Preventive Therapies for Migraine Headache

James W. Banks, MD

Educational Objectives

- Review current guidelines for the preventive treatment of migraine headache.
- Review the evidence for agents commonly used in preventive therapy for migraine headache.
- Discuss the goals of preventive therapy for migraine headache.

Introduction

Headache is a common and significantly disabling problem that affects nearly 14% of all Americans, more than asthma and diabetes combined. It causes moderate-to-severe disability in approximately 53% of sufferers. The World Health Organization has rated migraine as one of the top 10 most disabling health disorders, and a survey by Consumer's Union revealed that migraine patients rated a lower quality of life on several measures than did patients with diabetes, rheumatoid arthritis, heart disease, or depression.

Recent evidence has suggested that, at least for some patients, migraine can be a progressive disease leading to changes in the periaqueductal gray matter and the white matter of the brain. These data are supported by findings that many clinicians have noted experientially for years—that patients with chronic daily headaches usually began with relatively infrequent, episodic headaches that gradually increased over the years. The recognition that migraine is more than just an acute episodic disorder has brought forth much greater emphasis on preventive therapies. This is akin to recognizing that managing asthma requires more than just treating the acute exacerbations.

The goals of prophylaxis are as follows:

- preventing or reducing the frequency of acute attacks
- improving the efficacy of acute abortive therapies
- improving the level of functioning and reducing disability from the disease

In most cases, patients do not experience complete resolution of their headaches; rather, the headaches become less frequent and less severe. As a result, the usual measure of success in prevention is a reduction of headache occurrence by 50% or more. Reducing headache frequency and severity can significantly improve quality of life and lessen the use of acute pharmacological treatment. Preventive therapy for migraine also significantly decreases costs associated with the disease.

A study in a managed care population by Silberstein revealed that prophylaxis reduced physician office visits by 51%; emergency department visits by 82%; computed tomography (CT) scans by 75%; magnetic resonance imaging by 88%; and medication costs by $48 to $138 per member per month.

In the past, the guideline for initiating preventive medications for migraine was based on an arbitrary figure of four or more headaches a month (Table 1). With triptans greatly improving the treatment of acute headache, clinicians and patients alike have become confused about when to start preventive therapy. Six headaches that can be adequately treated with a triptan might be preferable to taking a daily medication, or two headaches a month requiring repeated doses of the same triptan on successive days might easily exceed a patient’s triptan monthly allotment from his or her health plan. Either way, in light of the evidence suggesting the potential for chronic, progressive disease, specialists are now recommending more aggressive guidelines for initiating preventive medications.

Based upon frequency and disability guidelines, 57% of migraine patients meet the criteria for taking preventive agents; however, fewer than 5% of all migraine patients are following a prophylaxis regimen.

Review of Preventive Pharmacological Agents

Numerous medications have been used to prevent headache. Because no single panacea exists for headache treatment and no agent works uniformly for every patient, therapy must be individualized and comorbid conditions must be addressed.

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as well. The only drugs that the Food and Drug Administration (FDA) has approved for preventing migraine are:

- the synthetic ergot alkaloid methysergide (Sansert®, Novartis), which is no longer available in the U.S.
- the beta blocker propranolol (Inderal®, AstraZeneca).
- the beta blocker timolol (Blocadren®, Merck).
- the anticonvulsant agent valproic acid (Depakote®, Depakene®, Abbott).
- the antiepileptic agent topiramate (Topamax®, Ortho-McNeil).

Other medications associated with varying reported success include: 11–14

- amitriptyline and other tricyclic antidepressants (TCAs).
- selective serotonin reuptake inhibitors (SSRIs).
- other beta blockers.
- calcium-channel antagonists (CCAs).
- angiotensin-converting enzyme inhibitors.
- angiotensin II receptor blockers.
- gabapentin (Neurontin®, Pfizer).
- lamotrigene (Lamictal®, GlaxoSmithKline).
- zonisamide (Zonegran®, Elan).
- cyproheptadine (Periactin®, Merck).

The U.S. Headache Consortium has reviewed and categorized the most commonly used medications for migraine prevention based upon the available evidence at that time (the late 1990s). Their report classifies medications into the following areas:10–12

- drugs with documented high efficacy and mild-to-moderate adverse drug events (ADEs), including beta blockers, amitriptyline, divalproate (divalproex sodium [Depakote®, Abbott]), and topiramate
- drugs with lower documented efficacy and mild-to-moderate ADEs, including SSRIs, CCAs, gabapentin, riboflavin (vitamin B2), and nonsteroidal anti-inflammatory agents (NSAIDs)
- agents used, according to the clinician’s judgment, with (1) mild-to-moderate ADEs or (2) major ADEs or complex management
- medications that are associated with significant ADEs or that are difficult to use (e.g., methysergide and monoamine oxidase inhibitors [MAOIs])
- drugs that have limited or no efficacy (e.g., lithium, nifedipine [Procardia®, Pfizer], nimodipine [Nimotop®, Bayer], phenytoin [Dilantin®, Pfizer], and cyproheptadine)

Unfortunately, it is difficult to make solid, evidence-based comparisons of the various agents. All of the initial studies on the effectiveness of beta blockers, amitriptyline, and the antiarrhythmic agent verapamil (e.g., Calan®, Pfizer) were performed before the FDA issued more stringent guidelines on research for drug approvals and new indication application studies and before the International Headache Society (IHS) established diagnostic criteria for migraine in 1991. In addition, most of the studies at that time evaluated only patients who had completed the study (“completers”) rather than the full study, or intent-to-treat, population. Although much clinical experience exists, the actual scientific data are not all that solid; they have been based on less than optimally designed and relatively small population studies, particularly for beta blockers, amitriptyline, and calcium-channel blockers.12 A brief review of the studies reveals the weakness of the evidence upon which many clinicians have been basing their treatment decisions.

### Beta Blockers

The 1999 Evidence Report: Drug Treatments for the Prevention of Migraine, prepared by the Agency for Health Care Policy and Research (AHCPR), now called the Agency for Healthcare Research and Quality, identified and examined 75 separate controlled trials of beta blockers for migraine prophylaxis.13 The preponderance of data supports propranolol as consistently effective for this purpose, but only 38 of the studies were placebo-controlled and 10 of the studies compared different beta blockers with one another. There were 22 placebo-controlled studies of propranolol, the largest of which enrolled 96 patients but analyzed only 80 completers.15 This was a crossover design comparator study between propranolol and timolol. Both experimental groups of patients achieved a significant reduction in the frequency of monthly headaches (48% and 44%), compared with patients receiving placebo (24%). On the basis of a number of small, limited trials, other nonselective beta blockers are likely to be effective, but this is said most confidently based on similar pharmacology rather than data. Beta blockers with intrinsic sympathomimetic activity have not been effective for migraine prevention.16

#### Mechanism of Action

The exact mechanism of action of beta blockers is not certain, but it seems to result from the inhibition of central beta receptors in the adrenergic system, thus down-regulating the “hypersensitive” migraine brain (Table 2). Other mechanisms

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**Table 1 Guidelines for Initiating Preventive Therapy for Migraine Headache**

<table>
<thead>
<tr>
<th>Frequency of headache greater than two per month, with disability more than three days per month</th>
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<tbody>
<tr>
<td>Use of an acute abortive medication more than one to two times per week</td>
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<tr>
<td>Acute medications contraindicated, not tolerated, or ineffective</td>
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<tr>
<td>Presence of uncommon migraine conditions</td>
</tr>
<tr>
<td>Hemiplegic migraine</td>
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<tr>
<td>Migraine with prolonged aura or migrainous infarction</td>
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<tr>
<td>Patient preference</td>
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</table>

Data from American Academy of Family Practice/American Society of Internal Medicine Guidelines.
Adverse Drug Events and Dosing

All beta blockers can produce fatigue, lethargy, drowsiness, depression, and sleep disturbances. Most of these symptoms are fairly well tolerated, especially if the dose is slowly titrated upward (Table 3). Gastrointestinal (GI) complaints and decreased exercise tolerance are commonly reported as well. Patients with congestive heart failure, asthma, and diabetes should not be given beta blockers. In patients with comorbid hypertension and migraine, beta blockers would be considered an excellent first-line agent to help treat both disorders with one medication.

Antidepressants

Antidepressants other than the TCAs, while widely used to prevent migraine, do not offer significant evidence to support their use for migraine prevention. The most widely used medication in this class, amitriptyline, was reviewed in the 1999 Evidence Report.12 The report identified and examined 16 controlled trials of TCAs, as well as some SSRIs, used for preventing migraine. The studies in the analysis examined six trials of amitriptyline, four trials of the experimental 5-HT reuptake inhibitor fomoxetine, two trials each of clomipramine (Anafranil®, Mallinckrodt) and fluoxetine (Prozac®, Eli Lilly), and a single trial of fluvoxamine (Luvox®, Solvay). Eleven of the trials were placebo-controlled. Two trials compared two antidepressants against each other; five trials compared antidepressants with beta blockers. Three placebo-controlled trials found amitriptyline to be significantly better than placebo at lowering Migraine Headache Index scores (a compilation of frequency, severity, duration, and disability ratings).

Only the study by Couch and Hassanein was large enough to have power for measuring statistical significance between groups.17,18 This study enrolled 162 patients, but only 72 completed the study. The data were analyzed before the study was completed (week eight of 12), when 100 subjects were still enrolled.

Of the 100 patients who completed the eighth week of the trial, 26 patients (55%) taking amitriptyline had a 50% or greater reduction in the frequency of headaches, compared with their values at the end of the placebo run-in period; 18 patients (34%) had a similar response while receiving placebo (P < .05). At the end of the 12th week, only 72 patients remained in the trial (37 amitriptyline patients and 35 placebo patients). Of these, 20 patients receiving amitriptyline and 13 receiving placebo experienced a 50% or greater reduction in the average frequency of monthly headaches.

In a trial comparing amitriptyline and propranolol, amitriptyline was significantly more efficacious in patients with mixed-migraine and tension-type headaches, whereas propranolol was more effective in patients with migraine alone.11,19 However, this study was conducted before the development of the International Headache Society’s Diagnostic Criteria for Headache in 1991. It is likely that by the current criteria, most of the patients in the mixed-headache group would be reclassified into the migraine category. The evidence from the studies on clomipramine and fluvoxamine was not sufficient to support their efficacy.

Studies on fluoxetine and citalopram (Celexa®, Forest), as well as some atypical antidepressants, have been performed, but none of them have been large enough to support any recommendations for or against their use beyond individual case considerations.11

Mechanism of Action

TCAs, SSRIs, and most antidepressants work by increasing norepinephrine, serotonin, or both. TCAs also modulate gamma-aminobutyric acid (GABA) and adenosine. Antidepressants are effective in treating migraine and have some efficacy in other chronic pain conditions independent of depression (see Table 2).

Adverse Drug Events and Dosing

TCAs are well known for causing side effects. Their multiple sites of action are also responsible for the abundance of ADEs. Dry mouth, constipation, dizziness, mental confusion or cloudiness, taste disturbances, tachycardia, palpitations, orthostatic hypotension, and weight gain are all well documented and fairly common but may vary, depending on the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Potential Mechanisms of Migraine-Preventive Agents</th>
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<tbody>
<tr>
<td></td>
<td>Glutamate</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>↓</td>
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<tr>
<td>TCAs</td>
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<tr>
<td>CCAs</td>
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<tr>
<td>Valproate</td>
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<tr>
<td>Gabapentin</td>
<td>–</td>
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<tr>
<td>Topiramate</td>
<td>↓↓</td>
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</table>

CCAs = calcium-channel antagonists; GABA = gamma-aminobutyric acid; TCAs = tricyclic antidepressants.

Key: ↑ = increases; ↓ = decreases; + = positive effect; – = little or no effect.

Adapted from Silberstein SD, Lipton RB, Dalessio DJ, eds. Wolff’s Headache and Other Head Pain. Oxford University Press; 2001.
specific agent, dose, and titration schedule.

The dose of antidepressants for migraine should start low and should gradually be increased to an effective level or until the dose is limited by side effects. A slow upward titration may well improve tolerance, and in most cases there is no reason to rush to attain a therapeutic dosage (see Table 3).

**Calcium-Channel Antagonists**

Despite their widespread use as first-line agents and their perceived benefits based on anecdotal clinical experience, CCAs have not shown any solid experimental evidence (except for one compound) to support their use in preventing episodic migraine headache. The AHCPR’s 1999 Evidence Report identified and examined 45 separate controlled trials of CCAs for migraine prevention.13 Most of these trials examined flunarizine, which is not available in the U.S. It is unlikely that this product will be approved for use in this country because of its ADE profile, although it has shown efficacy in multiple trials.

Verapamil, the most widely used agent in the U.S., has been compared with placebo in only three studies, the largest of which included only 30 subjects.20 Although two of the three studies demonstrated efficacy, each of these studies had high dropout rates, which might have exaggerated the effectiveness of the studies. The sample size was too small to calculate effect or to demonstrate statistical significance.

**Mechanism of Action**

CCAs were first used in the treatment of headache on the basis of the vascular theory of migraine and on the assumption that they prevented the contraction of vascular smooth muscle. Our current understanding of the diversity of calcium-ion channels and our knowledge of a specific abnormality in an alpha-1α subunit (P/Q channel) in familial hemiplegic migraine lends support to the role of calcium in migraine.11 However, the exact mechanism of action for CCAs has not been elucidated. CCAs appear to interfere with the development of neurovascular inflammation and with cortical spreading depression that has been demonstrated in the phenomenon of migraine aura (see Table 2).

**The Modern Era**

In 1991, the International Headache Society released its diagnostic criteria for headache and the FDA established stricter criteria for drug-approval studies. Headache-prevention studies had to evaluate all subjects, including those who dropped out of the study for any reason; furthermore, “improvement in headache” was defined more accurately for a population as a headache reduction rate of 50% or more in order to avoid skewing of results. It is now more reasonable to compare results from one study to another and even between different medications (Figure 1).

**Valproate**

Nadine valproate was the first medication to receive the FDA’s approval for headache prevention after its imposition of stricter guidelines and after the release of the International Headache Society’s diagnostic guidelines. Several randomized, placebo-controlled trials of valproate for migraine prophylaxis have been conducted.

Two of five studies showed significant improvement with valproate compared with placebo, and another two studies comparing valproate with propranolol showed improved headache response (i.e., decreased frequency of headaches); however, the response was not statistically significantly greater than with propranolol.11,13 The extended-release form of valproate has been shown to be as effective as the tablet formulation.21 The results have been fairly consistent in demonstrating a response rate of about 47% to 50%; that is, approximately 50% of the patients taking valproate experienced a reduction in headache frequency by at least half.21–24

The largest study included 160 patients who were randomly assigned to one of four groups: valproate 500 mg/day, 1,000 mg/day, and 1,500 mg/day or placebo.22 After a titration phase, the subjects were monitored for 12 weeks. The overall response rate for all doses was 44% of patients with at least a

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1962</td>
<td>Methysergide receives indication</td>
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<tr>
<td>1979</td>
<td>Propranolol receives indication</td>
</tr>
<tr>
<td>1988</td>
<td>IHS diagnostic criteria established</td>
</tr>
<tr>
<td>1990</td>
<td>Timolol receives indication</td>
</tr>
<tr>
<td>1991</td>
<td>IHS clinical trial guidelines</td>
</tr>
<tr>
<td>1996</td>
<td>Divalproex sodium receives indication</td>
</tr>
<tr>
<td>2000</td>
<td>Divalproex sodium ER receives indication</td>
</tr>
<tr>
<td>2004</td>
<td>Topiramate receives indication</td>
</tr>
</tbody>
</table>

Figure 1  The evolution of migraine prevention. ER = extended-release formulation; IHS = International Headache Society. (Courtesy of Ortho-McNeil.)
50% reduction in headaches. The mean reduction in headache frequency was statistically significant at all three doses: 38% for patients taking 500 mg; 42% for patients taking 1,000 mg; and 36% for patients taking 1,500 mg.

These studies differed from those involving propranolol and amitriptyline and the others by including all subjects (intent-to-treat) in the analysis, even those who dropped out of the study because of intolerable side effects, lack of drug effectiveness, or other reasons. In contrast, the previous studies assessed only patients who completed the study, thereby possibly increasing the perceived positive effects. Although the reported effectiveness was not any higher than that for beta blockers, CCAs, or amitriptyline, headache specialists anecdotally report that valproate is more effective than the previous medications.

**Mechanism of Action**

Valproate modulates GABA (increases GABA activity); elevates potassium levels; and causes neuronal hyperpolarization, which decreases spontaneous neuronal activity. With the decreased firing of serotonergic neurons in the dorsal raphe, the “hypersensitive migraine brain” is stabilized (see Table 2).

**Adverse Drug Events and Dosing**

GI side effects are the most common reported problems with valproate. Other patient complaints include asthenia, somnolence, hair loss, and tremor. On rare occasions, valproate therapy has been observed to result in hepatitis or pancreatitis. This reaction is idiosyncratic and unpredictable, but it does seem to be related to the patient’s overall state of health or to the use of other medications.

Valproate is a potential teratogen and should not be given to women who are pregnant or who are considering becoming pregnant. Unlike most anticonvulsant agents, valproate does not interfere with the metabolism of oral contraceptives. Because of the potential for additive central nervous system depression, patients using valproate should not be given barbiturate-containing combination analgesics (see Table 3).

The usual recommendation for the dosing of valproate is to start at 250 mg/day (usually at night) and to increase it by 250 mg every few days (for three to seven days) to a dose range of 500 to 1,500 mg/day. The extended-release formulation (Depakote® ER) allows for once-daily dosing, whereas the standard formulation of divalproex sodium (Depakote®) should be dosed twice a day. At doses greater than 1,500 mg/day, it is recommended that the patient’s drug levels and hepatic enzymes be checked. At lower doses, the risk of hepatic dysfunction is significantly lower and the monitoring of hepatic function may be individualized.

**Gabapentin**

Gabapentin is another antiepileptic or neurostabilizer medication that has undergone systematic trials. It has been widely used in migraine prevention, in the treatment of neuropathic pain, and in many other disorders in addition to epilepsy. The largest placebo-controlled study of gabapentin enrolled 143 patients for 12 weeks after the dose was titrated upward to either 1,800 or 2,400 mg/day. The 50% responder rate was 36% for gabapentin and 14% for placebo.

**Mechanism of Action**

Gabapentin’s mechanism of action is not clear, but it is probably related to enhancement of GABA activity within the brain (see Table 2).

**Adverse Drug Events and Dosing**

The most common ADEs reported with gabapentin are dizziness and drowsiness. Starting at a low dose and titrating upward over several weeks helps to minimize side effects and decrease patients’ withdrawal from therapy. The starting dose is 300 mg once daily, with increases every few days to a target dose of 600 to 2,400 mg/day in divided doses three times a day (see Table 3).

**Topiramate**

Topiramate is the newest FDA-approved neurostabilizer medication indicated for the prevention of migraine. It has undergone the largest number of systematic trials of any preventive medication and, as such, has the most solid scientific evidence to support its use as prophylaxis. In addition, there has been rapid acceptance of and significant use of this medication in the clinical setting.

Two nearly identical randomized, double-blind, placebo-controlled studies published in 2004 involved more than 960 patients. Both studies evaluated the effectiveness of topiramate at 50, 100, and 200 mg/day. The 50% responder rate ranged from 36% to 39% for the 50-mg dose; from 49% to 53% for the 100-mg dose; and from 47% to 52% for the 200-mg dose.

Information that was available from the topiramate studies that was not reported from any of the others involved a breakdown of the effectiveness within the responder group: 23% of responders had a 50% to 75% reduction in headache frequency, 26% experienced a 76% to 99% reduction, and 6% experienced complete resolution of their headaches during the study period.

| Table 3 Dose and Titration of Drug Therapy for Migraine |
|-----------------|-----------------|-----------------|-----------------|
| **Dose Range**  | **Onset of Action** | **Need to Titrate** |
| Tricyclic antidepressants* | 25–150 mg/day | 4–6 weeks | Yes |
| Beta blockers† | 60–320 mg/day | 4–6 weeks | Yes |
| Calcium-channel blockers‡ | 240–320 mg/day | 4–6 weeks | Yes |
| Valproic acid | 500–3,000 mg/day | 4–6 weeks | Yes |
| Gabapentin | 1,800–2,400 mg/day | 4–6 weeks | Yes |
| Topiramate | 100–200 mg/day | 4–6 weeks | Yes |

* Amitriptyline and nortriptyline.
† Propranolol.
‡ Verapamil.
Mechanism of Action
Topiramate’s mechanism of action is thought to be a result of multiple sites of action (see Table 2). The drug exerts modulating activity upon both glutamate (inhibitory) and GABA (enhancing), and it modulates state-dependent, voltage-gated sodium and calcium-ion channels and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors. Topiramate is also a weak carbonic anhydrase inhibitor.

Adverse Drug Events and Dosing
The frequency of ADEs for topiramate was high, but when treatment-limiting ADEs (those that caused patients to withdraw from the study), were considered, topiramate was fairly well tolerated. The most commonly reported side effect was paresthesia in 35% to 51% of patients in pooled study data; however, only 8% of subjects withdrew from the studies because of complaints of paresthesia. Other reported side effects were fatigue (in 14%–19% of patients), loss of appetite (in 9%–15%), nausea, abdominal pain, or diarrhea (in 9%–14%), with all of these ADEs accounting for a dropout rate of only about 5%. Somnolence, sleep disturbances, memory or concentration problems, and language difficulties occurred in approximately 6% of subjects, but only 2% of patients or fewer withdrew from the studies because of such ADEs. Side effects were common, but most patients seemed to tolerate them because of the perceived benefits in a reduced frequency and severity of headache (see Table 3).

The risks of serious side effects from topiramate are kidney stones (which may be able to be minimized by maintaining good hydration); acute angle-closure glaucoma; and acute myopia (for which there are no predictors). Because the symptoms of acute angle-closure glaucoma are acute and not subtle, they are rarely missed; stopping the medication resolves the problem.

The remaining ADEs are usually avoided or minimized by initiating therapy at a low dose and titrating upward slowly, or the ADEs usually resolve with time after the dosage is stabilized. Patients seem to tolerate some side effects (e.g., frequently reported paresthesias) if they are given reassurance, and these ADEs usually resolve over time. There have been reports of improved paresthesias after potassium supplementation.30 The risks of serious side effects from topiramate are kidney stones (which may be able to be minimized by maintaining good hydration); acute angle-closure glaucoma; and acute myopia (for which there are no predictors). Because the symptoms of acute angle-closure glaucoma are acute and not subtle, they are rarely missed; stopping the medication resolves the problem.

The risk of metabolic acidosis is valid; in practice, however, this ADE has been rare. Simply monitoring patients clinically and, if necessary, checking bicarbonate and chloride levels can be useful. It is interesting that many patients who cannot tolerate topiramate, regardless of the dose, do not have metabolic abnormalities.

Although cognitive dysfunction has been reported with topiramate in a small percentage of patients even at low dosages, most patients do not have significant cognitive dysfunction if they start with a low dose (12.5–15 or 25 mg) nightly and if the dose is titrated upward slowly (50–200 mg/day). Incidentally, at doses of 200 mg/day or below, topiramate does not appear to interfere with conventional oral contraceptives.31,32 The most significant difference in ADEs for topiramate, when compared with other neurostabilizer agents (e.g., valproate and gabapentin) is that topiramate is likely to cause weight loss rather than weight gain. In the two large studies, patients lost an average of 6 kg (approximately 13 pounds) from their baseline weight. Various studies of other agents did not address weight, but it is well known (and stated in the prescribing information for divalproex) that weight gain is a side effect. The weight loss effect of topiramate is significant and sufficiently consistent such that ongoing research is focusing on topiramate as a potential anti-obesity drug.

Alternative and Complementary Preventive Therapies

Petasites hybridus
Many nonpharmacological agents have been tried over the years, but most have not been tested in controlled trials by which to truly judge their merit. One agent, Petadolex®, a proprietary butterbur root extract (Petasites hybridus), has undergone a randomized, double-blind, placebo-controlled trial in which 235 patients were enrolled for 12 weeks to evaluate the effectiveness of 50 mg and 75 mg daily in divided doses.33 Patients taking the 75-mg dose experienced a 48% reduction in headache frequency, and the 50% responder rate was 69%, which was significantly greater than that with placebo. However, the placebo responder rate was 49%, which is quite high, thus making the results less robust. The 50-mg dose of the extract was not statistically superior to placebo.

Another randomized, double-blind, placebo-controlled study of P. hybridus from Germany involved 60 subjects. Results were similar, demonstrating a significant reduction in headache frequency from baseline measures (60% at three months), with only a minimal response in the placebo group of patients. A 50% responder rate was not calculated.34

The side effects of P. hybridus primarily include GI upset (nausea, vomiting, heartburn, diarrhea, abdominal pain, or burping). Butterbur extract has been reported to cause liver abnormalities, although the proprietary preparation used in the studies and promoted for migraine prophylaxis has not been associated with any hepatic dysfunction. Apparently, the process of its preparation removes the hepatotoxic elements common to the less purified Petasites extracts.35

The mechanism of action of Petasites extracts is believed to be related to its antimuscaryl effects as well as its anti-inflammatory effects, which are mediated through inhibition of leukotriene synthesis.

Botulinum Toxin
Botulinum toxin has undergone numerous trials, most of which have not been placebo-controlled. Additional studies are under way. The results have been mixed, and there is not enough solid evidence to recommend the agent at this time.

Magnesium
Magnesium supplementation has been evaluated both as a preventive agent for migraine and as an acute abortive therapy.
when given as a rapid intravenous infusion. However, most of the studies on prophylaxis have involved small numbers of patients and have used differing magnesium salts and dosages.\textsuperscript{36,37} Efficacy reports vary, and a comparison between studies is difficult because of the design differences in the studies.

Overall, there appears to be some positive benefit to magnesium over placebo. There has been evidence to suggest that some migraine patients have problems in maintaining normal magnesium levels and that alterations in magnesium predispose these patients to migraine. Supplementation with magnesium would lessen such variations and perturbations. Magnesium is known to cause gastric irritation and diarrhea.

**Riboflavin (Vitamin B\textsubscript{2})**

Riboflavin has been found to be effective in reducing migraine in several open-label and other less well-controlled studies and in a placebo-controlled, double-blind study.\textsuperscript{38} The results in the latter study showed a 50% responder rate of 59% with riboflavin and a rate of 15% with placebo after three months. Riboflavin is well tolerated. The recommended dosage is 400 mg/day.

**Coenzyme Q10**

Coenzyme Q10 has been studied for the treatment of neurological disorders because of its ability to improve mitochondrial dysfunction. It is now receiving some attention in headache prevention.\textsuperscript{39}

The results are preliminary, but the pathophysiological and pharmacological concept is rational. However, coenzyme Q10 can be expensive. The dosage used in one study (150 mg) and the amount being used in some headache specialty clinics (200–400 mg/day) can cost between $50 and $90 per month. Prices vary considerably, as does the quality of the various products, because coenzyme Q10 is not regulated by the FDA.

**Feverfew**

Three of four trials of the herb feverfew (\textit{Chrysanthemum parthenium}), also called “bachelor’s buttons,” as a treatment for migraine prevention have shown efficacy in reducing headache frequency and intensity.\textsuperscript{40} However, the studies have been small, have not been well designed, and have used different preparations, thus limiting the comparison of data. Feverfew is widely available in the U.S. Because the preparations are not regulated by the FDA, they may vary widely in quality and dosage. The mechanism of action is uncertain.

**Summary**

Migraine is a common and frequently disabling condition that is often treated only as an acute, episodic event when, in fact, it may well be a chronic, progressive disease. While that debate continues, there is no question that preventive therapy is underutilized for most migraine patients. The goals of prophylactic therapy are to completely prevent, or at least lessen, the frequency and the severity of headaches; to improve the efficacy of acute treatments; and to improve function and reduce disability from the disease.

The agents most commonly used to prevent migraines have been categorized by the U.S. Headache Consortium as (1) drugs with high efficacy and mild-to-moderate ADEs (beta blockers, amitriptyline, divalproate, and topiramate) and (2) medications with lower efficacy and mild-to-moderate ADEs (SSRIs, CAs, gabapentin, riboflavin, and NSAIDs).

In most cases, an appropriate medication can be selected from within these two groups. Selection should be based upon the patient’s preferences; comorbid conditions, if any (Table 4); and the risk of the drug’s side effects for that patient. It is crucial to inform patients of the medication’s risks and benefits and to advise them that preventive therapy rarely means complete cessation of their headaches and that improvement takes time.

The most important caveat for clinicians when initiating preventive therapy is to “start low and go slow” in order to minimize ADEs and to maximize patient tolerance. It is also important to give the patient an adequate trial of the drug at an appropriate dose.

After the dose is titrated upward to the recommended therapeutic range, it should be maintained for eight to 12 weeks before the drug is considered ineffective. Clinicians should be aware that patients might continue to overuse abortive medications that may well inhibit the success of prophylactic therapy. They should also be persistent in having patients try various medications. If one agent is ineffective, another might be helpful, or perhaps combination therapy is indicated if the patient has multiple comorbid conditions.

Finally, all treatment programs should address lifestyle and behavioral issues as well as pharmacological modalities.

### Table 4 Therapeutic Opportunities and Limitations in Migraine Prevention

<table>
<thead>
<tr>
<th>Condition</th>
<th>Consider</th>
<th>Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>TCA</td>
<td>Beta blocker</td>
</tr>
<tr>
<td>Anxiety</td>
<td>TCA, beta blocker</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>TCA</td>
<td></td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>Topiramate</td>
<td>TCA, gabapentin, valproate</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>Valproate, topiramate</td>
<td>TCA</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Topiramate, valproate</td>
<td>TCA</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Calcium-channel blocker</td>
<td>Beta blocker, ergot</td>
</tr>
</tbody>
</table>

TCA = tricyclic antidepressant.

### References


20. Silberstein SD. Control of topiramate-induced paresthesias with supplemental potassium. *Headache* 2002;42:85:


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*Grant/research support:* AstraZeneca, GlaxoSmithKline, and Ortho-McNeil Pharmaceuticals.

*Consultant:* Ortho-McNeil Pharmaceuticals, AstraZeneca, and GlaxoSmithKline.

*Speakers Bureau:* Ortho-McNeil Pharmaceuticals, AstraZeneca, Pfizer, GlaxoSmithKline, and MedPointe.
CONTINUING EDUCATION CREDIT

Continuing Education for Physicians and Pharmacists
P&T® 2004;29(12):784–791
ACPE Program # 079-999-04-024-H01
Expiration Date: December 31, 2005
Topic: Preventive Therapies for Migraine Headache

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**Topic:** Preventive Therapies for Migraine Headache  
**ACPE Program #** 079-999-04-024-H01  

**CE Evaluation:** Select the one best answer to each of the following questions, and record your response on the examination answer sheet. Complete the additional requested information. Forward the answer sheet, with appropriate payment, to the Department of Health Policy, Thomas Jefferson University Hospital, at the address indicated. A certificate of completion will be mailed within six to eight weeks of receipt of your exam/payment. (A minimum test score of 70% is required.)

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**Multiple Choice**  
Select the one correct answer.  

1. According to the article, the goal of preventive therapy for migraine is to:  
a. prevent or reduce the frequency of acute attacks.  
b. improve the efficacy of acute abortive therapies.  
c. improve the level of function and reduce the disability from the disease.  
d. all of the above  

2. Which of the following statements is incorrect?  
a. The usual measure of success in migraine prevention is a reduction of headache frequency by half or more.  
b. Preventive therapy for migraine significantly increases the costs associated with the disease.  
c. Reducing the frequency and severity of migraine can significantly improve the patient’s quality of life and reduce the use of acute abortive medications.  
d. In most cases, patients do not experience complete resolution of their headaches.  

3. The following medications have been approved by the FDA for the preventive treatment of migraine except:  
a. propranolol.  
b. gabapentin.  
c. timolol.  
d. valproate.  

4. According to the classification of medications most commonly used to prevent migraine by the U.S. Headache Consortium, which of the following is incorrect?  
a. Beta blockers and amitriptyline are among the drugs with documented high efficacy and mild-to-moderate adverse drug events (ADEs).  
b. Phenytoin has been shown to be very effective.  
c. Selective serotonin reuptake inhibitors (SSRIs) are among the drugs that have lower documented efficacy and mild-to-moderate ADEs.  
d. Cyproheptadine is among the drugs that have proven limited efficacy and mild-to-moderate drug events (ADEs).  

5. Which of the following statements is incorrect about antidepressants used in the treatment of migraine?  
a. Antidepressants do not have significant evidence to support their use with the exception of the tricyclic agents (TCAs).  
b. TCAs, SSRIs, and most antidepressants work by increasing norepinephrine and/or serotonin.  
c. Studies of fluoxetine and citalopram, as well as some atypical antidepressants, do not support any recommendations for or against their use beyond individual case considerations.  
d. In a trial comparing amitriptyline and propranolol, amitriptyline was significantly less efficacious in patients with mixed-migraine and tension-type headaches.  

6. Calcium-channel antagonists exert their action in the treatment of headaches by:  
a. augmenting contraction of vascular smooth muscles.  
b. interfering with the development of neurovascular inflammation and cortical spreading.  
c. aiding the development of neurovascular inflammation and cortical spreading.  
d. an abnormality in the beta-2 subunit in familial hemiplegic migraine supporting the role of calcium.  

7. All of the following statements are true regarding valproate for preventive treatment of migraines except:  
a. Sodium valproate was the first medication to receive FDA approval for headache prevention after the imposition of stricter guidelines.  
b. General trends from the five studies showing significant improvement with valproate are fairly consistent with a response rate of 47% to 50%.  
c. Valproate stabilizes the “hypersensitive migraine brain” by decreasing GABA and potassium activity.  
d. Valproate has been known to cause hepatitis or pancreatitis as a rare side effect.  

8. Which of the following statements is true concerning topiramate for preventive migraine therapy?  
a. Topiramate has undergone no systematic trials to support its use as a prophylactic medication.  
b. Topiramate acts at several sites, including glutamate, GABA, voltage-gated sodium and calcium channels, AMPA/kainate receptors, and carbonic anhydrase receptors.  
c. Topiramate’s treatment-related side effects were intolerable for most patients.  
d. While topiramate causes weight gain, valproate and gabapentin cause weight loss; this is the most significant difference between them.  

9. Select the statement that matches the drug with the probable mechanism of action:  
a. Petasites hybridus is believed to inhibit leukotriene synthesis.  
b. Magnesium exerts its effects through improvement of mitochondrial dysfunction.  
c. Coenzyme Q10 is believed to mediate serotonin reuptake.  
d. Botulinum toxin is believed to inhibit GABA.  

10. Please select the incorrect statement concerning prophylactic surgery:  
a. After a patient’s dose has reached the therapeutic range, it should be maintained for eight to 12 weeks before the medication is considered ineffective.  
b. Overuse of acute abortive therapy may inhibit the success of prophylactic therapy.  
c. Prophylactic therapy should be started at the maximum dose in order to achieve efficient therapeutic results.  
d. Patients may have to try several different prophylactic regimens in order to find one that is appropriate.
CE Registration and Evaluation Form

Date of publication: December 2004
Title: Preventive Therapies for Migraine Headache
Authors: James W. Banks, MD
Submission deadline: December 31, 2005
ACPE Program # 079-999-04-024-H01

Registration

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City: ___________________________________ State: _________ Zip:__________ Telephone: ___________________________
E-mail Address: _______________________________________ Check one: □ Physician □ Pharmacist □ Other
Time needed to complete this CE activity in hours:  □ 0.5 hr □ 1 hr □ 1.5 hr □ 2 hr □ Other _____________________
Certification: I attest to having completed this CE activity. _______________________________________________________
Signature (required) Date _______________

Answer Sheet
Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □  6. a □ b □ c □ d □
2. a □ b □ c □ d □  7. a □ b □ c □ d □
3. a □ b □ c □ d □  8. a □ b □ c □ d □
4. a □ b □ c □ d □  9. a □ b □ c □ d □
5. a □ b □ c □ d □  10. a □ b □ c □ d □

Evaluation
Rate the extent to which:  

1. Objectives of this activity were met  
2. You were satisfied with the overall quality of this activity  
3. Content was relevant to your practice needs  
4. Participation in this activity changed your knowledge/attitudes  
5. You will make a change in your practice as a result of participation in this activity  
6. This activity presented scientifically rigorous, unbiased, and balanced information  
7. Individual presentations were free of commercial bias  
8. Adequate time was available for Q&A  
9. Which ONE of the following best describes the impact of this activity on your performance:
   □ This program will not change my behavior because my current practice is consistent with what was taught.
   □ This activity will not change my behavior because I do not agree with the information presented.
   □ I need more information before I can change my practice behavior.
   □ I will immediately implement the information into my practice.
10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)
   □ Discuss new information with other professionals  
   □ Consult the literature  
   □ Discuss with industry representative(s)  
   □ Participate in another educational activity  
   □ Other ____________________________________________________________________________  
   □ None

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