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Migraine: Burden of disease, treatment, and prevention

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Abstract Migraines are perhaps the most studied of the headache syndromes secondary to the high incidence and have significant effect on the quality of life of those suffering from this condition. Despite the high prevalence of migraines, an estimated two-thirds of sufferers either have never consulted a doctor or have stopped doing so. Therefore, it is an underdiagnosed and undertreated condition. The prevalence of migraine attacks is estimated to be 17% in women and 6% in men each year. Evidence-based guidelines for both the immediate treatment as well as preventive therapy have been established. These guidelines outline several management strategies for migraine headaches, including immediately aborting the migraine at the onset of headache, controlling the pain once it has fully evolved, and prophylactic therapy. Abortive treatment should be initiated as soon as an aura or other warning sign is noted. Patient education plays an integral role in any management plan. Headache journals may help patients identify and avoid migraine triggers and document the response to therapeutic intervention. Physicians must be aware of warning signs that may reflect more severe underlying pathology and when neuroimaging, neurology consultation, and hospitalization are warranted.
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Migraine prevalence and disease burden

The World Health Organization has estimated that over 300 million people worldwide suffer from migraines. The American Migraine Prevalence and Prevention study estimates that the prevalence of migraine attacks is 17% in women and 6% in men each year.[1] In the United States, the ratio of females to males suffering from migraines is 2:1.[2] In childhood, migraines affect boys and girls equally. This trend continues until puberty, when the predominance shifts to women. Peak incidence of migraines occurs between the ages of 30 and 39. Approximately 30% of the people in this age range are affected by migraines, of which 24% are women and 7% men. Prevalence of migraines is lowest in those older than 60 years of age (Figure 1). In both men and women, prevalence is significantly higher in whites than in blacks.[3]

The World Health Organization lists severe migraines along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders.[4] Migraines constitute approximately 16% of the primary headaches. Approximately 90% of the patients who experience migraines have moderate to severe pain, 75% have decreased ability to function during their headache attacks and 33% require bed rest during an attack.[1]

The American Migraine Prevalence and Prevention study of more than 160,000 patients found that a large majority of patients who suffer from migraine headaches had 1-4 headaches per month (62.7%). About 54% of the patients reported severe impairment or need for bed rest during attacks and only about 7% of the patients reported no significant impairment during episodes.[1]

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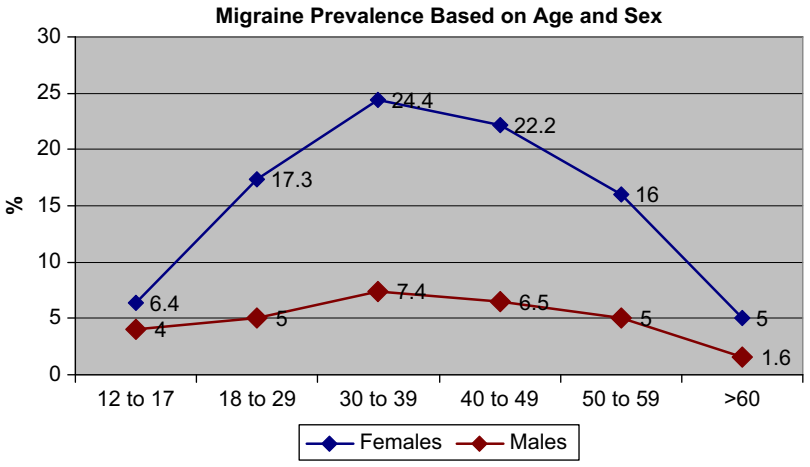

Figure 1 Prevalence of migraine headaches in the United States based on age and sex. Peak incidence of migraines occurs between the ages of 30 and 39. Prevalence is lowest in those older than 60 years of age. Adapted with permission from: Lipton et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68;343.[1]

Of migraine sufferers, approximately 10.8% of the patients report 1 attack per week, whereas 14.4% report 1 or more per week.[2] Onset of pain is usually gradual, followed by a crescendo pattern with slow but ultimately a complete resolution. Mean duration of headache is 24 hours. The majority of patients report unilateral migraines that are associated with pulsatile pain, light sensitivity, sound sensitivity, and nausea. Approximately 60%-70% of the migraine sufferers report a prodrome, whereas 20% experience an aura prior to headache attack[2] (Table 1). Prodromes, as opposed to auras, consist of the occurrence of euphoria, depression, fatigue, hypomania, food cravings, dizziness, cognitive slowing, or asthenia that occurs up to 24 hours before headache.

Migraine triggers

Migraines often have a triggering event. A headache diary helps to identify factors that may precipitate migraines. Common migraine triggers include but are not limited to the following[6,7]:

- Diet, caffeine excess, or withdrawal and foods that contain phenylethylamines, tyramines, and xanthines including aged cheeses, red wine, beer champagne, and chocolate. Nitrates and nitrites, monosodium glutamate, aspartate, dairy products, and fatty foods;
- sudden drop in estrogen levels associated with menses, pregnancy, and oral contraception;
- stress;
- infections, especially in the head and neck;
- trauma or surgery;
- medications;
- exercise;
- changes in weather or climate;
- strong odors including cigarette smoke and pollutants; and
- irregular sleep habits, bright sunlight, or flickering lights.

Table 1 Common migraine symptoms

Migraine symptoms	Total (%)
Pulsatile pain	85
Unilateral pain	60
Same side always affected	20
Light sensitivity	80
Sound sensitivity	76
Nausea	73
Prodrome	60-70
Aura	20

Adapted with permission from: Lipton RB et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41:646-657.[2]

Migraine therapy

The American Academy of Family Physicians, the American College of Physicians-American Society of Internal Medicine, and the American College of Neurology have established guidelines for the management of migraine headaches.[8,9] Though these guidelines differ in some respect, nonsteroidal anti-inflammatory drugs (NSAIDs) are uniformly recommended as first-line therapy. In those patients who fail to respond to NSAIDs or combination analgesics including aspirin plus acetaminophen and caffeine, a migraine-specific medication (triptans, dihydroergotamine [DHE]) should be recommended.

There are several strategies in approaching the treatment of migraine headaches: immediately aborting the migraine at onset of headache, controlling the pain once it has fully evolved, and prophylactic therapy.

Therapeutic considerations in tailoring medication regimen include side effects, comorbidities, pregnancy, and route of administration.

Migraine nonspecific therapy

Abortive treatment should be initiated as soon as an aura, prodrome, or pain is noted.

NSAIDs are indicated as the first-line treatment of choice for migraine attacks because of safety, wide availability, tolerability, and low side-effect profile. Strong evidence exists for the treatment of acute migraine with the NSAIDs and the combination of acetaminophen plus aspirin and caffeine.[9]

In patients who present with migraine accompanied by nausea and vomiting, a nonoral route of administration is preferred and antiemetics should be considered. Such therapies include intravenous (IV) metoclopramide, IV or intramuscular prochlorperazine. IV diphenhydramine is sometimes given in conjunction with these drugs to prevent akathisia and acute dystonic reactions. Oral antiemetics should not be considered as monotherapy.[8,9]

In severe migraine, rescue medications including opioids and butalbitol may be effective. Short-term therapy with any of these regimens should be limited to a maximum of 2 times per week, as overuse of these medications has been associated with drug-induced headache. In these patients preventive therapy should be considered.[10] Although commonly prescribed, there are few studies documenting the effectiveness of opioids for the treatment of migraines. Because of the high potential for abuse and dependence, utilization of these medications should be minimized.

For patients with severe recurrent or refractory headaches, dexamethasone in addition to standard short-term migraine therapy has been shown to reduce the rate of early headache recurrence.[11] Frequent use of adjunctive dexamethasone increases the risk of glucocorticoid toxicity and should be avoided.

Various studies found that agents given in large single doses work better than repetitive smaller doses. Many oral agents may be ineffective because of poor absorption secondary to migraine-induced gastric stasis.[12]

Migraine-specific therapy

The introduction of serotonin 1B1D agonists (triptans) has revolutionized therapy. They are considered to be specific therapies for migraines because of their mechanism of action. They inhibit the release of vasoactive peptides, promote vasoconstriction, and block pain pathways in the brainstem. They also act in the descending brainstem pain modulation pathways and therefore inhibit dural nociception.[13] There is good evidence demonstrating the efficacy in management of acute migraine headache with the following triptans.[14]

Triptans have provided migraine sufferers a quick and effective treatment modality that can be used several times per month with a minimal side-effect profile. It is recommended that triptans should be avoided in patients with uncontrolled hypertension, pregnancy, or ischemic heart disease. Because of the risk of serotonin syndrome, triptans are contraindicated with concomitant monoamine oxidase inhibitors (MAOI) and within 24 hours of the use of ergotamine preparation. Caution should also be used with selective serotonin reuptake inhibitors (SSRIs) and triptans because of the increased risk of serotonin syndrome.

DHE 45 is a potent cranial and peripheral vasoconstrictor. It is available in IV, intramuscular, subcutaneous, and intranasal forms. The IV form is usually administered in combination with an antiemetic drug (ie, metoclopramide). Intranasal DHE 45 has also been safe and effective as monotherapy in the short-term treatment of migraines. DHE 45 is contraindicated in patients with ischemic heart disease, hypertension, in combination with MAOI, and in the elderly.[15]

Migraine preventive therapy

All patients suffering from migraines should be evaluated for use of preventive therapy. Despite the large number of patients that would benefit from preventative therapy, only a small percentage of patients receive it. It is believed that 40% of the people who get migraines would benefit from preventative medication, yet only 12.4% of the adults with migraines take preventative medication.[16] Prevention begins with limiting triggers associated with the onset of migraines as well as educating patients about their condition, available treatment options, and encouraging them to actively participate in their care. The goal of preventative therapy is to reduce the severity and frequency of headaches by 50%.

Guidelines for the use of preventative therapy (Table 2) for migraines are based on an expert panel of 12 physicians reviewing the United States headache consortium guidelines. Recommendations are based on the number of headache days per month and impairment during a headache attack. Level of impairment is categorized as severe impairment if patients are unable to function or require bed rest, some impairment if patients are able to function, but with reduced performance, or no impairment if patients are able to function normally.[1]

Clinical guidelines differ as to when it is appropriate to start migraine preventive therapy. Other generally accepted indications include 2 or more attacks per month that produce disability lasting 3 or more days per month; contraindications to, or failure of abortive treatments; the use of abortive medication more than twice per week; the presence of uncommon migraine conditions, including hemiplegic migraine, migraine with prolonged aura, or migrainous infarction.[10] Severely impaired quality of life, business duties or school attendance, as well as frequent, long or uncomfortable auras may also be indications that initiation of preventive therapy is appropriate[17] (Tables 3–5).

Medications with established efficacy in migraine prevention[14]

Level A evidence: Medications with established efficacy (> 2 class I trials)

Class	Notes
Antiepileptic drugs	Common adverse effects: weight gain, hair loss, tremor, and teratogenic potential
Divalproex sodium	
Sodium valproate*	Particularly useful in patients with prolonged or atypical migraine aura, benefits seen within first 4 weeks
Topiramate*	Common side effects: paresthesia, tiredness, GI disturbance
β- Blockers	Common adverse effects: dizziness, fatigue, and depression[13]
Metroprolol	
Propanolol	
Timolol	
Triptans	
Frovatriptan	For menstrually related migraine

GI, gastrointestinal.
*Considered first-line therapy.

Table 2 Migraine diagnostic criteria

Diagnostic criteria for migraine without aura
1. At least 5 attacks fulfilling the criteria below.
2. Headache attacks lasting 4-72 hours.
3. Headache has at least 2 of the following characteristics:
   A. Unilateral location
   B. Pulsating quality
   C. Moderate or severe pain intensity
   D. Aggravation by or causing avoiding of routine activity (ie, walking)
4. During headache at least 1 of the following:
   A. Nausea or vomiting or both
   B. Photophobia or phonophobia
5. Not attributed to another disorder.

Diagnostic criteria for migraine with typical aura
1. At least 2 attacks fulfilling the criteria below.
2. Aura consisting of at least 1 of the following but no motor weakness:
   A. Fully reversible visual symptoms including positive features (ie, flickering lights, spots or lines) or negative features (ie, loss of vision) or both
   B. Fully reversible sensory symptoms including positive features (ie, pins and needles) or negative features (ie, numbness) or both
   C. Fully reversible dysphasic disturbance
   At least 2 of the following:
3. A. Homonymous visual symptoms or unilateral sensory symptoms or both
   B. At least 1 aura symptom develops gradually over greater than 5 minutes or different aura symptoms occur in succession over greater than 5 minutes or both
   C. Each symptom lasts greater than 5 minutes and less than 60 minutes
4. Headache fulfilling criteria for migraine without aura begins during the aura or follows the aura within 60 minutes.
5. Not attributed to another disorder.

International Headache Society ICHD-II Diagnostic criteria for migraine headaches.[5]

Table 3 Triptan medications

Name	Route	Notes
Amlotriptan	Tabs	Recommended for children over 12 years of age
Eletriptan	Tabs	>18 years of age, metabolized by cytochrome P450
Fovatriptan	Tabs	>18 years of age
Naratriptan	Tabs	>18 years of age, Caution: renal or hepatic impairment
Rizatriptan	Tabs/ODT	>18 years of age, Caution: concomitant propanolol use
Sumatriptan	SQ	Fastest onset of action
	Nasal	Side effect: unpleasant taste
	Tabs	>18 years of age, Caution: hepatic impairment
Zolmitriptan	Tabs/ODT/ Nasal	>18 years of age, Caution: hepatic impairment

SQ, subcutaneous.

There are currently only 5 Food and Drug Administration–approved medications for the prevention of migraine headaches. These include propranolol, timolol, valproate, topiramate, and methysergide (no longer available in the United States).[14]

β- Blockers have consistently been shown to be effective in the prevention of migraines. Use should be limited in patients with erectile dysfunction, peripheral vascular disease, bradycardia, and hypotension. Caution is advised in patients with asthma and diabetes mellitus. There is little evidence supporting the use of calcium channel blockers, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers in migraine prevention.

Tricyclic antidepressants, particularly amitriptyline, have been shown to be probably effective in migraine prevention in various studies. There is limited evidence of moderate efficacy of fluoxetine, a SSRI; however, there is no evidence of efficacy for other SSRIs in migraine preventive therapy.[10] If an SSRI is being considered for migraine preventive therapy, physicians must be aware of the potential for

Table 4 Acute therapy

Nonspecific pain management	Migraine-specific treatment
NSAIDs	Triptans
Acetaminophen	DHE 45
Opioids	
Barbiturate	
Antiemetics	
Metoclopramide	
Chlorpromazine	
Prochlorperazine	
Corticosteroids	

Table 5 Guidelines for the use of preventative therapy in migraine headaches

Prevention should be offered
- Migraine patients reporting 6 or more days of headache per month
- Four or more days of headache with at least some impairment
- Three or more days of headache with severe impairment or requiring bed rest

Prevention should be considered
- Migraine patients with 4-5 number of migraine days per month with normal functioning
- Three days of migraine per month with some impairment
- Two days of migraine with severe impairment

Prevention is not indicated
- Migraine patients with less than 4 days of headache per month and no impairment
- Subjects with no more than 1 day of headache per month regardless of impairment

Adapted with permission from: Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68;343.[1]

serotonin syndrome, a potentially life-threatening drug interaction. SSRIs are contraindicated with MAOI. Other drug interactions associated with an increased risk of serotonin syndrome are triptans, tricyclic antidepressants, opioids, and antiemetics to name a few.[18]

Time-release DHE has consistently shown efficacy in migraine prevention; however, there is limited data with respect to adverse effects.

Alternative therapy

Several supplements and herbs have been evaluated for the prevention of migraines. Butterbur (*Petasites hybridus* root), coenzyme Q10, magnesium oxide, and riboflavin have all shown some benefit in migraine prevention, however data are limited.[17]

Randomized controlled trials have shown that relaxation training, thermal biofeedback with relaxation training, electromyogram biofeedback, and cognitive behavioral therapy reduce migraine frequency by 30%-50%. These data suggest that behavioral therapies can be as effective as many pharmacologic treatments.[19]

Proper sleep hygiene is also very important. Restful sleep decreases irritability in the brain, and therefore may decrease the frequency and severity of migraine.

Treatment of chronic migraine

Though classification of chronic migraine varies, the most commonly accepted general definition by the International Headache Society is 15 or more days of headache per month for at least 3 months.[20,21] The treatment of chronic migraine should be focused on prevention. Many of the same prophylactic agents are used for the treatment of chronic migraine, including β-blockers, topiramate, and valproic acid. Second-line agents include botulinum toxin type A, calcium channel blockers, fluoxetine, gabapentin, and SSRIs.

It is advised to start medication at the lowest possible dose and increase gradually, allow for an appropriate trial period before deeming a medication ineffective, and avoid overuse. When choosing an agent it is important to factor a patient's comorbidities, psychiatric disorders, sleep disorders, and child-bearing status.

With appropriate preventive therapy, approximately 50% of the patients will have a 50% reduction in frequency of migraines after 3 months. Complete eradication of headaches in chronic migraine sufferers is unlikely. The primary goal of preventive therapy should be to reduce the frequency and severity of headaches. As such it is important for physicians to discuss and set realistic goals for the treatment of chronic migraines.

The role of osteopathic medicine in the treatment and prevention of migraines

Several studies have looked into the role of osteopathic manipulative therapy (OMT) and spinal manipulative therapy (SMT) and their role in treatment and prevention of migraines. Although some studies have shown no benefit, others have shown that OMT may play a role in the treatment of migraines.[22]

Schabert et al. examined the use of OMT in an osteopathic family medicine clinic and its effect on the cost of treating patients with migraines compared with an allopathic clinic in which migraine sufferers did not receive OMT. Average cost per patient visit was approximately 50% less at the osteopathic clinic compared with the allopathic clinic. This difference was attributed to fewer medications prescribed in the osteopathic clinic resulting in lower average medication cost. OMT techniques in this study included counterstrain, high-velocity, low-amplitude technique, ligamentous articular strain technique, muscle energy, and osteopathic cranial techniques.[23]

Voigt et al. examined 42 female patients with a known diagnosis of migraines in a randomized controlled trial to examine the efficacy of OMT in migraine treatment. The technique of OMT was dependent on the particular osteopathic findings and included manual, visceral and cranial techniques. Migraine sufferers who received OMT reported decreased pain intensity, reduction in the number of migraine days and improved health-related quality of life.[24]

In another analysis, Keays et al. reviewed a trial comparing migraine prophylaxis with amitriptyline vs SMT, a component of osteopathy. A total of 218 patients were randomized to receive either SMT for 2 months or oral amitriptyline. A headache index, used to measure daily pain intensity, was equivalent in both groups in the last 4 weeks of treatment. Though statistically nonsignificant, there was a trend toward a lower headache index in the group that received SMT compared with the amitriptyline group. Also

of note, 10% of the patients receiving amitriptyline withdrew from the study secondary to side effects, whereas no adverse effects were reported in the SMT group.[25]

Investigational agents

Several drug classes are being investigated for their use in the treatment of acute migraine headaches. These drugs include calcitonin gene-related peptide receptor antagonists and serotonin 1F receptor agonists. However because of the high number of adverse effects, most notably hepatotoxicity, some studies have been halted, and therefore continued research is necessary.[12]

Neuroimaging and specialist consultation

Neuroimaging is not always necessary in patients with migraine headaches. The American Academy of Neurology suggests neuroimaging in the following patients with nonacute headaches:

- patients with an abnormal finding on neurologic examination;
- patients with atypical headache features;
- headaches that do not fulfill the strict definition of migraine or other primary headache disorder; and
- immunocompromised patients.

Physicians should have a low threshold for neuroimaging testing in patients who present with a sudden onset severe headache. These patients warrant neuroimaging because of the suspicion of subarachnoid hemorrhage and require immediate hospital evaluation.

In most patients, a computed tomography scan of the head with and without contrast is sufficient. A magnetic resonance (MR) imaging is indicated when posterior fossa lesions or cerebrospinal fluid leaks are suspected. Additional imaging, including MR angiography and MR venography, are indicated when arterial or venous lesions, respectively, are suspected. No other diagnostic tests are typically necessary.[8]

Practioners should prompt referral for further investigation or specialist consultation in the following[8]:

- progressive neurologic symptoms;
- a change in headache pattern in patients over 50;
- sudden onset severe “thunderclap” headache;
- postural headaches;
- new onset headache in patients with HIV or cancer;
- severe headaches that wake patients from sleep;
- headaches caused by physical exertion;
- jaw claudication; and
- fever and neck stiffness.

Risk of cardiovascular disease

Migraine with aura has been associated with an adverse cardiovascular risk profile. In a large prospective cohort of women, Kurth et al. showed an association of migraine with aura and increased risk for ischemic stroke, angina, and other ischemic vascular events including myocardial infarction. In this study, migraine without aura was not shown to be associated with an increased risk for cardiovascular disease.[26]

A cohort study in healthy men did not include information regarding aura but did show that those suffering from migraines had a higher risk for cardiovascular events than those without migraines, but not associated increased risk of ischemic stroke.[27]

MacClellan et al. studied women with probable migraine with visual aura and similarly found an increased association with ischemic stroke, particularly among women without other medical conditions associated with stroke. Risk factors including smoking and oral contraceptive use increase the risk of migraine with aura.[28]

Migraine with aura has also been associated with an unfavorable vascular risk profile measured by the Framingham risk score for coronary heart disease. It is associated with an increased risk of ischemic stroke among women with low vascular risk profiles, whereas it is associated with an increased risk of myocardial infarction among women with high vascular risk scores.[29]

A systemic review and meta-analysis of migraine and cardiovascular disease by Schurks et al. showed a 2-fold increased risk for ischemic stroke in women suffering from migraine with aura. This review again supported an increased risk among women as compared with men, as well as an increased risk in women less than 45 years of age, smokers, and the use of oral contraception. This review did not however show an overall increased risk or association between migraines with or without aura and myocardial infarction.[30]

Information with regard to history of migraine and vascular risk status might help to identify women at increased risk for specific future cardiovascular disease events.[29] Migraine with aura has been consistently associated with ischemic stroke. This risk appears to be amplified in younger women, smokers, and with the use of oral contraceptives. Consequently, young women who suffer from these types of headaches should be counseled extensively regarding smoking cessation and birth control other than oral contraceptives should be considered.[30]

Long-term complications

The International Headache Society recognizes the following as potential long-term complications of migraine headaches[31]:

- chronic migraines;
- status migrainosus (headaches lasting over 72 hours);
- persistent aura without infarction;
- migrainous infarction; and
- migraine-induced seizure.

Symptoms may last for days, weeks, years, or in some cases leave permanent neurologic deficit.

Conclusions

The proper evaluation and treatment of migraine headaches is pivotal for practitioners to understand. Patients must be educated about their condition and encouraged to participate in their care. All the available treatment options should be discussed and realistic goals should be established. Engaged patients are more likely to provide vital input regarding their treatment plan allowing the physician to better understand and accommodate patient goals.

Lifestyle changes with the help of headache diaries assist patients in avoiding migraine triggers. Patients suffering from migraines should be thoroughly screened and evaluated for the need of preventive therapy. Guidelines have been established to aid practitioners in the treatment and prevention of migraines. With the help of these guidelines, physicians are able to individualize therapeutic plans. Medication changes should be adequately evaluated before being dismissed as ineffective, and all medications should be started 1 at a time at the lowest dose. The use of manual manipulative medicine should also be considered in the management of acute and chronic migraines. The short-term treatment of migraines, as well as preventive therapy, should be reevaluated on a regular basis.

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