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Assessment and Management of Migraine Headaches

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Overview

Treatment for headache, including the migraine headache, has significantly changed in the past decade. Causes for headaches, specifically of the migraine type, are still the subject of much debate. Headaches are currently divided simply as primary and secondary. (*See Tables 1 and 2.*) Primary headaches are described as being "idiopathic," or not due to an actual disease process or external stimulus. Secondary headaches are classified as being due to an underlying disease/illness, such as sinusitis, or due to an external stressor, for example, trauma resulting in a closed head injury. The most frequently seen primary headache disorders are the migraine, tension-type, and cluster. New research suggests that patients who commonly suffer from migraine-type headaches, in particular, have inherent differences in brain circulation and neuronal activation when compared to those who do not suffer from migraines.

Although migraine headaches are frequently seen, there continues to be a significant misunderstanding in their diagnosis and treatment. A possible explanation as to why migraine headaches are often undiagnosed may be the clinician's greater concern to exclude more life-threatening etiologies of a headache. At 24 hours after discharge, 60% of patients who leave the emergency department (ED) with a headache after treatment continue to experience a headache, and 31% of patients whose headaches are cured in the ED have a recurrence.[1] Migraine affects about 12% of adults with prevalence rates three times higher in women than men, and if poorly managed can lead to lost annual productivity estimated in the range of $16.2-$28.7 billion.[2]

This discussion will focus on the common and classic migraine syndromes and their treatment. Familial hemiplegic migraine is rare and is associated with at least two genetic defects.[3] Ophthalmoplegic migraines usually involve the oculomotor nerve, although rarely the abducens nerve or even the trochlear nerve may be involved. These will not be mentioned further in this article.[4]

Epidemiology

In 2008, more than three million ED visits had a principal diagnosis of migraine, or approximately 2.4% of all visits. Of these, there were about 81,000 ensuing hospitalizations.[5]

There are significant gender differences with regard to headaches, and an even larger difference specifically when due to migraines. Women were 2.7 times more likely to present for a general headache when compared to men. When the presentation was due to migraine, they were 4.6 times more likely to visit the ED.[5]

Of particular interest, there seems to be a significant difference in ED visits for headaches with respect to race and age.[1,5] The prevalence of migraine

Executive Summary

Migraine headaches are a significant challenge for identification and effective management. In the coming age of accountable care organizations and patient-centered medical homes, primary care physicians will be expected to accurately diagnose these patients and provide them with cost-effective abortive/prophylactic therapies while reducing the risk of unnecessary and expensive visits to the emergency departments.

- Twelve percent of adults suffer from migraine each year, with prevalence in women being three times higher than in men.
- The International Headache Society has established a classification that distinguishes between primary and secondary headaches with the primary importance of recognizing red flag symptoms that point to life-threatening headache conditions.
- The three major types of migraine management are behavioral/nonpharmacologic, abortive, and preventive.
- Opiods are in general to be avoided in treatment due to the availability of superior agents and the risk of substance abuse.

headaches is higher in Caucasians than in any other racial group, including African Americans and Asians. Those younger than 18 years old and older than 44 years old were significantly less likely to present to the ED for a headache.[1,5] Thus, headaches disproportionately affect men and women of working age, potentially causing a tremendous debt to our society.[6] The prevalence and age distribution of migraine have remained stable over time. The cumulative lifetime incidence of migraine is 43% for women and 18% for men. At any given time, approximately 18% of women and 6% of men suffer from migraine.[7]

Individuals of lower socioeconomic status are more likely to present to the ED for a headache. Patients in the lowest income quartile were 2.3 times more likely to present to the ED when compared to its richest counterpart, although total ED utilization was similar for all income levels.[5] Lastly, rural residents had a higher rate of ED visits for headaches when compared to urban dwellers, possibly due to fewer options available for health care.[5]

Table 1: Secondary Causes for Headache: "Can't Miss" Diagnoses

• Meningitis	• Carbon monoxide poisoning
• Stroke: Intracranial hemorrhage	• Glaucoma temporal/giant cell arteritis
• Subarachnoid hemorrhage	• Mass: subdural hematoma, abscess, AIDS
• Extracranial dissection (carotid, vertebral)	• Venous sinus thrombosis
• Idiopathic intracranial hypertension/pseudotumor cerebri	

Etiology and Pathophysiology

There is a strong genetic component to migraine headaches. In individuals with migraine headaches, approximately 70% have a first-degree relative who suffers from migraines. This genetic relationship is even more pronounced among those who have migraine with aura, as their relatives are four times more likely to experience migraines.[8] For example, a subset of migraine headache with aura has been linked to a mutation in the calcium channel gene (CACNA1A4) and is now termed the familial hemiplegic migraine.[9] Type II familial hemiplegic migraine has been linked to a mutation in the sodium channel gene (ATP1A2).[9] However, most migraine disorders are likely polygenic and due to multiple factors.

There are several potential triggers of a migraine. Some of the more common precipitants may include stress, insomnia, tobacco smoke, certain odors, changes in hormonal pattern including menstruation and ovulation, specific foods, infectious diseases, head trauma, exercise, and certain medications. (*See Table 3.*)

Explanations of migraine pathophysiology have greatly evolved over the decades and continue to be a subject of much research. The vascular theory was one of the earliest concepts developed to explain migraines in which cerebral vasoconstriction leading to ischemia was the etiology of the migraine aura, and the resulting vasodilation was the source of the actual headache due to activation of perivascular pain receptors. The theory, however, cannot explain the utility of certain medications in the successful treatment of migraines as well as certain aspects of the migraine prodrome. Furthermore, new imaging studies such as Xenon blood studies/SPECT, positive emission tomography (PET), P magnetic resonance spectroscopy, and functional MRI have shown intracranial blood flow patterns could not support major concepts of the vascular theory. In fact, there is evidence that the headache may be triggered by hypoperfusion.[10] Leao hypothesized that cortical spreading depression (CSD) or cortical gray matter excitation was the cause of the migraine aura and the subsequent activation of trigeminal neurons was the source of the headache.[11] PET imaging has shown that this excitation results

Table 2: Primary Headaches[97]

- Migraine
- Tension-type
- Cluster
- Other trigeminal autonomic cephalalgias

Table 3: Precipitants of Migraine Attacks[98]

- Stress
- Hormone replacement/menses
- Not eating
- Weather
- Sleep disturbance
- Perfume/odor
- Neck pain
- Alcohol/red wine
- Foods: Chocolate, nuts
- Pickled foods
- Fatigue
- Head trauma
- Physical activity
- Loud noises
- Bright lights
- Caffeine
- Smoke
- Brewer's yeast
- Oral contraceptives

in reduction of blood flow and tissue metabolism and may indeed explain the migrainous aura. PET studies have also shown activation of the pons and midbrain during a migrainous attack, with the laterality of pain corresponding to the laterality of pons activation.[10] Indeed, a unique study using a substance that inhibits CSD showed that the substance helped prevent migraines with aura only, thus suggesting that the CSD theory may indeed explain migraines with aura.[9] CSD has also been hypothesized to activate the brainstem, releasing inflammatory markers that subsequently activate the trigeminal system, resulting in vasodilation and the migraine.[12]

A hypothesis that blends both neural and vascular concepts is the neurovascular theory, which holds that the migraine is mainly due to neuronal hyperexcitability with secondary changes in vascular perfusion.[13] This is currently the theory that is most supported by research. Compared to an individual who does not suffer from a migraine, the brain of a migraine sufferer is more excitable at baseline, especially in the occipital cortex, which has been verified by functional MRI studies. In many ways, this concept is similar to epilepsy. Burstein et al extended the concept of central neuronal hyperexcitability to cutaneous allodynia, in which secondary pain pathways in the trigeminothalamic system also get sensitized during a migraine episode.[14]

Researchers have attempted to discover the various vasoactive substances and neurotransmitters that are released during the above explained hyper-excitation. Perivascular nerve activation implicated in migraines causes the release of substances such as neurokinin A, calcitonin gene-related peptide (CGRP), nitric oxide, and substance P, which, upon interaction with blood vessels in the periphery, cause vasodilation and inflammation. What the role of the CGRP antagonist telcagepant will be in the acute management of migraine remains to be elucidated. This results in the activation and sensitization of the trigeminocervical complex, including the trigeminal nerve, which then relays information centrally to certain pain centers in the thalamus and cortex, resulting in a migraine.

In the past and of current interest, increased dopaminergic activity has been hypothesized to be a cause of migraine.[15] Indeed, many of the symptoms associated with migraines, such as nausea/vomiting and irritability, can be linked to dopamine and may explain why dopaminergic antagonists are helpful in treating acute migraines. However, the serotonin receptor has been postulated to be even more important in the headache pathway, as studies have shown that these receptors are found in the trigeminal sensory nerves. Activation of these receptors results in decreased release of noxious neuropeptides and may explain why triptans, which are serotonin agonists, decrease the recurrence of migraines. Thus, current research supports that migraine headaches may result from a combination of central and peripheral nerve excitability and vascular/inflammatory changes. A vulnerability to recurrent activations of the trigeminovascular and upper cervical pain systems causing headaches seems to be a common denominator in migraineurs, but so far has not been easily traced to a single pathological process.[3]

The complex interaction of several processes may explain why one manner of treatment is not effective for all migraine headaches.

Diagnosis

The diagnosis of migraine can be an extremely challenging task. Studies have shown that only 56% of migraine sufferers actually carry such a diagnosis and instead are mistakenly treated for sinus, tension, or stress headaches.[16] Part of the problem may reside in the clinician's fear of not identifying a life-threatening cause of headache. The first step in identifying a migraine lies in the clinician's familiarity with other headache disorders and, in particular, the ability to recognize red flag symptoms. The International Headache Society (IHS) has created a classification that distinguishes between primary and secondary headaches. (*See Tables 1 and 2.*) Certain features of a particular headache should alert the clinician to consider such potentially life-threatening headaches, including a thunderclap feature (sudden onset and maximum intensity on onset), chronic progressive headache, new neurologic symptoms and/or focal neurologic deficits/meningeal signs on exam, change in vision or altered mental status, abnormal vital signs such as severe hypertension or fever, new-onset seizure, recent traumatic event, and onset of a new headache after middle age.[17] The severity of a headache may not always predict

Table 4: Migraine Types[102,105,106]

Common: Without Aura
• At least five prior headaches without aura • Headache duration 4-72 hours • Either nausea or vomiting or photophobia/phonophobia
At least two of the following: • Unilateral location of pain • Pulsating/throbbing quality • Moderate or severe intensity that inhibits daily activity • Aggravated by routine daily activity, movement
Classical: With Aura
At least two previous migraines with aura
At least one of the following developing within 4 minutes of migraine and lasting less than 1 hour: • Unilateral visual symptoms • Slowly expanding and moving geometric shapes • One-sided numbness and abnormal traveling sensation • One-sided weakness • Speech difficulty • Pulsating quality

whether a headache may be of the life-threatening subtype, and this feature does not correlate with abnormalities on neuroimaging.[18] Thus, asking every patient presenting with a headache "Is this the worst headache of your life?" should possibly be reconsidered. In order to identify these red flags and potentially diagnose a migraine, attention should be paid to particular components of the physical exam. A patient's general demeanor and vital signs should be taken under consideration (i.e., toxic-appearing or febrile).

A general eye exam should always be performed to assess for visual acuity with complaints of blurry vision, papilledema, cranial nerve deficits, and pupil size and reactivity. The patient should be carefully assessed for any meningeal signs by performing a head and neck exam. An ear, nose, and throat exam can be considered, especially if a patient has complaints suggestive of a sinusitis, pharyngitis, or middle ear infection, which often coexist with a headache. Last but not least, a neurologic examination should be performed.[17]

In addition to creating a general headache classification, the International Headache Society has developed a classification system to help identify two of the more common migraine subtypes: the migraine with aura and without aura. (*See Table 4.*) It should be noted that this classification is now several years old. A more concise tool, the IDMigraine, has been developed, which has been determined to have a sensitivity of 94% in diagnosing a migraine according to one study.[19] The IDMigraine has only three components: nausea, photophobia, and headache-related functional disability, and requires only two to be positive in migraine diagnosis.[19] This system simplifies the findings of a systematic review that found certain features to be most useful in the diagnosis of a migraine, including nausea, pounding/throbbing headache, duration more than 72 hours, unilateral pain, and headache-related functional disability.[20]

About 90% of migraine sufferers have common migraines, or those that are not preceded by an aura.[21] In general, the headache is unilateral, pulsating/throbbing in nature, and is often associated with nausea, photophobia, phonophobia, and olfactophobia. Eighty-eight percent of migraine sufferers experience prodrome symptoms of fatigue, lethargy, dizziness, myalgias, change in mood, or food cravings, and these may precede the actual migraine by 1-2 days.[21] A classic migraine occurs with an aura described usually as visual disturbances such as temporary blind spots (scotoma), zigzag lines (fortification), and flashing lights, circles, or other shapes prior to a headache (scintilla), but may also be comprised of various other neurologic abnormalities such as paresthesias, hemiparesis, and cognitive or language disorders.[22] In fact, paresthesias occur in about 40% of migraine sufferers, speech and language disturbances in 17-20%, and motor symptoms in about 18%. The aura usually precedes the migraine by 30 minutes to one hour.[22] Once the prodrome and aura stages are complete, both common and classic migraines begin with a gradually worsening headache that may last several hours to a few days, is variable in intensity, and often worsens with physical activity, then gradually diminishes before terminating. Associated headache symptoms include nausea in about 70% of patients, photosensitivity (90%), and phonosensitivity (76%).[23] Often, patients describe symptoms of nausea and vomiting as being the most debilitating component of the migraine. Many patients finally experience postdrome symptoms of fatigue and depression that may last several days.[21] Of potential concern, a migraine attack may rarely be associated with temporary ataxia, blindness, dysarthria, vertigo, and central nervous system deficits that may raise concerns for a stroke, making the diagnosis of migraine even more difficult.[18]

Management Principles

A combination of nonpharmacologic techniques and medications can be effective in the treatment of migraine headaches. Despite much evidence for the usefulness of several classes of medications, there

Table 5: Some Medications for the Treatment of Migraine[59,98-100]

Drug	Usual Dosage	Considerations
NSAIDs		
Ketoprofen PR	100 mg	
Naproxen sodium	750-1750 mg	Dyspepsia
Ibuprofen	200/400/600/800 mg	Avoid if renal or ulcer disease
Tolfenamic acid	200 mg	
Diclofenac	50-100 mg	
Flurbiprofen	100-300 mg	
Piroxicam	40 mg	
Ketorolac	30 mg IV, 30-60 mg IM	
Aspirin	500-1000 mg PO	
Isometheptene Combination		
Midrin	130-780 mg	Drowsiness, nausea
Triptans 5-HT IB/ID agonists		
Sumatriptan oral	50-100 mg PO	Chest pressure/tightness
Sumatriptan nasal spray	5/10/20 mg	
Sumatriptan SQ	6 mg SC	
Almotriptan	12.5 mg	Avoid in pregnancy, ischemic heart disease
Zolmitriptan	2.5-5 mg	
Naratriptan	1-2.5 mg	Avoid in uncontrolled hypertension
Rizatriptan	5-10 mg	
Eletriptan	40-80 mg	Avoid in cerebrovascular disease
Antiemetics		
Prochlorperazine	10 mg IV	Extrapyramidal reaction
Metoclopramide	10 mg IV	Postural hypotension
Chlorpromazine	50 mg IM or 0.1 mg/kg slow IV over 20 minutes	Drowsiness
Hydroxyzine	25-50 mg	Dystonia
Domperidone	30-120 mg	

continues to be much confusion among the medical community with regard to the treatment of migraines. Indeed, even when carrying a diagnosis of migraine, at best only 50% of patients actually take a migraine-specific medication.[24]

In general, there are three major types of migraine management: behavioral/nonpharmacologic, abortive, and lastly preventive. There are currently several medications that are commonly used in the ED to treat an acute migraine attack. It should be noted that not all have been approved by FDA for use in treating migraine. (*See Tables 5 and 6.*) Ideally, a useful medication would be one that not only completely relieves the headache, with minimal side effects, but also one that prevents future attacks.

Behavioral and Nonpharmacologic Management

There are many proven techniques that do not involve medications in the treatment of migraine headaches. Knowledge of them can lead to greater clinician and patient understanding of this disease. Many of these therapies are effective in patients suffering from treatment-refractory migraines, those unable to tolerate most migraine-specific medications, or those who prefer nonpharmacologic treatments, women who are pregnant and, lastly, those who suffer from frequent rebound headaches.[25,26] Cognitive behavioral therapy, electromyographic feedback, biofeedback, and relaxation techniques have proven to be of significant benefit.[25,26] It is likely that these techniques, when used in combination with abortive management for migraines, lead to improved outcomes. Other modalities, such as acupuncture, hypnosis, transcutaneous electrical nerve stimulation, cervical manipulation, and hyperbaric oxygen, have shown mixed results and, thus, cannot be fully recommended.[27]

Abortive Management

Antiemetics. Many clinical trials have strongly supported the efficacy of antidopaminergic antiemetics. These include the phenothiazines chlorpromazine (Thorazine®) and prochlorperazine (Compazine®), as well as metoclopramide (Reglan®), promethazine (Phenergan®), and droperidol. The mechanism of action remains not fully known but is likely related to their powerful antiemetic effects in the limbic system and basal ganglia and its ability to alter pain perception. These medications also have antihistaminergic and anticholinergic properties, which further act to reduce nausea and photophonophobia, which are all common migraine symptoms.[28]

A meta-analysis has shown that antidopaminergic agents were superior to placebo for both complete headache relief and clinical success.[28] Given their efficacy in comparison to other commonly used medications for migraines, its low cost, and relatively minimal side effects, these medications should be considered first-line therapy for the treatment of acute migraines. Of the medications noted, chlorpromazine has fallen out of favor due to significant orthostatic hypotension that it may cause. Droperidol is possibly the most effective, with a two-hour headache relief rate approaching near 100% at

Table 6: Some Medications for the Treatment of Migraine[59,98-100]

Drug	Usual Dosage	Considerations
Ergots		
Dihydroergotamine/ DHE	0.5-1 mg IM, SC, or IV	Chest tightness, avoid if hypertension or renal disease
DHE nasal spray	2 mg	
Ergotamine	2 mg	Avoid if ischemic heart disease
Barbiturates		
Butalbital		Avoid if peripheral vascular disease
Pentobarbital		
Steroids		
Dexamethasone	6/12/25 mg IV or IM	
Hydrocortisone	50 mg	
Others		
Valproate	250-500 mg bid	Teratogenic
Lidocaine 4%	1-4 drops intranasally	
Methysergide	2-8 mg/day	Fibrotic complications
Acetaminophen	325-650 mg every 4 hours	
Opioids		
Butorphanol nasal spray	1 spray each nostril (1 mg)	Nausea, dysphoria
Codeine and fiorinal		
Methadone	10 mg	
Meperidine	50-100 mg	

a dose of 2.5 mg IV.[29] Droperidol, thus, has been considered as a treatment option even for intractable migraines and is usually reserved for severe migraines in the ED. Unfortunately, a slightly increased risk of prolonged QT interval has lead to an FDA warning, but the risk for this may be reduced by performing a quick pretreatment ECG.

Prochlorperazine, although not as effective as droperidol, is very effective in migraine treatment, and optimal dosing is usually given at 10 mg IV, which can be repeated.[29,30] Multiple studies have shown that prochlorperazine is more effective than metoclopramide, with a response rate up to 88%,[31] and is also superior to IV magnesium and ketorolac (Toradol®).[32]

Although possibly not as effective as prochlorperazine, metoclopramide has recently gained much favor due to its long proven safety during pregnancy and its relatively benign side effect profile when compared to prochlorperazine. It is also administered as 10-mg IV doses and can be repeated. Metoclopramide may improve the intestinal absorption of oral medications, and a study has shown that the combination of IV metoclopramide and aspirin provided relief similar to oral supmatriptan.[33] Another study has shown that a single dose of 20 mg IV metoclopramide had equal efficacy to a 6 mg SQ dose of sumatriptan.[20,34]

Although not an antiemetic, the dopaminergic antagonist haloperidol (Haldol®), which like droperidol is a butyrophenone, has been shown to provide significant pain relief in up to 80% of patients treated,[35] with a 2-5 mg IV dosing. However, like droperidol, the risk of side effects, including akathisia, sedation, and prolonged QT interval, are significantly greater with haloperidol, thus making it difficult to recommend them as first-line agents over other medications that have similar efficacy.[36]

Both prochlorperazine and metoclopramide can be given in 25 mg suppositories for those migraine sufferers with severe vomiting and not desiring IV placement. All of the phenothiazines can be used either alone or in combination with other medications, improving treatment efficacy. Lastly, giving repeat smaller doses of these medications is likely more effective than higher individual doses, as a randomized study has shown a 40-mg dose of metoclopramide is no more effective than the typical 20-mg dose.[31]

In head-to-head trials, antidopaminergic antagonists have often proven to be the superior agents. Metoclopramide achieved a higher pain reduction score when compared to hydromorphone (Dilaudid®) and also resulted in a decreased need for rescue medications and faster time to discharge with no increase in side effects.[37] In comparison to acetaminophen, metoclopramide monotherapy showed a more significant improvement of headache-related pain and at a faster rate.[38] Importantly, it has been shown that IV prochlorperazine may be superior to subcutaneous sumatriptan with regard to pain reduction at 80 minutes post-treatment or at time of ED discharge.[39]

The most common side effects of these medications are sedation, akathisia, dizziness, and, to a much lesser extent, hypotension. Of all these common side effects, akathisia is seen as the most distressing to patients. A 25-50 mg dose of IV diphenhydramine or 1 mg IV/IM dose of benztropine has been proven to be very successful in preventing this side effect,[40] and a slower infusion rate of these medications has been shown to significantly reduce the incidence of akathisia.[41] Lastly, the rare and potentially fatal side effect of prolonged QT and ventricular arrhythmias caused by these medications may necessitate the need for a pretreatment EKG, especially in patients with a known history of such.[16]

The major limitations to these medications are not these side effects, but the significant increase in efficacy when given parenterally in comparison to orally, thus leading to the need for IV placement and longer ED stays. This fact should encourage further research into finding an antidopaminergic agent or regimen that can be just as effective when given orally.

Triptans. Although triptans were proven more than 20 years ago to be effective in migraine treatment, this class of medications, which are serotonin 1B/1D receptor antagonists, continues to be underused. Part of the reason may be the lack of parenteral options, as sumatriptan remains the only injectable triptan available in the United States.[34] There is also significant fear among clinicians with regard to their possible cardiovascular risks, although adverse cardiovascular events are relatively infrequent with their use. Lastly, these medications are relatively more expensive than the above described antiemetics, although sumatriptan has recently been approved in a generic form. Nonetheless, triptans, especially subcutaneous sumatriptan, have been proven to be very effective in relieving a migraine headache.

Subcutaneous sumatriptan, which was the first marketed triptan in the United States, is almost three times more likely to relieve a migraine compared to placebo, and, by 2 hours, 70% of patients who received sumatriptan in this form were completely pain free in comparison to 22% who received placebo.[19] Another study showed a complete resolution of headache in up to 80% of patients at 2 hours after injection of sumatriptan.[42] About half of all patients who received the medication were headache free at 24 hours; however, a large portion of those treated with triptans (20-40%) suffered a recurrence within 24 hours of ED discharge.[43] The average time to headache relief is approximately 34 minutes.[43] In general, triptans are most effective when used early in a migraine attack.[44] The optimal dose of subcutaneous sumatriptan is 6 mg, and repeat doses are unlikely to be more effective.[34] The injectable option has the fastest onset of action at 10 minutes, and the nasal spray form achieves time of onset at 15 minutes, with 60% of patients achieving relief of headache at 2 hours.[45] The nasal spray may be an attractive option because no IV access is required. This is in contrast to oral sumatriptan, which can take up to 60 minutes for onset of action. Still, 70% of these patients achieve headache relief only after 4 hours,[45] making the oral form much less useful.

Since the development of sumatriptan, several others have entered the market. Importantly, rizatriptan given at a 10 mg oral dose has been shown to be more effective than sumatriptan.[46] Zolmitriptan (5 mg) can also be given in an intranasal form, and patients seem to prefer this medication compared to sumatriptan due to its preferred taste.[47] Naratriptan (2.5 mg) and frovatriptan (2.5 mg) have a slightly reduced rate of migraine recurrence when compared to sumatriptan, but are potentially less useful because of their slower onset of action. These medications may have a larger role in the outpatient setting due to their longer half-life. Lastly, a combination therapy with another medication may be more effective than triptan monotherapy. A combination pill of 85 mg sumatriptan and 500 mg of naproxen achieved better headache relief than either medication alone.[48]

In addition to the rare myocardial infarction (MI), arrhythmia, or cerbrovascular accident (CVA) that have been attributed to triptans, the most common side effects of these medications include a burning sensation at the injection site, as well as dizziness, flushing, fatigue, and chest tightness that may sometimes be confused with cardiac angina. A triptan should not be used when another one has been used in the last 24 hours, and the same applies to an ergot-containing medication due to the risk of potentiating vasoconstriction. Triptans should be avoided in pregnant patients, as they increase the risk of preterm labor. Lastly, triptans should be avoided in patients taking an MAO-inhibitor or within 2 weeks of stopping one. Despite these concerns, triptans, especially in the subcutaneous or intranasal form, should be strongly considered as a treatment option for acute migraine attacks. This is especially true for patients who have reported a response to triptans.[20,34]

Ergots. Ergotamine has been used for more than 100 years in the treatment of migraines. Its hydrogenated form, dihydroergotamine, has been available for more than 50 years and is better tolerated.[49] Both are nonspecific serotonin agonists and vasoconstrictors. Ergotamine tartrate is usually given as 2 mg sublingual doses and can be repeated every 30 minutes as needed, but can also be combined with caffeine in a pill form or suppository. Dihydroergotamine is usually given as a 1 mg IM/SC injection or slow IV infusion but can also be given intranasally.[34] Studies have shown that these medications are less effective than triptans in relieving an acute migraine.[50,51] Dihydroergotamine, when used alone, leads to more need for migraine rescue medications when compared to prochlorperazine use alone.[50] However, some studies have shown that dihydroergotamine may be more effective than triptans in preventing headache recurrence and, thus, may be a better option for patients suffering from frequent migraine attacks despite other treatment.[52] In fact, although dihydroergotamine relieves migraine attacks at 2 hours in about 50% of patients, only 15% experience a recurrence at 24 hours. A major limitation of ergot medications is the nausea that they induce and, thus, they are frequently administered with an antiemetic such as metoclopramide, which further improves migraine headaches, as discussed above. Major side effects in addition to nausea include drowsiness, flushing, vertigo, and local injection site rashes/discomfort, and these medications should be avoided in patients with uncontrolled hypertension, atherosclerotic vascular disease, and during pregnancy.

Valproate (Depakote®). Unknown to many clinicians, IV valproate has been proven to be an effective abortive agent for acute migraine headaches. Several preliminary studies have shown sodium valproate at 300-500 mg IV to significantly improve migraine-related pain within 30 minutes of administration.[53,54] Another study showed depakote at a dose between 300 to 1200 mg produced a significant improvement in headache in 64% of patients.[34] Dosages most often used for migraine headaches are between 500 mg to 1 g as a slow IV drip over 30 minutes. Several advantages to this medication include the lack of cardiovascular side effects, its nonsedating and nonaddicting properties, and its lack of interactions with other commonly used migraine medications, including triptans and ergots.[16] However, even as a single dose, valproic acid should probably be avoided in pregnant patients and those with liver disease. Although promising, further studies need to be performed to validate the efficacy and optimal dosing of valproate for acute migraine management and should not be considered a first-line agent.

Steroids. Despite early trials that showed mixed results for the use of dexamethasone in migraine treatment, some recent studies have been more positive. A recent meta-analysis showed a modest but statistically significant improvement in headache relief and decreased recurrence on 24- and 72-hour follow-ups when a single IV dexamethasone dose was added to standard migraine therapy.[55] A single dose of dexamethasone administered has been shown to decrease the rate of recurrence, but may take several hours to be effective.[56] The dosing in these trials ranged from 10 mg to 24 mg IV administered over 10 minutes. The most common side effect was dizziness; nausea was less likely when compared to other migraine treatments.[56] In summary, dexamethasone may be considered in patients with intractable migraines or in status migrainosus as an adjunct and when other proven treatments fail. Further studies need to be undertaken before the widespread use of steroids can be recommended for migraine management.

Magnesium Sulfate. As with steroids, the efficacy of magnesium sulfate in the literature is somewhat mixed. It has been shown that 1 g IV infusion of magnesium sulfate improved migraines with aura but not without aura when compared to placebo.[57] Interestingly, magnesium sulfate was most effective in improving phonophobia and photophobia in these patients, and may be the mechanism by which this medication is useful for migraine sufferers. This potential beneficial effect may be more significant in patients with lower serum magnesium levels; however, the impracticality of measuring magnesium levels of every headache patient further limits this medication's usage. Although some studies have shown positive effects, others have shown minimal improvement in migraine attacks after magnesium sulfate administration. In fact, a small study showed a less favorable response when magnesium sulfate was combined with metoclopramide.[58] Despite these equivocal findings, the benign side effect profile of magnesium sulfate and its proven safety during pregnancy makes this medication an option for intractable migraines.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Other Non-narcotic Pain Medications. Of some surprise, simple NSAIDs may be quite effective in the treatment of acute migraine attacks. Some studies have shown that they may be as effective as triptans in some patients.[59] As discussed earlier, combination therapy with naproxen and sumatriptan resulted in better outcomes than when either medication was used alone.[48] However, in comparison to many of the antiemetics, NSAIDs are less effective in the acute management of a migraine.[32,60] The NSAID ketorolac (Toradol®), in particular, which can be administered either IV or IM, has proven very effective in migraine relief.[34] Orally administered NSAIDs such as ibuprofen and naproxen remain first-line agents for the management of mild migraine attacks. Indomethacin suppositories have proven useful in migraine sufferers who experience significant nausea and vomiting.[22] For more moderate-to-severe migraine attacks, a 30-60 mg dose of IV/IM ketorolac has been proven to be an effective medication either alone or in combination with another migraine agent, such as a phenothiazine or triptan. Thus, ketorolac should be strongly considered, especially in combination with an antiemetic, for a significant acute migraine attack. Relative contraindications include a history of peptic ulcer disease or chronic kidney disease.

Although acetaminophen used alone has been shown to be fairly ineffective in the management of acute migraine attacks, when used in combination with aspirin or caffeine it is also considered a first-line agent for mild migraine attacks.[61] Acetaminophen has the added benefit over NSAIDs of being safe for use during all stages of pregnancy, and both classes of medications are very affordable and easily obtainable. Acetaminophen should be avoided in patients with significant liver disease, and patients should be counseled on recommended dosing and dangers of an overdose. Thus, both NSAIDs and acetaminophen should be a part of almost every migraine sufferer's arsenal.

Opioids. Although opioids are frequently used in the ED (up to 60% of visits) for the management of migraine headaches, their use has been proven to be less efficacious than several migraine-specific medications.[62] In addition, their frequent use often leads to rebound headaches. Medical data show that meperidine (Demerol®) is the most commonly used opioid for headaches presenting to the ED.[63] A meta-analysis revealed that meperidine was less effective than dihydroergotamine and antiemetics in its ability to alleviate a migraine headache and was only similar to ketorolac in efficacy.[63] Another retrospective study showed

that the use of metoclopramide instead of hydromorphone resulted in less need for rescue medications and faster times to discharge.[64] In addition, there is a strong suggestion that primarily using opioids increases the rate of return to the ED[65] and also leads to decreased effectiveness of triptans.[64] Another study showed that opioids used for migraines may result in longer ED stays.[66] Opioids often have a more adverse side-effect profile in comparison to many migraine-specific medications. For example, meperidine tends to cause more sedation and dizziness than dihydroergotamine and similar sedation and GI adverse effects when compared to ketorolac, as well as increased risk for dependence.[16]

Nonetheless, in patients with infrequent migraine attacks and proven response to opioids, this class of medications can sometimes be considered. Unfortunately, there remain scant data that compare one opioid agent to another with respect to efficacy in acute migraine management. Parenteral morphine and hydromorphone have not been compared to each other in any clinical trial. IM butorphanol has been shown to be more effective than meperidine and as well tolerated as dihydroergotamine and metoclopramide.[67] Thus, although opioids should not be withheld on principle, ED providers must be aware that in contrast to most other acute pain situations, there are several better agents available for acute migraine episodes. The Canadian Medical Society has recommended narcotic analgesics for migraine headaches as a "last resort."[68]

Other Medications. There are a few other medications that are under consideration for acute migraine attacks. Both intranasal lidocaine and, more recently, IV lidocaine infusions for refractory migraines lead to significant improvement in migraine intensity and duration.[69] The major limitation is the need for cardiac monitoring, but lidocaine infusions are otherwise very well-tolerated and may have a larger role soon in the management of status migrainosus. Another trial has shown that IM injection of small amounts of 0.5% bupivacaine bilateral to C6-C7 spinous processes significantly improves severe migraine attacks, with an overall therapeutic response of 85% in this difficult headache group.[70]

Butalbital, a barbiturate, is another treatment option available. It is often combined with caffeine as well as more typical pain medications such as acetaminophen, aspirin, and even an opioid such as codeine. Although this medication has a proven benefit for the treatment of tension-type headaches, no controlled trial has yet been performed testing its efficacy in treating migraine headaches. In addition, there are several significant side effects associated with this medication, including significant sedation, arrhythmias, and addiction. Butalbital should only be considered for patients who suffer from intractable and frequent migraine attacks that are not alleviated by the more common migraine-specific medications. Lastly, new promising studies have shown some efficacy of oral calcitonin gene-related peptide (CGRP) receptor antagonists for the acute treatment of migraines. These medications are well-tolerated and, in some studies, have shown similar efficacy when compared to triptans.[71]

Special Populations

Status Migrainosus. This subgroup of migraine patients is defined as those suffering from an acute migraine that lasts for more than 72 hours, with headache-free intervals lasting less than 4 hours.[16] This may result from analgesic overuse, but no definite cause has yet been identified. There are no randomized trials that have studied the most effective medication regimen, but a combination therapy is likely indicated. An acceptable regimen would be starting off with prochlorperazine after premedication with diphenhydramine, and, if the headache does not abate, hospital admission and treatment with either a triptan or DHE in addition to dexamethasone.[69,72] Lastly, ketorolac and valproate can be added if the migraine attack persists.

Frequent Migraine Visitors to the ED. In some EDs, frequent migraine visitors account for 50% of all headache visits.[73] This may represent "drug seeking" behavior, lack of social support, and treatment failure, but the exact reason for frequent visits is unclear. Often, these patients request particular medications, especially opioids.[34] To date, there have been no studies carried out delineating the best means to treat this group of patients. A uniform departmental approach to these chronic pain patients, thereby limiting physician to physician variability, is likely most effective. Possible strategies when encountering these patients include offering migraine-specific medications in conjunction with a single low-dose opioid, referring them to pain management clinics, stressing the importance of follow-up with a headache specialist/neurologist, and, finally, starting preventive medications.

Migraine During Pregnancy. Most headache disorders improve during pregnancy for unknown reasons. Several medications commonly used to treat migraines have been shown to be harmful to embryos in animal models. Sumatriptan proved to be lethal for rabbit embryos when given in large doses and also produced skeletal and vascular abnormalities.[74] A review of human births has shown sumatriptan use during pregnancy may lead to an increased rate of preterm delivery and low birth weight and, possibly, a small number of recorded birth defects.[75] Thus, the FDA currently gives triptans a class C recommendation. In contrast, the ergots and valproate are considered class X medications and should be completely avoided during pregnancy.

Currently, acetaminophen with caffeine is considered a first-line medication in the treatment of a migraine attack during pregnancy.[76,77] This should be given in conjunction with more conservative measures, including placing the patient in a quiet dark room, reassurance, and possibly IV hydration.

For more severe migraines, metoclopramide can be considered. It has been used in all stages of pregnancy without proven harm, is very effective in the management of nausea, and is currently a class B medication.[74] Although NSAIDs should be avoided during the first trimester due to increased risk of spontaneous abortion and during the third trimester due to the possibility of inducing premature ductus arteriosus closure, these medications are considered safe in the second trimester.[77,78] Lastly, opioids, if absolutely unavoidable, can used for migraines, but should only be considered for very short-term use, such as in cases of status migrainosus.[74] They should be avoided during the third trimester, as their use can cause neonatal addiction and respiratory depression.

Migraine in the Pediatric Population. Despite migraine headaches having a prevalence between 3-10% in the pediatric population, there continues to be a lack of clinical trials targeting this specific group and few treatment guidelines. The Canadian Headache Society published a first set of guidelines in 1997, followed by the American Academy of Neurology in 2004. None of these provide any recommendations for children with a migraine attack presenting to the ED.[79] Thus, there continues to be significant variation in the techniques and medications used by ED clinicians when treating migraines in children.

Based on a systematic review of the limited studies performed in children as of now, ibuprofen seems to be the most effective initial treatment for headache relief.[80,81] These studies have shown that nausea and pain are relieved in 60% and 69% of patients, respectively, but photophobia and phonophobia had minimal improvement. The benefits of acetaminophen are possibly similar to those of ibuprofen, but neither prevented recurrence.[80,82] One study showed that ibuprofen prevented the need for rescue medications, while there was no study that supported this with regard to acetaminophen.[81] This may suggest that ibuprofen may be slightly superior to acetaminophen in the management of mild migraine headaches.

Of all the pediatric treatment options available for the management of acute migraine attacks that have failed outpatient management and, hence, present to the ED, intravenous prochlorperazine was the only medication found to be significantly effective for pain relief.[72] After failure of ketorolac, approximately 85% of these patients achieved headache relief after IV administration of 0.15 mg/kg of prochlorperazine. In contrast, only 55% of these patients obtained relief with a 0.5 mg/kg dose of ketorolac.[83] Unfortunately, prochlorperazine did not reduce the rate of headache recurrence.

In contrast to adults, triptans are not nearly as effective for children. Of all the triptans available, nasal sumatriptan seems to be the most beneficial, with oral sumatriptan, rizatriptan, and zolmitriptan being not very effective for pain relief.[82,84] Once again, none of these medications limited migraine recurrences, but intranasal sumatriptan may decrease the need for rescue medications. With regard to dihydroergotamine, a single study failed to show a benefit in terms of headache relief; however, it only evaluated 12 children.[52]

In summary, an acceptable regimen for pediatric migraine management may be an initial trial of ibuprofen or acetaminophen, followed by intranasal sumatriptan in an outpatient setting, and, if this fails, the use of prochlorperazine on ED arrival.[85]

Table 7: Migraine Disability Assessment Scale: Measurements[87]

- Number of days of work missed over the past 3 months due to headaches?
- Number of additional days during the past 3 months in which one's productivity was reduced by half or more because of headaches?
- Number of days in the past 3 months in which the patient could not perform household work because of headaches?
- Number of days within the past 3 months in which household work/productivity was reduced by more than half because of headaches?
- Number of days within the past 3 months in which family, social, or leisure activities were missed due to your headaches?
- On how many days in the past 3 months did you have a headache?
- On a scale of 0-10, on average how painful were these headaches?

Medication Overuse Headache

One of the biggest issues encountered by patients who suffer from especially severe and frequent migraines is the headache that is caused by medication overuse. Overuse is defined as needing either analgesics, such as opioids, acetaminophen, ergots (except DHE), or triptans for 2 or more days a week for longer than 3 months. This leads to decreased responsiveness to medications that were previously effective.[34] The headache is usually described as a dull discomfort that is persistent for at least 15 days a month and often is confused with an actual migraine, or even a life-threatening headache that necessitates further invasive workup. These patients are often encountered in the ED. Appropriate treatment is difficult and, despite initial successes, this form of headache has a high recurrence rate. A possible treatment regimen may be a combination of dihydroergotamine with IV metoclopramide every 6 hours for up to 72 hours.[86] Thus, these patients often have to be admitted for stabilization, and, once achieved, preventive measures include restriction of medications commonly used and, when needed, incorporating prophylactic measures.[23]

Table 8: Initiation of Preventive Therapy for Migraine

- Patients with > 6 days of headache/month
- Abortive medication needed two or more times/week
- Hemiplegic migraine
- Migraine with prolonged aura
- Symptomatic medications are ineffective or contraindicated

Migraine Prevention and Long-term Management

The first step in prevention and long-term management for migraine sufferers is the physician's ability to diagnose a migraine headache and, once diagnosed, provide patient education. Measurement tools such as the Migraine Disability Assessment Scale[87] (*see Table 7*) and the Migraine Therapy Assessment Questionnaire (MTAQ) have proven to increase both physician and patient awareness of migraine symptoms and triggers, as well as improved patient satisfaction and knowledge, which has even led to a decrease in headache frequency.[88] In general, patients should be educated that migraines are often a chronic but relapsing disease so that they know what to expect.

Some migraine sufferers have recognizable triggers. (*See Table 3.*) Importantly, however, many acute attacks are not due to an identifiable trigger. Patients should be educated that at the onset of a migraine, he or she should limit exposure to external stimuli as much as possible, which may include remaining in a dark room away from loud noises and refraining from consuming caffeinated or alcoholic beverages.[89] These patients should get adequate sleep, nutrition, and hydration.

Although often not considered to be within the normal scope of emergency care, prophylactic treatment for those who suffer frequently from migraines should at least be considered. Prophylaxis could be started in certain migraine sufferers, possibly in consultation with a neurologist or provider specializing in migraine treatment. This group of people may include those who suffer from two or more attacks per week, those in whom the usual migraine abortives are contraindicated/poorly tolerated or ineffective, individuals who suffer from recurrent and debilitating migraines that prevent them from completing activities of daily living, and, finally, those who experience high-risk hemiplegic migraines.[29] (*See Table 9.*) Current effective migraine prophylactic medications reduce about 50% of acute attacks, but only in half of all sufferers.[10]

There are several effective prophylactic medications that are available. (*See Table 6.*) Beta-blockers, most frequently propranolol, are considered first-line agents for migraine prophylaxis, with several randomized studies showing reduced migraine frequency and severity with their use.[90] Anti-epileptics, such as valproic acid and topiramate, are usually used next in prophylaxis if beta-blockers fail, or if the patient has

Table 9: Medications for the Prevention of Migraine[59,99,101]

Drug	Usual Dosage	Considerations
Beta-Blockers		
Metoprolol, generic	50-100 mg bid (100-200 mg daily)	
Extended-release-generic	100-200 mg daily	Reduced energy, tiredness, asthma/COPD exacerbations
Propranolol, generic	80-240 mg divided bid, tid or qid 40-120 mg twice daily	Low pulse, lowered blood pressure
Extended-release, generic	160-240 mg daily	
Timolol, generic	10-15 mg bid or 20 mg daily	
Anti-epileptic Drugs		
Valproate	250-500 mg bid	Drowsiness, weight gain, tremors, fetal abnormalities, liver abnormalities
Valproate extended release	500-1000 mg daily	
Topiramate	50 mg bid (25-200 mg daily)	Paresthesias, confusion, renal calculi
Gabapentin	900-2400 mg daily	Lethargy
Tricyclic Antidepressants		
Amitriptyline	30-150 mg daily	Drowsiness, dry mouth
Venlafaxine	150 mg daily	Nausea, vomiting
Calcium Channel Blockers		
Verapamil, generic	80 mg tid or qid	Constipation, atrioventricular conduction disturbances
Extended-release, generic	240 mg daily	
Angiotensin-Converting Enzyme (ACE) Inhibitor		
Lisinopril, generic	5-40 mg daily	
Angiotensin Receptor Blocker (ARB)		
Candesartan	8-32 mg daily	
Miscellaneous		
Methysergide	2-8 mg daily	Retroperitoneal fibrosis, hair loss, drowsiness
Flunarizine	5-15 mg daily	Tiredness, sedation, Parkinsonian symptoms, depression
Magnesium	300-600 mg daily PO	Soft stools, diarrhea
Dexamethasone	4/6/8/10 mg IV, 20 mg PO	

Table 10: General Recommendations for Migraine Management[24,102-104]

- Encourage patients to participate in their own management and educate migraine sufferers about their condition.
- In severe migraine, use migraine-specific agents such as triptans and ergots. Opiates do not suppress the pathophysiologic mechanism of the attack, and may leave the patient with impaired cognition.
- Administer parenteral or nonoral route of medications in patients who present with nausea and vomiting.
- Consider the use of prophylactic medications in patients with frequent headaches, those that are long-lasting, and in patients for whom migraines cause a significant amount of disability.
- Medication overuse with analgesic rebound headache can occur with nearly any analgesic, including aspirin, acetaminophen, triptans, and ergots. Consider preventive therapies.

an intolerance or contraindication to them. Valproic acid (Depakote®) has been shown to be as efficacious as propranolol,[91] and topiramate reduced the frequency of migraine attacks by about 40-50%.[92] Further studies are required to assess the true effectiveness of gabapentin and lamotrigine.[93,94] The antidepressant amitriptyline, which is a tricyclic antidepressant (TCA), has been extensively studied and shown to decrease migraine recurrences; however, the data to support the use of other TCAs are more limited. Amitriptyline is less preferred because of its potential serious side effects, especially in the setting of an overdose. Lastly, calcium channel blockers, such as flunarizine and verapamil, may have similar success rates as propranolol.[95] In summary, if a prophylactic medication is started, propranolol should be strongly considered, and the patient should be referred to a neurologist or clinician who specializes in migraine treatment.

Prognosis

Although migraine is a chronic condition, prolonged remissions can be achieved for a good portion of patients. (*See Table 10.*) Of note, the frequency and intensity of acute migraine attacks diminish as one ages.[96] Estrogen decline in women after menopause may be the cause of this decrease. Also of much debate, migraine headaches may increase the sufferers' risk for cerebrovascular and cardiovascular disease. A 2009 study showed that women who suffered from migraines with aura had a 91% increased risk of an MI and a 108% increased risk of a CVA, whereas those who suffer from migraines without aura had only a 25% increased risk of both.[86] Thus, those who suffer from migraines with aura seem to have an increased risk of MIs and strokes. Migraines, especially when frequent, have a negative impact on quality of life, family relations, and work productivity. A National Headache Foundation survey found 90% of migraine sufferers could not function fully on the day of headache, 30% required significant bed rest, and 25% missed at least one day of work.

Summary

Migraine headaches are quite prevalent and debilitating. Because headaches are a frequent complaint, it is very important that clinicians are able to quickly diagnose and effectively treat this condition. Opioids should almost always be avoided. After placing the patient in a quiet dark room, treatment should be initiated with an antiemetic such as prochlorperazine or metoclopramide, perhaps after pretreatment with diphenhydramine with or without IV hydration and an NSAID. A triptan or ergot should be considered in more persistent headaches and in patients for whom these medications have worked. Other medications, such as valproate, magnesium sulfate, and dexamethasone, can be considered for more intractable migraines that fail to respond to the above measures, with patient admission if even these treatment options fail.

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Primary Care Reports CME Objectives

Upon completion of this activity, participants should be able to:

1. Summarize recent, significant studies related to the practice of primary care medicine;
2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

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Physician CME Questions

1. The following group is *least* likely to experience a migraine headache:
   a. Caucasian female
   b. elderly African-American male
   c. Asian-American female
   d. college student
2. All of the following are vasoactive substances thought to be involved in a migraine headache *except*:
   a. CGRP (calcitonin gene-related peptide)
   b. histamine
   c. neurokinin A
   d. substance P
3. Which medication is absolutely contraindicated during pregnancy?
   a. metoclopramide
   b. ibuprofen
   c. acetaminophen with caffeine
   d. valproate
4. Which antiemetic has been found to be most effective in the treatment of migraine headaches?
   a. prochlorperazine
   b. promethazine
   c. metoclopramide
   d. ondansetron
5. All of the following are commonly associated symptoms with migraines *except*:
   a. nausea
   b. fatigue
   c. palpitations
   d. blurry vision
6. All of the following are true regarding migraine headaches *except*:
   a. Studies have shown that DHE is more effective than sumatriptan in resolving an acute migraine attacks.
   b. SC sumatriptan is equally effective as oral sumatriptan.
   c. Some studies have shown benefit to valproate in improving migraine headaches.
   d. Both A and B are false.
7. Some common side effects of triptan include all of the following *except*:
   a. chest tightness
   b. burning sensation at injection site
   c. abdominal discomfort
   d. dizziness

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