Migraine Headache: Updated Recommendations for Preventive Therapy

Authors:
Emily White, PharmD
Kris Harrell, PharmD
Deborah Minor, PharmD
The University of Mississippi Medical Center, Departments of Pharmacy, Pharmacy Practice and Medicine
Jackson, Mississippi

This article may appear in other state pharmacy association publications as it was previously published by Mississippi Pharmacists Association.

INTRODUCTION
Headache is one of the most common complaints encountered by healthcare practitioners and among the top three reasons given by adults for visiting United States emergency departments. Migraine headache, one of the most common primary headache disorders, affects approximately 6% of men and 18% of women and occurs during the most productive years of life (18 to 59 years of age).1,2 The pain and other associated symptoms of migraine can not only diminish the quality of life for those with the headache, but also have a great impact on family members and employers.

Despite the high prevalence of migraine headaches, studies indicate that most headache sufferers do not seek appropriate medical care. Patients with migraines are underdiagnosed and undertreated.1,2 In 2004, it was found that only one-half of patients with evident symptoms of migraine had been formally diagnosed by a physician.2 Appropriate care with an individualized approach to treatment can result in a reduction in attack frequency and severity, thus minimizing headache-related disability and emotional distress and improving the patient’s quality of life.1,2

Goal:
The goal of this review is to discuss migraine headaches and recent guideline updates for evidence-based preventive treatment.

Objectives:
1) Review the pathophysiology and clinical presentation of migraine
2) Discuss indications for and considerations in selection of preventive migraine therapy
3) Describe preventive therapy recommendations based on evidence provided in recent guideline updates
American Academy of Neurology (AAN) and the American Headache Society (AHS). These guidelines build upon the previous standards and review contemporary evidence supporting the use of pharmacologic, nonsteroidal anti-inflammatory drug (NSAID) and complementary therapies for migraine prevention. The goal of this review is to discuss the general pathophysiology and clinical presentation of migraine headaches and describe options for preventive therapy, in reference to the recently published guidelines for preventive treatment.

PATHOPHYSIOLOGY OF MIGRAINE
Migraine headaches are defined as episodic, neurovascular events involving severe, pulsating head pain often accompanied by a wide variety of secondary symptoms. Theories of the etiology and pathophysiology of migraine have evolved over the past decade, but remain less than completely understood. Migraines appear to result from complex central nervous system (CNS) dysfunctions in the trigeminovascular system. Cerebral vascular tone and nociception are altered and the associated pain and symptoms are a combination of altered perceptions resulting from neural suppression and activation of subcortical structures and trigeminal systems. Neuronal and broad sensory processing are thought to be regulated at least in part by serotonergic neurons in the brainstem. Genetic factors appear to influence CNS sensitivity to migraine-specific triggers or environmental factors and the susceptibility to attack occurrence and frequency.

CLINICAL PRESENTATION OF MIGRAINE
The clinical presentation of the migraine attack can typically be divided into several phases (Table 1). Migraine headaches, with or without aura, typically begin with a gradual onset of pain, most often unilaterally, near the frontal or temporal regions of the brain. The pain can become more generalized as the headache progresses. “Premonitory symptoms” are experienced by 20% to 60% of migraineurs and can occur in the hours or days before the onset of headache. These symptoms can vary widely among migraineurs but usually are consistent within an individual. The terms “prodrome” and “warning symptoms” should be avoided as these are often used mistakenly to include aura. Approximately one-third of migraine patients do experience auras, a multifaceted combination of focal neurological symptoms that occur just before or occasionally during a migraine attack.

Migraines frequently occur in early mornings, but can happen at any time of day. Secondary symptoms including sensory, cognitive, and especially gastrointestinal-related can accompany the headache and further impair daily activities. Even after the headache pain dissipates, psychological or neurological symptoms may persist for hours.

CONSIDERATIONS FOR PREVENTIVE TREATMENT
Approximately 25% of patients who suffer from severe migraines experience four or more attacks over a month. Frequent use of acute treatments is less than optimal management and can exacerbate headaches, leading to the development of medication-overuse or rebound headaches. To prevent medication-overuse headaches from occurring, it is recommended that acute treatments be limited and prophylactic therapy be considered. Unfortunately, it is estimated that only 3% to 13% of the 38% of patients who qualify for migraine preventive therapy actually receive it.
Preventive therapy should be considered in the setting of recurring migraines that produce significant disability; frequent attacks requiring symptomatic medication more than twice per week; symptomatic therapies that are ineffective, intolerable, or contraindicated; if migraines are more severe and/or have a risk of neurological damage; or if patients prefer this approach. Preventive therapy also may be administered preemptively or intermittently when headaches recur in a predictable pattern (e.g., exercise-induced migraine or menstrual migraine). The goals of therapy for long-term migraine treatment are identified in Table 2.\textsuperscript{2,5,9-11}

The preventive management of migraine should begin with the identification and avoidance of factors that consistently provoke migraine attacks in susceptible individuals. Patients should be encouraged to keep a headache diary to document the frequency, severity, and duration of attacks as well as responses to medications and potential trigger factors. Patients also can benefit from adherence to a general wellness program that includes regular sleep, exercise, and eating habits, avoidance of headache triggers, smoking cessation, and limited caffeine intake.\textsuperscript{2,5,10,11}

Preventive migraine therapies are usually administered on a daily basis with the goal of reducing the frequency, severity, and duration of attacks and improving responsiveness to symptomatic therapies.\textsuperscript{3,5} The lowest effective dose should be used for initiation and then gradually titrated upward until a therapeutic effect is achieved or side effects become intolerable. Drug doses for migraine prophylaxis are often lower than those necessary for other indications.\textsuperscript{5,9}

Though some reduction in attack frequency may be evident after the first month, 2 to 3 months is usually necessary to achieve an observable clinical benefit. An adequate therapeutic trial (usually 6 months) should be given to judge maximal efficacy. Patients should be counseled and monitored closely for therapeutic response, adverse reactions, abortive therapy needs, and management compliance.\textsuperscript{3,5,9} Overuse of acute headache medications can interfere with the effects of preventive treatment.\textsuperscript{11} Prophylactic treatment should usually be continued for at least 6 to 12 months after the frequency and severity of headaches have diminished. Gradual dosage reduction or discontinuation of therapy may be reasonable after a prolonged headache-free interval. Many patients with migraines experience less severe and fewer attacks over a lengthy period following discontinuation of prophylactic medications or taper to a lower dose.\textsuperscript{3,5}

The selection of an agent for migraine prophylaxis should be based on patient response, tolerability, convenience of the drug formulation, and coexisting conditions.\textsuperscript{3,11} The recent guideline updates provide recommendations as to the level of efficacy for particular agents, though there is insufficient evidence as to how to choose one therapy over another. Those with the highest level of efficacy should be used for treatment, with consideration of individual patient factors.\textsuperscript{3,4}

**RECOMMENDATIONS FOR PREVENTIVE TREATMENT**

To develop the recent guidelines, the AAN and AHS reviewed and evaluated studies of preventive migraine therapies. To be included in the analysis, trials had to be randomized, controlled studies with masked outcome assessments of safety and efficacy (considered class I or II studies).\textsuperscript{3,4} Results of the included studies were then categorized into levels based upon the proven efficacy of each therapy. Agents
were considered effective if they reduced migraine frequency, the number of migraine days, or the severity of migraine attacks. Therapies with definitive evidence of treatment efficacy were assigned a Level A recommendation and Level B where evidence indicated probable effectiveness.\textsuperscript{3,4} Therapies recognized with Level A and B recommendations, along with dosages and general medication comments, are summarized in Table 3.\textsuperscript{2-4} Further information regarding the specific details from their evaluation can be found within the published updates and at the website, www.neurology.org.\textsuperscript{3,4}

Of note, though other agents have established or probable efficacy, only propranolol, timolol, divalproex sodium, and topiramate are currently approved by the Food and Drug Administration for migraine prophylaxis.\textsuperscript{2}

**Beta Adrenergic Antagonists**

Beta blockers have a long history of established use and evidence for migraine prevention. Metoprolol, propranolol, and timolol have the strongest evidence of efficacy (Level A), reducing the frequency of attacks by 50\% in greater than 50\% of patients. Atenolol and nadolol are classified as probably effective (Level B), while nebivolol and pindolol are possibly effective.\textsuperscript{3} The mechanism for migraine prevention with beta blockers is not fully understood. They appear to raise the migraine threshold by affecting adrenergic or serotonergic neurotransmission in specific CNS pathways.\textsuperscript{2} Agents possessing intrinsic sympathomimetic activity are typically not effective for migraine prevention.\textsuperscript{5}

Beta blockers are generally well tolerated. Side effects can include drowsiness, fatigue, sleep disturbances, memory disturbances, depression, impotence, bradycardia, hypotension, and weight gain. These medications should generally be prescribed with caution in patients with preexisting asthma, peripheral vascular disease, cardiac conduction disturbances, bradycardia, depression, and hypotension. Although not used first line to treat hypertension, beta blockers may be useful along with other therapies in migraine patients with hypertension or angina.\textsuperscript{2,3,5}

**Antidepressants**

Various classes of antidepressants have been used for migraine prevention, with beneficial effects that are independent of their antidepressant activity.\textsuperscript{2,5} The antimigraine properties of antidepressants may be related to downregulation of central 5-HT2 receptors, increased levels of synaptic norepinephrine, and enhanced endogenous opioid receptor activity. The only antidepressants with probable effectiveness for migraine prevention (Level B) are the tricyclic antidepressant (TCA) amitriptyline and serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. The use of other antidepressants is based primarily on clinical and anecdotal experience. No selective serotonin reuptake inhibitors, including fluoxetine, have demonstrated effectiveness as prophylactic therapy.\textsuperscript{3}

Anticholinergic properties limit the use of TCAs in patients with benign prostatic hypertrophy or glaucoma. Orthostatic hypotension and cardiac toxicity also can occur. Sedation, increased appetite, and weight gain are more common side effects with TCAs. The most common side effects reported with venlafaxine are drowsiness, nausea, and vomiting.\textsuperscript{2,3} Concomitant therapy of SNRIs and triptans can potentially cause serotonin syndrome. Although it appears that the likelihood of CNS adverse events is extremely low, regulatory agencies caution against concurrent administration. The potential risk
of these combinations should be carefully considered and discussed with each patient.\(^2\)

**Antiepileptics**

Antiepileptic medications are increasingly popular and have emerged as important therapeutic options for migraine prevention. Topiramate is the most extensively studied medication for migraine prevention to date. Per the guidelines, topiramate and valproic acid/divalproex sodium have established efficacy and Level A recommendations for use. Antiepileptic drugs have multiple proposed mechanisms in migraine prevention, including increased inhibition facilitated by \(\gamma\)-aminobutyric acid (GABA), modulation of the reduction of excitatory neurotransmitter glutamate, and hindering sodium and calcium ion channel activity. This class is particularly useful in migraineurs with comorbid seizure, bipolar illness, or anxiety disorders.\(^2,3\)

Common early side effects with valproic acid/divalproex sodium are nausea and vomiting. These are typically self-limiting and less frequently to occur with gradual titration. Other side effects include alopecia, tremor, asthenia, somnolence, and weight gain. The risk of hepatotoxicity appears to be low in patients with no underlying metabolic or neurologic disorder; however, liver function tests should be obtained at baseline and with dosage adjustments or symptoms. Valproates are contraindicated in pregnant women and patients with a history of chronic liver disease or pancreatitis.\(^2,3\)

Topiramate should be initiated at a low dose and slowly titrated upward to minimize adverse effects. Approximately 50% of patients treated to target doses are responders with a 50% or greater reduction in mean headache frequency. Benefits can be observed within as early as two weeks of beginning therapy, with significant reductions in migraine frequency within the first month. Paresthesia, fatigue, anorexia, diarrhea, weight loss, memory/language problems, taste perversion, and nausea are adverse events associated with treatment. Weight loss occurs in 9% to 12% of patients and is a unique adverse effect, as weight gain in a common reason for discontinuation of other preventive medications. Topiramate should be used with caution or avoided in patients with a history of cognitive impairment or kidney stones.\(^2,3,5\) As more evidence is available, there may be a role for other antiepileptics in migraine prevention. Carbamazepine is possibly effective, and a recent study evaluated gabapentin, though data are insufficient to determine efficacy. Lamotrigine is classified as possibly or probably ineffective according to the guidelines.\(^3\)

**Nonsteroidal Anti-inflammatory Drugs**

Regular or daily use of NSAIDs for the treatment of migraine attacks or other headaches may be associated with the development of medication overuse headache. However, intermittent use of NSAIDs to prevent headaches that recur in a predictable pattern, such as menstrual migraine, can be a reasonable option.\(^4\) Administration of NSAIDs in the perimenstrual period can be beneficial in women with true menstrual migraine. NSAIDs should be initiated 1 to 2 days prior to the expected onset of headache and continued during the period of vulnerability.\(^2\) Agents that have demonstrated probable effectiveness (Level B) include ibuprofen, ketoprofen, and naproxen sodium.\(^4\) NSAIDs inhibit prostaglandin synthesis and appear to prevent neurogenically mediated inflammation in the trigeminovascular system. Potential gastrointestinal and renal toxicity limit the prolonged use of these agents and NSAIDs should be avoided or used cautiously in patients with previous
Serotonin Receptor Agonists
Three of the available serotonin receptor agonists (triptans) have been shown to have some efficacy for short-term prevention of menstrually associated migraine. 
Frovatriptan, the triptan with the longest half-life, has the most conclusive evidence (Level A). Naratriptan and zolmitriptan are probably effective and should be considered (Level B). Triptans work through vasoconstriction of intracranial arteries, inhibition of vasoactive peptide release, and inhibition of neural transmission. Adverse effects to the triptans are common but usually mild to moderate in nature and of short duration. These include paresthesias, fatigue, dizziness, flushing, warm sensations, and somnolence. “Triptan sensations,” including tightness, pressure, heaviness, or pain in the chest, neck, or throat are also reported by up to 25% of patients. The mechanism of these symptoms is unknown, but a cardiac source of pain seems unlikely in most patients. The triptans are contraindicated in patients with a history of ischemic heart disease (e.g., angina pectoris, Prinzmetal’s angina, or previous myocardial infarction), uncontrolled hypertension, and cerebrovascular disease. For migraine prevention, the triptan is usually started 1 or 2 days before the expected onset of headache and continued during the time of vulnerability. A separate indication for pure menstrual migraine is currently being deliberated by regulatory authorities.

Complementary Treatments
Various complementary therapies have been used and studied for the prevention of migraine. Butterbur, or petasites, is the only herbal treatment with established efficacy (Level A) and appears to act on calcium channels, preventing peptide-leukotriene formation. Riboflavin, or vitamin B<sub>2</sub>, has been found to have probable effectiveness (Level B) and appears to work centrally, increasing energy efficiency. It is well tolerated by most patients; however, the benefits of therapy became significant only after 3 months. Various formulations of magnesium have been studied for migraine prevention with mixed results, though overall probable effectiveness (Level B). CNS levels of magnesium are known to be significantly low during migraine attacks and supplementation is thought to decrease neuronal excitability. Magnesium may be particularly useful in patients experiencing migraines accompanied by auras or those associated with menstruation. MIG-99, the relatively stable extract of feverfew, is the most studied herbal preparation for migraine prevention. Feverfew, also Level B, may work by inhibiting the release of serotonin as well as prostaglandin synthetase, thereby reducing inflammation. Subcutaneous histamine has been compared to traditional therapies (i.e., sodium valproate, topiramate) with favorable results in improving headache frequency, duration, and intensity, indicating probable effectiveness (Level B).

Possibly Effective and Other Agents
The guidelines review various other agents that have been used for migraine prevention. Based on limited evidence, some of these are considered possibly effective and may be considered for migraine prevention. Others, such as verapamil, have been widely used but have conflicting or inadequate evidence to support or refute their use.

The angiotensin-converting enzyme inhibitor lisinopril and the angiotensin II receptor blocker candesartan provided effective migraine prevention in recent studies and are considered possibly effective. Selection of one of these agents could be useful in patients with hypertension, diabetes mellitus, renal
disease or those needing secondary stroke prevention, however, they should be used cautiously in those with hypotension. Based on other studies, telmisartan is probably ineffective. Clonidine and guanfacine have demonstrated possible efficacy, though use is limited by common side effects (e.g., depression, drowsiness). Coenzyme Q10 was well tolerated and effective for migraine prevention in a small, controlled study. In one study, cyproheptadine (4 mg/day) was as effective as propranolol (80 mg/day) in reducing migraine frequency, duration, and severity, while the combination was more effective in reducing the frequency of attacks.

The calcium channel blockers have been widely used for preventive treatment, though evidence supporting their use is inadequate or conflicting. Extensive clinical experience with verapamil suggests a possible role in migraine prevention and choosing this medication may be valuable in patients with hypertension. Side effects of verapamil can include constipation, hypotension, bradycardia, atrioventricular block, and exacerbation of congestive heart failure.

CONCLUSION
Many migraineurs receive inadequate care and experience substantial levels of pain and disability. Improvements in migraine diagnosis and treatment can improve the quality of life for these patients and those around them. Recent guideline updates for preventive therapy identify agents with established and probable efficacy. These recommendations should be considered when selecting an agent and medications with the highest level of efficacy should be used. There is insufficient evidence as to how to choose one therapy over another. Selection of an agent should be based on individual patient response, tolerability, convenience of dosing, coexisting conditions, and preference. Patient counseling and careful monitoring are essential in initiating the most appropriate pharmacotherapy, documenting therapeutic successes and failures, identifying medication contraindications, and preventing or minimizing adverse events.

References
Table 1: Clinical Presentation of Migraine Headache

<table>
<thead>
<tr>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common, recurrent, severe primary headache disorder that interferes with normal functioning. Two major subtypes - migraine without aura and migraine with aura. A thorough headache history should include age at onset, attack frequency and timing, duration of attacks, precipitating or aggravating factors, ameliorating factors, description of neurologic symptoms, characteristics of the headache pain (quality, intensity, location, and radiation), and associated signs and symptoms.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characterized by recurring episodes of throbbing pain, that last from 4 to 72 hours when untreated. Signs include a stable pattern, absence of daily headache, positive family history for migraine, normal neurologic examination, presence of triggers, menstrual association, longstanding history, improvement with sleep, and subacute evolution.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Premonitory Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occur in the hours or days before headache onset. Include neurologic (e.g., allodynia, phonophobia, photophobia, hyperosmia, difficulty concentrating), psychological (e.g., anxiety, depression, euphoria, irritability, drowsiness, fatigue, hyperactivity, restlessness), autonomic (e.g., polyuria, diarrhea, constipation) and constitutional symptoms (e.g., anorexia, food cravings, stiff neck, excessive yawning, extreme thirst).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aura</th>
</tr>
</thead>
<tbody>
<tr>
<td>A complex of positive and negative focal neurologic symptoms that precede or accompany an attack. Aura is most often visual, frequently affecting half the visual field. Sensory and motor symptoms (e.g., paresthesias or numbness of arms/face, dysphasia or aphasia, weakness, hemiparesis) may also occur. Symptoms typically evolve over 5 to 20 minutes and last &lt; 60 minutes, with headache usually occurring within 60 minutes of the end of the aura.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Headache</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain is usually gradual in onset, peaking in intensity over minutes to hours and often severe. Headache is typically unilateral, in the frontotemporal region, but can occur anywhere or become generalized during the attack. Gastrointestinal symptoms almost invariably accompany the headache (e.g., nausea, vomiting, diarrhea, cramping). Other systemic symptoms (e.g., facial/scalp/periorbital edema, nasal stuffiness) and sensory hyperacuity (e.g., photophobia, phonophobia, osmophobia) are also common. Pain is usually aggravated by physical activity. Not all symptoms are present at every attack.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>As the headache pain wanes, various symptoms and mood changes are experienced. Symptoms range from tiredness, irritability, malaise, impaired concentration, and scalp tenderness to feeling unusually refreshed or euphoric.</td>
</tr>
</tbody>
</table>
Table 2: Goals of Therapy in Long-term Migraine Treatment

- Reduce migraine frequency, severity, and disability
- Reduce reliance on poorly tolerated, ineffective, or unwanted acute pharmacotherapies
- Improve quality of life
- Prevent headache
- Avoid escalation of headache medication use
- Educate and enable patients to manage their disease
- Reduce headache-related distress and psychological symptoms
### Table 3: Preventive Migraine Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Usual Range</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β-Adrenergic antagonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol&lt;sup&gt;B&lt;/sup&gt;</td>
<td>50 mg/day</td>
<td>50–200 mg/day</td>
<td></td>
</tr>
<tr>
<td>Metoprolol&lt;sup&gt;A&lt;/sup&gt;</td>
<td>100 mg/day in divided doses</td>
<td>100–200 mg/day in divided doses</td>
<td>Dose short-acting 4 times a day and long-acting 2 times a day; available as extended release</td>
</tr>
<tr>
<td>Nadolol&lt;sup&gt;B&lt;/sup&gt;</td>
<td>40-80 mg/day</td>
<td>80–240 mg/day</td>
<td></td>
</tr>
<tr>
<td>Propranolol&lt;sup&gt;A&lt;/sup&gt;</td>
<td>40 mg/day in divided doses</td>
<td>40–160 mg/day in divided doses</td>
<td>Dose short-acting 2-3 times a day and long-acting 1-2 times a day; available as extended release</td>
</tr>
<tr>
<td>Timolol&lt;sup&gt;A&lt;/sup&gt;</td>
<td>20 mg/day in divided doses</td>
<td>20–60 mg/day in divided doses</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline&lt;sup&gt;B&lt;/sup&gt;</td>
<td>10 mg at bedtime</td>
<td>20–50 mg at bedtime</td>
<td></td>
</tr>
<tr>
<td>Venlafaxine&lt;sup&gt;B&lt;/sup&gt;</td>
<td>37.5 mg/day</td>
<td>75–150 mg/day</td>
<td>Available as extended release; increase dose after 1 week</td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate&lt;sup&gt;A&lt;/sup&gt;</td>
<td>25 mg/day</td>
<td>50–200 mg/day in divided doses</td>
<td>As effective as amitriptyline, propranolol or valproate; increase by 25 mg/week</td>
</tr>
<tr>
<td>Valproic acid/ divalproex sodium&lt;sup&gt;A&lt;/sup&gt;</td>
<td>250-500 mg/day in divided doses, or daily for extended release</td>
<td>500–1,500 mg/day in divided doses, or daily for extended release</td>
<td>Monitor levels if compliance is an issue</td>
</tr>
<tr>
<td><strong>Nonsteroidal anti-inflammatory drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen&lt;sup&gt;B&lt;/sup&gt;</td>
<td>400-1,200 mg/day in divided doses</td>
<td></td>
<td>Use intermittently, such as for menstrual migraine prevention; daily or prolonged use may lead to medication-overuse headache and is limited by potential toxicity</td>
</tr>
<tr>
<td>Ketoprofen&lt;sup&gt;B&lt;/sup&gt;</td>
<td>150 mg/day in divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naproxen sodium&lt;sup&gt;B&lt;/sup&gt;</td>
<td>550-1,100 mg/day in divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triptans</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frovatriptan&lt;sup&gt;A&lt;/sup&gt;</td>
<td>2.5 mg/day or 5 mg/day in divided doses</td>
<td></td>
<td>Taken in the perimenstrual period to prevent menstrual migraine.</td>
</tr>
<tr>
<td>Naratriptan&lt;sup&gt;B&lt;/sup&gt;</td>
<td>2 mg/day in divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zomitriptan&lt;sup&gt;B&lt;/sup&gt;</td>
<td>5-7.5 mg/day in divided doses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Miscellaneous

<table>
<thead>
<tr>
<th>Product</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>1-10 ng 2 times/week</td>
<td>May cause transient itching and burning at injection site</td>
</tr>
<tr>
<td>Magesium gluconate</td>
<td>400 mg/day</td>
<td>800 mg/day in divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be more helpful in migraine with aura and menstrual migraine</td>
</tr>
<tr>
<td>MIG-99 (feverfew)</td>
<td>10-100 mg/day in divided doses</td>
<td>Withdrawal may be associated with increased headaches</td>
</tr>
<tr>
<td>Petasites</td>
<td>100-150 mg/day in divided doses</td>
<td>150 mg/day in divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use only commercial preparations, plant is carcinogenic</td>
</tr>
<tr>
<td>Riboflavin</td>
<td>400 mg/day in divided doses</td>
<td>400 mg/day in divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benefit only after 3 months</td>
</tr>
</tbody>
</table>

A Level A - established efficacy; should be used (≥ 2 Class I studies)
B Level B - probably effective (1 Class I or 2 Class II studies)
INSTRUCTIONS: This page is intended to help participants REVIEW the quiz prior to submitting their answers online. Please take the quiz online using the members section of the website.

1. Migraine headaches affect approximately what percent of women?
   a. 5%
   b. 10%
   c. 18%
   d. 25%

2. Migraines appear to result from CNS neurovascular dysfunctions in which system?
   a. trigeminovascular
   b. neurofundibular
   c. nigrostriatal
   d. vagosomatic

3. Auras are experienced by approximately what percent of patients with migraine headache?
   a. 10%
   b. 25%
   c. 33%
   d. 50%

4. Each of the following is a reason to start prophylactic migraine therapy EXCEPT:
   a. attacks are infrequent and controlled with acute therapy
   b. the patient prefers that approach
   c. migraines cause significant impairment
   d. acute therapies are contraindicated

5. Patients should take preventive therapies:
   a. only when not taking acute therapies
   b. only if they experience aura associated with headaches
   c. usually daily regardless of migraine occurrence

6. Based on the updated guidelines, all of the following beta blockers are recommended for migraine prevention EXCEPT:
   a. atenolol
   b. metoprolol
   c. propranolol
   d. acebutolol

7. Based on the updated guidelines, which of the following antidepressants is recommended for migraine prevention?
   a. bupropion
   b. fluoxetine
c. sertraline

d. venlafaxine

8. Based on the updated guidelines, which of the following antiepileptic drugs should NOT be used for migraine prevention?
   a. divalproex sodium
   b. lamotrigine
   c. topiramate
   d. valproic acid

9. Of the triptans, _________ has the most evidence of efficacy for menstrually associated migraine.
   a. frovatriptan
   b. naratriptan
   c. sumatriptan
   d. zolmitriptan

10. Among complementary therapies, _________ has demonstrated the most effectiveness in preventing migraines.
    a. niacin
    b. petasites
    c. St John’s Wort
    d. thiamine

11. Did the article help you achieve EACH of the stated objectives? If not, describe in the comment box at the end of this section. Refer to the article for the list of learning objectives.
    a. Yes
    b. No

12. Quality of the written material/content?
    a. Very good quality
    b. Good quality
    c. Neutral
    d. Poor quality
    e. Very Poor Quality

13. Overall evaluation of this article?
    f. Very good quality
    g. Good quality
    h. Neutral
    i. Poor quality
    j. Very Poor Quality
13. How much time was required to complete this article?
   a. 0.5 hrs.
   b. 1.0 hrs.
   c. 1.5 hrs.
   d. 2.0 hrs.
   e. 2.5 hrs

14. The learning activities (e.g. case studies, quiz) were effective?
   a. Strongly agree
   b. Agree
   c. Neutral
   d. Disagree
   e. Strongly disagree

15. The information in this article will help assist and reinforce my practice/treatment habits?
   a. Strongly agree
   b. Agree
   c. Neutral
   d. Disagree
   e. Strongly disagree

16. The author(s) did NOT appear to be promoting a product or company? Please use COMMENT box at end of evaluation to explain or provide comment.
   a. Strongly agree
   b. Agree
   c. Neutral
   d. Disagree
   e. Strongly disagree

17. Author(s) communicated material clearly? Strongly agree
   a. Agree
   b. Neutral
   c. Disagree
   d. Strongly disagree

18. ACPE universal Program Number for PEF reporting purposes to CPE Monitor. Please select ANSWER (A) for this question
   a. 0120-9999-13-207-H01-P
   b. Not a valid answer choice