,6,11,12,14-18]

Predicting individual response to a specific medication is difficult. Complete pain relief is not always achievable. For example, studies report complete pain relief within

Table 3. Medications for Abortive Therapy of Acute Migraine

Therapy	*Dosing*
First-line therapies	
Combination analgesics	
Acetaminophen, 250 mg/aspirin, 250 mg/caffeine, 65 mg (Excedrin Migraine)	1 or 2 tablets (or capsules) every 6 hours, not to exceed 8 tablets per day
NSAIDs	
Ibuprofen	200 to 800 mg orally every 6 to 8 hours, not to exceed 2.4 g per day
Naproxen	250 to 500 mg orally every 12 hours, not to exceed 1 g per day
Triptans	
Almotriptan (Axert)	6.25 to 12.5 mg orally, can be repeated in 2 hours, not to exceed 25 mg per day
Eletriptan (Relpax)	20 to 40 mg orally, can be repeated in > 2 hours, not to exceed 80 mg per day
Frovatriptan (Frova)	2.5 mg orally, can be repeated in 2 hours, not to exceed 7.5 mg per day
Naratriptan (Amerge)	1 to 2.5 mg orally, can be repeated in 2 hours, not to exceed 5 mg per day
Rizatriptan (Maxalt)	5 to 10 mg orally, can be repeated in 2 hours, not to exceed 30 mg per day
Sumatriptan (Imitrex)	*Intranasal:* 5 to 20 mg, can be repeated in 2 hours, not to exceed 40 mg per day *Oral:* 25 to 100 mg, can be repeated in 2 hours, not to exceed 200 mg per day *Subcutaneous:* 4 to 6 mg, may repeat in 1 hour, not to exceed 12 mg per day
Zolmitriptan (Zomig, Zomig-ZMT‡)	*Intranasal:* 5 mg, may repeat in 2 hours, not to exceed 10 mg per day *Oral disintegrating tablets:* 2.5 mg, can be repeated in 2 hours, not to exceed 10 mg per day *Oral:* 1.25 to 2.5 mg, can be repeated in 2 hours, not to exceed 10 mg per day
Combination triptans and NSAIDs	
Sumatriptan, 85 mg/naproxen, 500 mg (Trexima)	1 tablet at onset, may repeat in 2 hours, not to exceed 2 tablets per day
Other effective therapies	
Antiemetics	
Metoclopramide (Reglan)	10 mg IV every 8 hours
Prochlorperazine	10 mg IV every 8 hours, not to exceed 40 mg per day
Dexamethasone	*IV:* 10 to 25 mg, one-time dose
Ergotamines	
Dihydroergotamine (DHE; Migranal§)	*Intranasal:* 1 spray in each nostril, repeat once after 15 minutes; not to exceed 4 sprays per attack, 6 sprays per day, 8 sprays per week *IV:* 0.5 to 1 mg repeated every 8 hours, *or* continuous IV infusion totaling 3 mg per 24 hours; not to exceed 3 mg per attack *Subcutaneous:* 1 mg every hour; not to exceed 3 mg per day
Isometheptene compounds	
Acetaminophen, 325 mg/dichloralphenazone, 100 mg/isometheptene, 65 mg (Midrin)	1 to 2 capsules orally every 4 hours; not to exceed 8 capsules per day
Lidocaine (Xylocaine)	*Intranasal:* 0.5 mL of topical lidocaine 4% solution dripped into the nostril on the affected side over 30 seconds; administered by a clinician while patient lies in the supine position with head hyperextended and tilted to 30 degrees

**—Estimated retail price based on lowest dose provided. Information obtained at http://www.drugstore.com (accessed December 2, 2010). Generic price listed first; brand price listed in parentheses.*

†—Estimated cost to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. *Montvale, N.J.: Medical Economics Data; 2010. Cost to the patient will be higher, depending on prescription filling fee.*

‡—Zomig-ZMT is brand name for oral disintegrating tablet form.

§—Migranal is brand name for intranasal form.

*Cost of generic (brand)**	*Major adverse effects*	*Comments*
Varies	See individual medications	Available without a prescription
Varies Varies	Heartburn, gastric bleeding, ulcers, rebound headache, renal toxicity; can exacerbate heart failure and hypertension	Available without a prescription; many patients have already tried nonprescription NSAIDs before seeking medical advice Cannot be used in the third trimester of pregnancy Generally well-tolerated
NA ($154) for 12 tablets NA ($155) for 6 tablets NA ($242) for 9 tablets NA ($276) for 9 tablets NA ($287) for 3 tablets *Intranasal:* $39† ($55) *Oral:* $620 ($792) for 27 tablets *Subcutaneous:* $184 for 2 vials ($445 for 5 vials) *Intranasal:* NA ($38) *Oral disintegrating tablets:* NA ($154) for 6 tablets *Oral:* NA ($156) for 6 tablets (2.5 mg)	Hypertension, vasospasm, chest pain, malaise, fatigue, rebound headache	Should be avoided in patients with a history of myocardial infarction, cerebrovascular accident, Prinzmetal angina, uncontrolled hypertension, or other vascular diseases, and in pregnant women Do not use with monoamine oxidase inhibitors Case reports of serotonin syndrome when combined with selective serotonin reuptake inhibitors
NA ($206 for 9 tablets)	See individual medications	—
$1† ($2†) for 5-mg vial $3† for 5-mg vial	Dystonic reaction; parkinsonism with metoclopramide use	—
IV: $42 for 25 vials (4 mg)	Hyperglycemia, mood changes, insomnia; multiple adverse effects with long-term use	Use as adjunctive therapy only
Intranasal: NA ($100) *IV:* $32 ($124) *Subcutaneous:* $32	Nausea; rhinorrhea with intranasal use; similar adverse effects as triptans	IV dosing can be used in combination with 10 mg metoclopramide every 8 hours as needed for nausea
$43 ($22†) for 30 capsules	—	Use caution in patients with cardiovascular risk factors
NA ($22†) for 50 mL	Rare cardiac adverse effects if systemically absorbed	Not all patients will benefit, and symptoms may recur

NOTE: *None of the prescription medications are available at discounted prices ($10 or less per prescription) at national retail chains.*

IV = intravenous; NA = not available in generic form; NSAIDs = nonsteroidal anti-inflammatory drugs.

Information from references 7 through 13.

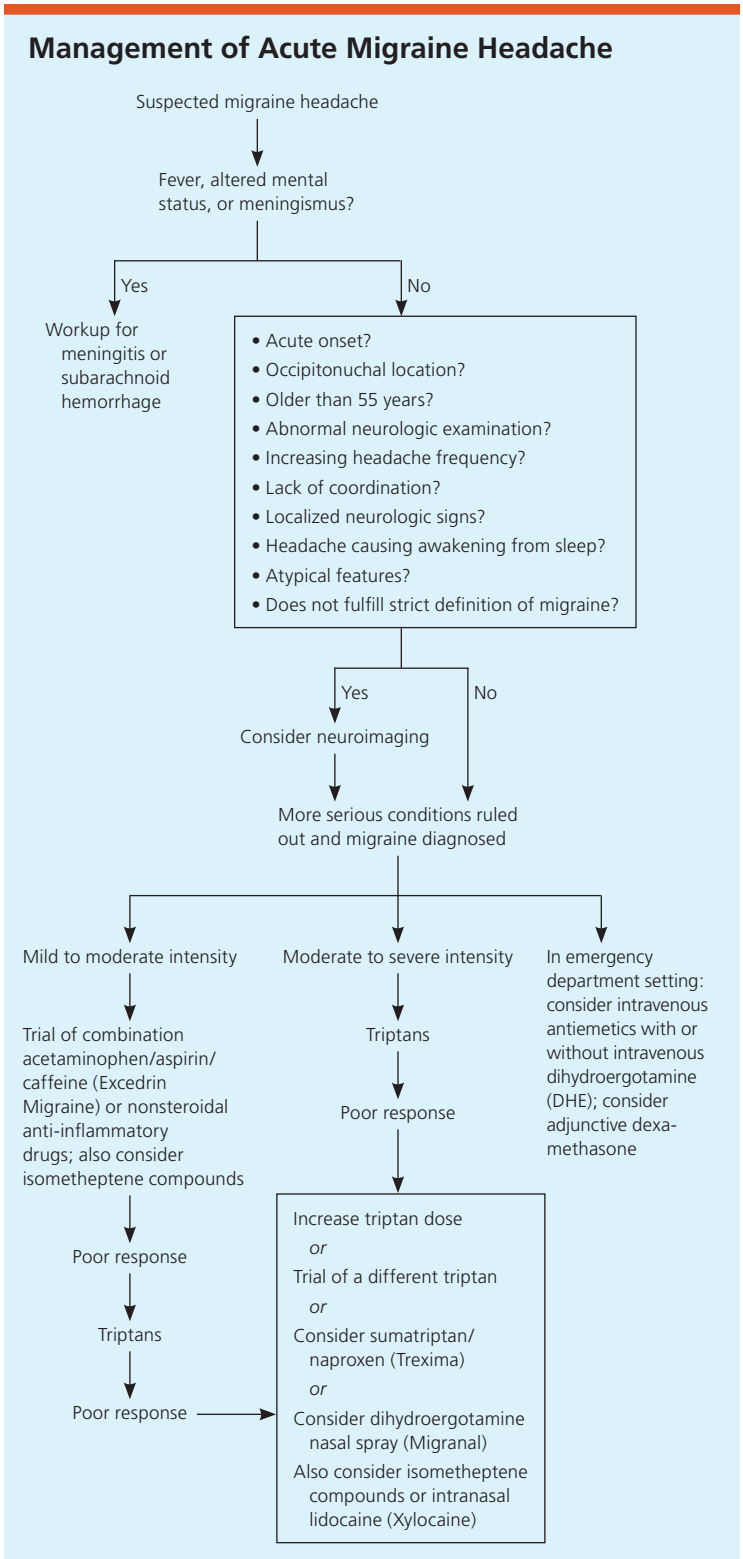

Figure 1. Algorithm for management of suspected migraine headache.

Information from references 5, 6, 11, 12, and 14 through 18.

two hours in 45 to 77 percent of patients taking triptans.[1,8] Potential adverse effects, contraindications, pharmacokinetics, and route of administration are often primary determinants of medication choice. Patients with severe nausea and vomiting often require nonoral medication.

Evidence suggests that abortive therapy works best if taken soon after the onset of migraine or during aura, before pain progresses. A trial using almotriptan (Axert) showed that early users (i.e., therapy initiated within one hour of headache onset) had greater relief and lower recurrence rates of pain than non-early users.[19] Nonprescription analgesics have shown comparable effectiveness with triptans if used in adequate doses soon after headache onset.[9]

Prophylactic therapy may be appropriate for selected patients. The U.S. Headache Consortium's recommended indications for prophylactic therapy in patients with migraine headache are[20]:

- Contraindications or intolerance to abortive therapies
- Headache symptoms occurring more than two days per week
- Headaches that severely limit quality of life despite abortive therapy
- Presence of uncommon migraine conditions, including hemiplegic migraine, basilar migraine, migraine with prolonged aura, or migrainous infarction.

First-Line Therapies

COMBINATION ANALGESICS

The combination analgesic acetaminophen/aspirin/caffeine (Excedrin Migraine) is effective, inexpensive, available without prescription, and free from most vascular contraindications associated with triptans. Its use in migraine treatment has shown favorable results when compared with 50 mg of sumatriptan (Imitrex) in one trial and with placebo in previous trials.[9] Patients with severe pain were included, but patients requiring bed rest or who were consistently vomiting during headaches were excluded.[9] A study that included these more severe cases reported that acetaminophen/aspirin/caffeine is superior to 400 mg of ibuprofen.[7]

NSAIDs

NSAIDs are a convenient first-line therapy for mild to moderate migraine or historically responsive severe attacks. A 2007 meta-analysis of ibuprofen for moderate to severe migraine showed that 200-mg and 400-mg doses were effective for short-term pain relief, but had 24-hour pain-free rates similar to placebo.[21] The 400-mg dose also helped relieve photophobia and phonophobia. A study comparing ketoprofen with zolmitriptan (Zomig) showed zolmitriptan to be modestly more effective (two-hour relief in 61.6 versus 66.8 percent of participants, respectively), but it was associated with more adverse events, such as tight throat and flushing.[22] Ketorolac, a parenteral NSAID commonly used in emergency departments, was found to be effective in reducing self-reported headache symptoms one hour after injection, including one study showing more effectiveness than intranasal sumatriptan.[23]

Triptans

Triptans are migraine-specific drugs that bind to serotonergic receptors. They are considered first-line therapy for moderate to severe migraine, or mild to moderate attacks unresponsive to nonspecific analgesics.[14] Seven triptans are currently available, but data guiding which to select for an individual patient are limited. A Cochrane review found that all triptans are similar in effectiveness and tolerability.[24] A meta-analysis of 53 trials using oral triptans found that the three most effective agents for pain relief were 10 mg of rizatriptan (Maxalt), 80 mg of eletriptan (Relpax), and 12.5 mg of almotriptan.[8] A Cochrane review found a dose of 100 mg of sumatriptan to be more effective than lower doses.[24] It is sometimes necessary to increase the dose of an individual agent before judging response. Trials suggest that nonresponders to one triptan may respond to another; therefore, switching triptans is also reasonable.[25]

Triptans differ from one another in pharmacokinetics. Rizatriptan has a quicker onset of action than sumatriptan; frovatriptan (Frova), naratriptan (Amerge), and eletriptan have longer half-lives than sumatriptan.[26] In practice, route of administration or pharmacokinetics often guide choice. Some triptans are available as nasal sprays, rapidly dissolving tablets (absorbed despite vomiting), or subcutaneous injections. Some physicians choose a triptan by matching pharmacokinetics to the temporal pattern of their patient's migraine (e.g., rapid-onset medication for short course of migraine versus longer-acting medication with slower onset for longer lasting symptoms); however, there is no definitive evidence to support this approach.

The vasoconstrictive properties of triptans preclude their use in patients with ischemic heart disease, stroke, uncontrolled hypertension, or hemiplegic or basilar migraine. However, the chest pain occurring in 3 to 5 percent of oral triptan users has not been associated with electrocardiographic changes and is rarely ischemic.[8] A post-marketing study of subcutaneous sumatriptan in 12,339 patients without ischemic heart disease revealed 36 cardiac events, only two of which occurred within 24 hours of sumatriptan use.[27] Nonetheless, if patients taking triptans develop suspected cardiac symptoms, triptans should be discontinued pending further evaluation. Cardiac evaluation is reasonable before triptan initiation in patients with multiple vascular risk factors.[28]

Triptans are contraindicated in patients taking monoamine oxidase inhibitors.[14] Combining triptans with selective serotonin reuptake inhibitors can lead to serotonin syndrome, a potentially life-threatening condition characterized by altered mentation, autonomic instability, diarrhea, neuromuscular hyperactivity, and fever. The true incidence of serotonin syndrome in this setting is unknown. A 2006 U.S. Food and Drug Administration (FDA) alert cited 29 case reports over five years, although almost 700,000 patients per year are prescribed both selective serotonin reuptake inhibitors and triptans.[29] Physicians treating patients who are taking triptans and selective serotonin reuptake inhibitors should be vigilant for serotonin syndrome, and should minimize drug dosages.

A Cochrane review found similar effectiveness and tolerability among all triptans for migraine therapy, but individual patients may respond better to one triptan over another.

Combination Triptans and NSAIDs

A fixed-dose combination of sumatriptan, 85 mg/naproxen, 500 mg (Trexima) is an option for acute treatment. One trial showed that the combination provided superior pain relief compared with either monotherapy.[10] Another trial found similar results in previous nonresponders to triptans.[15] Patients also may take triptans and NSAIDs concurrently.

Other Effective Therapies

Antiemetics

Evidence supports a role for parenteral antiemetics in acute migraine, independent of their antinausea effects. A meta-analysis of 13 randomized controlled trials concluded that intravenous metoclopramide (Reglan)

should be considered a primary agent in the treatment of migraine in emergency departments.[11] Given the potential for rebound and dependence associated with opiates, antiemetics offer a reasonable alternative in acute settings. No evidence supports migraine-specific effects of oral antiemetics, other than relieving nausea.

DEXAMETHASONE

Intravenous dexamethasone has been used as adjunctive therapy for migraine in emergency departments. Two meta-analyses, each with seven randomized controlled trials in which dexamethasone was added to other standard therapies, showed that about 10 patients needed treatment to prevent headache recurrence within 24 to 72 hours.[12,18]

ERGOTAMINES

Like triptans, ergotamines and dihydroergotamine (DHE) are migraine-specific drugs that bind to serotonergic receptors. Although their use has been largely supplanted by triptans, ergot alkaloids still have a role in selected patients. Little evidence supports the use of oral ergotamines. Poor absorption and high rates of adverse events preclude their use in most situations. Combination medications containing ergotamines (e.g., ergotamine/caffeine [Cafergot]) may have fewer adverse effects than pure ergotamines.[30]

Nine placebo-controlled trials have demonstrated the effectiveness of dihydroergotamine nasal spray (Migranal), making it an option for nonoral medication.[30] Comparison with subcutaneous sumatriptan showed lower effectiveness but fewer adverse effects.[31] Intravenous dihydroergotamine, combined with antiemetics, may be a reasonable option in emergency departments. A meta-analysis showed comparable effectiveness to opiates and ketorolac when combined with an antiemetic, but inferiority to phenothiazines and triptans when used alone.[16] Trials comparing subcutaneous dihydroergotamine with subcutaneous sumatriptan showed that dihydroergotamine had inferior effectiveness but fewer adverse events and headache recurrences.[32]

ISOMETHEPTENE COMPOUNDS

The combination drug acetaminophen/isometheptene/dichloralphenazone (Midrin) includes a sympathomimetic (isometheptene) and a muscle relaxant (dichloralphenazone). One trial showed similar effectiveness to low-dose sumatriptan when used early in mild to moderate migraine.[17] Due to sympathomimetic effects, it should be used cautiously in patients with cardiac risk factors.

LIDOCAINE

Intranasal lidocaine (Xylocaine) has a rapid onset of action and may be useful as a temporizing measure until longer-acting treatment can take effect. Lidocaine 4% solution administered into the nostril, either by a clinician or self-administered by patients, resulted in rapid symptom reduction compared with control, although recurrences were common.[13,33]

Non-Preferred Therapies

Acetaminophen alone is not effective therapy for acute migraine.[30] There are no placebo-controlled trials documenting the effectiveness of barbiturate-containing analgesics (e.g., butalbital/aspirin/caffeine [Fiorinal]) for acute migraine.[30] The U.S. Headache Consortium recommends limiting opiate use in migraine treatment because of its potential for abuse and rebound headache.[14] Intranasal butorphanol is effective, but its use should be limited because of these concerns.[14] One study linked opiate or barbiturate use with an increased risk of episodic migraine becoming chronic.[34] Opiates or barbiturate-containing medications should be used only in patients with migraine headaches resistant to other therapies.

Experimental Therapies

Calcitonin gene-related peptide is a neuropeptide thought to be central to migraine pathogenesis. Intravenous infusion of a calcitonin gene-related peptide antagonist showed promising results in one small study.[35] Transcranial magnetic stimulation, a modality where a magnetic field is generated on the scalp to create currents in the adjacent cortex, seems promising. A controlled trial of 200 patients who had migraine with aura showed that this therapy is superior to sham in two-hour pain relief and sustained responses over 24 to 48 hours.[36] Further research is needed to evaluate its role in treating migraine without aura and in migraine prophylaxis.

Special Populations

PREGNANCY

Acetaminophen, despite questionable effectiveness, is reasonable in the treatment of migraine in pregnant women because of its established safety. NSAIDs are effective and generally considered safe until the third trimester. The combination analgesic acetaminophen, 250 mg/aspirin, 250 mg/caffeine, 65 mg also must be used with caution; aspirin is FDA pregnancy category C, but is downgraded to category D for third trimester use, and consuming more than 100 mg of caffeine daily is associated with mild fetal growth restriction, although the clinical significance of this is

unclear.[37] The American Congress of Obstetricians and Gynecologists recommends limiting daily caffeine consumption to 300 mg during pregnancy.[38] Avoidance of triptans is recommended during pregnancy, although limited data on first-trimester exposures are reassuring.[17,25] Metoclopramide is FDA pregnancy category B and may be used intravenously for migraine or orally for associated nausea. Opiates may be used for intractable cases, but pose risks of neonatal withdrawal and maternal dependence. The safety of isometheptene in pregnancy is unknown, so its use is not recommended. Ergotamines are abortifacients and are therefore absolutely contraindicated in pregnant women and women of childbearing age who are not using reliable contraception. Given scant data and cautions regarding medication safety, preventive approaches are key.

MENSTRUAL MIGRAINE

Many women report migraine or migraine exacerbations occurring exclusively near the time of menses. Long-acting triptans frovatriptan and naratriptan, taken perimenstrually around-the-clock for short-term prevention, have been found effective in reducing frequency and severity of menstrual migraine.[39] For abortive therapy, the highest-quality evidence supports the use of sumatriptan, rizatriptan, and the NSAID mefenamic acid (Ponstel).[39]

CHILDREN AND ADOLESCENTS

Limited evidence is available to guide pharmacologic treatment of acute migraine in children and adolescents.[40] A systematic review found acetaminophen and ibuprofen safe and effective in children.[41] Triptans are often prescribed, although this is not FDA-approved or recommended by drug manufacturers. Intranasal sumatriptan and nasal zolmitriptan, but not oral formulations, have shown effectiveness in children and adolescents, perhaps because of the quicker onset of nasal formulations and shorter duration of migraines in children.[40,41] Given limited data, prevention is important.

DATA SOURCES: A PubMed search was completed in Clinical Queries using the key terms migraine and treatment, with separate searches for specific drug classes. A similar search was performed using Google Scholar. The Cochrane database was searched for relevant reviews, and the National Guideline Clearinghouse was searched for relevant guidelines. We also searched the Evidence Summary provided by *AFP* for relevant articles. Search date: January 4, 2010, repeated September 20, 2010.

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