

Preventive Migraine Treatment

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KEYWORDS

• Migraine • Prevention • Treatment

Migraine is a central nervous system disorder that is characterized by moderate or severe headaches that last 4 to 72 hours. The attacks are often aggravated by routine physical activity and may be associated with a variety of other symptoms, including photophobia, phonophobia, osmophobia, nausea, or vomiting. Approximately 15% of patients experience attacks of migraine with aura. The typical aura consists of visual, sensory, or language symptoms. Aura usually develops over a period of at least 5 minutes and lasts less than 1 hour. Attacks vary widely from patient to patient in regard to frequency, severity, duration, and impact on quality of life. The pharmacologic treatment of migraine may be acute (abortive) or preventive (prophylactic), and patients with frequent or severe headaches often require both approaches.

Preventive therapy is used to try to reduce the frequency, duration, or severity of attacks. Additional benefits include enhancing the response to acute treatments, improving a patient's ability to function, and reducing disability.¹ Preventive treatment may also result in health care cost reductions.² Recent US and European guidelines^{3,4} have established the circumstances that might warrant preventive treatment. These include (1) recurring migraine that significantly interferes with a patient's quality of life and daily routine despite acute treatment; (2) four or more attacks per month; (3) failure of, contraindication to, or troublesome side effects from acute medications; and (4) frequent, extremely long, or uncomfortable auras.^{3,4} A migraine preventive drug is considered successful if it reduces migraine attack frequency by at least 50% within 3 months. A migraine diary is highly recommended for treatment evaluation.^{3,4}

US evidence-based guidelines for preventive treatment of migraine include the following:

1. Recurring migraine that significantly interferes with the patient's daily routine despite acute treatment (eg, two or more attacks a month that produce disability that lasts 3 or more days, headache attacks that are infrequent but produce profound disability)

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2. Failure of, contraindication to, or troublesome side effects from acute medications
3. Overuse of acute medications
4. Special circumstances, such as hemiplegic migraine or attacks with a risk for permanent neurologic injury
5. Frequent headaches (more than two a week) or a pattern of increasing attacks over time, with the risk for developing medication overuse headache
6. Patient preference, that is, the desire to have as few acute attacks as possible

Prevention is not being used to the extent that it should be; only 13% of all migraineurs currently use preventive therapy to control their attacks.⁴ According to the American Migraine Prevalence and Prevention (AMPP) study, 38.8% of patients who have migraine should be considered for (13.1%) or offered (25.7%) migraine preventive therapy.⁵

The major medication groups for preventive migraine treatment include anticonvulsants, antidepressants, β -adrenergic blockers, calcium channel antagonists, serotonin antagonists, botulinum neurotoxins, nonsteroidal anti-inflammatory drugs, and others (including riboflavin, magnesium, and petasites). If preventive medication is indicated, the agent should be chosen from one of the first-line categories based on the drug's relative efficacy in double-blind placebo-controlled trials, its side effect profile, and the patient's preference, in addition to coexistent and comorbid conditions.⁶ The following are general principles of preventive therapy, based on the author's experience.

PRINCIPLES OF PREVENTIVE THERAPY

- Start the chosen drug at a low dose, and increase it slowly until therapeutic effects develop, the ceiling dose for the chosen drug is reached, or adverse events (AEs) become intolerable.
- Give each treatment an adequate trial. The full benefit of the drug may not be realized until 6 months have elapsed.
- Set realistic goals. Success is defined as a 50% reduction in attack frequency, a significant decrease in attack duration, or an improved response to acute medication.
- Set realistic expectations regarding AEs. The risk and extent of AEs vary greatly from patient to patient, and we presently have no way of predicting the presence or severity of AEs for an individual patient. Most AEs are self-limited and dose-dependent, and patients should be encouraged to tolerate the early AEs that may develop when a new medication is started.
- Avoid acute headache medication overuse and drugs that are contraindicated because of coexistent or comorbid illnesses.
- Re-evaluate therapy, and, if possible, taper or discontinue the drug after a sustained period of remission (6–9 months).
- Be sure that a woman of childbearing potential is aware of any potential risks, and choose the medication that has the least potential for AE on a fetus.⁷
- To maximize compliance, involve patients in their own care. Take patient preferences into account when deciding between drugs of relatively equivalent efficacy and tolerability.
- Consider comorbidity, which is the presence of two or more disorders whose association is more likely than chance. Conditions that are comorbid with migraine are shown in **Box 1**.^{8–11}

Box 1**Migraine comorbid disease**

Cardiovascular

- Hypertension or hypotension
- Raynaud's disease
- Mitral valve prolapse (migraine with aura)
- Angina or myocardial infarction
- Stroke

Psychiatric

- Depression
- Mania
- Panic disorder
- Anxiety disorder

Neurologic

- Epilepsy
- Essential tremor
- Positional vertigo
- Restless legs syndrome

Gastrointestinal

- Irritable bowel syndrome

Other

- Asthma
- Allergies

Preventive treatment is often recommended for only 6 to 9 months; however, to date, no randomized placebo-controlled trials have been performed to investigate migraine frequency after the preventive treatment has been discontinued. Diener and colleagues¹² assessed 818 patients who had migraine and were treated with topiramate for 6 months to see the effects of topiramate discontinuation. Patients received topiramate in a 26-week open-label phase. They were then randomly assigned to continue this dose or to switch to placebo for a 26-week double-blind phase. Of the 559 patients who completed the open-label phase, 514 entered the double-blind phase and were assigned to topiramate ($n = 255$) or placebo ($n = 259$). The mean increase in number of migraine days was greater in the placebo group (1.19 days in 4 weeks, 95% confidence interval [CI]: 0.71–1.66; $P < .0001$) than in the topiramate group (0.10 days in 4 weeks, 95% CI: -0.36 – 0.56 ; $P = .5756$). Patients in the placebo group had a greater number of days on acute medication than did those in the topiramate group (mean difference between groups = 0.95, 95% CI: -1.49 to -0.41 ; $P = .0007$). Sustained benefit was reported after topiramate was discontinued, although the number of migraine days did increase. These findings suggest that patients should be treated for 6 months, with the option to continue to 12 months.

SPECIFIC MIGRAINE PREVENTIVE AGENTS***β-Adrenergic Blockers***

Beta-blockers, the most widely used class of drugs in prophylactic migraine treatment, are approximately 50% effective in producing a greater than 50% reduction in attack frequency (**Table 1**). Evidence has consistently demonstrated the efficacy^{13,14} of the nonselective beta-blocker propranolol^{9–11,13–18} and the selective β₁-blocker metoprolol.^{9,10,15,19–21} Atenolol,²² bisoprolol,^{21,23} nadolol,^{24,25} and timolol^{13,26} are also likely to be effective. Beta-blockers with intrinsic sympathomimetic activity (eg, acebutolol, alprenolol, oxprenolol, pindolol) are not effective for migraine prevention. Propranolol is effective for migraine prevention at a daily dose of 120 to 240 mg, but no correlation has been found between its dose and its clinical efficacy.

The action of beta-blockers is probably central and could be mediated by (1) inhibiting central β-receptors that interfere with the vigilance-enhancing adrenergic pathways, (2) interaction with 5-HT receptors (but not all effective beta-blockers bind to the 5-HT receptors), and (3) cross-modulation of the serotonin system.¹⁶ Propranolol inhibits nitric oxide (NO) production by blocking inducible NO synthase. Propranolol also inhibits kainate-induced currents and is synergistic with *N*-methyl-D-aspartate blockers, which reduce neuronal activity and have membrane-stabilizing properties.¹⁷

Contraindications to the use of beta-blockers include asthma and chronic obstructive lung disease, congestive heart failure, atrioventricular conduction defects, Raynaud's disease, peripheral vascular disease, and brittle diabetes. All beta-

Table 1		
Beta-blockers and antidepressants in the preventive treatment of migraine		
Agent	Daily Dose	Comment
Beta-blockers		
Atenolol	50–200 mg	Use qd Fewer side effects than propranolol
Metoprolol	100–200 mg	Use the short-acting form bid Use the long-acting form qd
Nadolol	20–160 mg	Use qid Fewer side effects than propranolol
Propranolol	40–400 mg	Use the short-acting form bid or tid Use the long-acting form qd or bid 1–2 mg/kg in children
Timolol	20–60 mg	Divide the dose Short half-life
Antidepressants		
Tertiary amines		
Amitriptyline	10–400 mg	Start at 10 mg at bedtime
Doxepin	10–300 mg	Start at 10 mg at bedtime
Secondary amines		
Nortriptyline	10–150 mg	Start at 10–25 mg at bedtime If insomnia, give early in the morning
Protriptyline	5–60 mg	Start at 10–25 mg at bedtime
Selective serotonin and norepinephrine reuptake inhibitors		
Venlafaxine	75–225 mg	Start at 37.5 mg in morning

Abbreviations: bid, twice daily; qd, every day; tid, three times daily.

blockers can produce behavioral AEs, such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance, and hallucinations.¹³ Other potential AEs include gastrointestinal complaints, decreased exercise tolerance, orthostatic hypotension, bradycardia, and impotence. Although stroke has been reported to occur after patients who had migraine with aura were started on beta-blockers, there is neither an absolute nor a relative contraindication to their use by patients who have migraine, with or without aura.

Antidepressants

Antidepressants consist of several different drug classes with different mechanisms of action (see **Table 1**). Only one member of the class of tricyclic antidepressants (TCAs) (amitriptyline) has proved efficacy in migraine.¹⁴ Although the mechanism by which antidepressants work to prevent migraine headache is uncertain, it does not result from treating masked depression. Antidepressants are useful in treating many chronic pain states, including headache, independent of the presence of depression, and the response occurs sooner than the expected antidepressant effect.^{21,22} In animal pain models, antidepressants potentiate the effects of coadministered opioids.²³ The antidepressants that are clinically effective in headache prevention inhibit noradrenaline and 5-HT reuptake or are antagonists at the 5-HT₂ receptors.²⁴

The TCA dose range is wide and must be individualized. Most TCAs are sedating. Start with a low dose of the chosen TCA at bedtime, except when using protriptyline, which should be administered in the morning. If the TCA is too sedating, switch from a tertiary TCA (eg, amitriptyline, doxepin) to a secondary TCA (eg, nortriptyline, protriptyline). AEs are common with TCA use. Antimuscarinic AEs include dry mouth, a metallic taste, epigastric distress, constipation, dizziness, mental confusion, tachycardia, palpitations, blurred vision, and urinary retention. Other AEs include weight gain (rarely seen with protriptyline), orthostatic hypotension, reflex tachycardia, and palpitations. Antidepressant treatment may change depression to hypomania or frank mania (particularly in bipolar patients). Older patients may develop confusion or delirium.²⁵ The muscarinic and adrenergic effects of these agents may pose increased risks for cardiac conduction abnormalities, especially in the elderly, and these patients should be carefully monitored or other agents should be considered.

Amitriptyline and doxepin are sedating TCAs. Patients with coexistent depression may require higher doses of these drugs to treat underlying depression. Start at a dose of 10 to 25 mg at bedtime. The usual effective dose for migraine ranges from 25 to 200 mg. Nortriptyline, a major metabolite of amitriptyline, is a secondary amine that is less sedating than amitriptyline. Start at a dose of 10 to 25 mg at bedtime. The dosage ranges from 10 to 150 mg/d. Protriptyline is a secondary amine that is similar to nortriptyline. Start at a dose of 5 mg in the morning. The dosage ranges from 5 to 60 mg/d as a single or split dose.

Evidence for the use of selective serotonin reuptake inhibitors (SSRIs) or other antidepressants for migraine prevention is poor. Fluoxetine at doses between 10 and 40 mg was effective in three placebo-controlled trials and not effective in one.²⁷⁻²⁹ Other antidepressants not effective in placebo-controlled trials were clomipramine and sertraline; for other antidepressants, only open or non-placebo-controlled trials are available. Because their tolerability profile is superior to that of tricyclics, SSRIs may be helpful for patients with comorbid depression.³⁰ The most common AEs include sexual dysfunction, anxiety, nervousness, insomnia, drowsiness, fatigue, tremor, sweating, anorexia, nausea, vomiting, and dizziness or lightheadedness. The combination of an SSRI and a TCA can be beneficial in treating refractory depression³¹ and, in the author's experience, resistant cases of migraine. The combination may

require the TCA dose to be adjusted, because TCA plasma levels may significantly increase.

Recently, venlafaxine, an SSRI and selective norepinephrine reuptake inhibitor (SNRI), has been shown to be effective in a double-blind placebo-controlled trial³² and in a separate placebo and amitriptyline controlled trial.³³ The usual effective dosage is 150 mg/d. Start with the 37.5-mg extended-release tablet for 1 week, then the 75-mg tablet for 1 week, and then the 150-mg extended-release tablet in the morning. AEs include insomnia, nervousness, mydriasis, and seizures.

Calcium Channel Antagonists

Two types of calcium channels exist: calcium entry channels, which allow extracellular calcium to enter the cell, and calcium release channels, which allow intracellular calcium (in storage sites in organelles) to enter the cytoplasm (**Table 2**).³⁴ Calcium entry channel subtypes include voltage-gated, opened by depolarization; ligand-gated, opened by chemical messengers, such as glutamate; and capacitative, activated by depletion of intracellular calcium stores. The mechanism of action of the calcium channel antagonists in migraine prevention is uncertain, but possibilities include inhibition of 5-HT release, neurovascular inflammation, or the initiation and propagation of cortical spreading depression.³⁵ Flunarizine, a nonselective calcium channel antagonist with antidopaminergic properties, was superior to placebo in six of seven randomized clinical trials.^{18,20,32–40} The dose is 5 to 10 mg given at night (women seem to need lower doses than men). The most prominent AEs include weight gain, somnolence, dry mouth, dizziness, hypotension, occasional extrapyramidal reactions, and exacerbation of depression. Because of its side effect profile, flunarizine should be considered as a second-line drug for migraine prevention, after beta-blockers. Flunarizine is widely used in Europe but is not available in the United

Table 2
Selected calcium channel blockers and selected anticonvulsants in the preventive treatment of migraine

Agent	Daily Dose	Comment
Selected calcium channel blockers		
Verapamil	120–640 mg	Start at 80 mg bid or tid Sustained-release form can be given qd or bid
Flunarizine	5–10 mg	qd at bedtime Weight gain is the most common side effect
Selected anticonvulsants		
Carbamazepine	600–1200 mg	tid
Gabapentin	600–1200 mg	Dose can be increased to 3000 mg
Topiramate	100 mg	Start at 15–25 mg at bedtime Increase 15–25 mg/wk Attempt to reach 50–100 mg Increase further if necessary Associated with weight loss rather than weight gain
Valproate/divalproex	500–1500 mg	Start at 250–500 mg/d Monitor levels if compliance is an issue Maximum dosage is 60 mg/kg/d

Abbreviations: bid, twice daily; qd, every day; tid, three times daily.

States, where verapamil is the recommended calcium channel antagonist. Verapamil was more effective than placebo in two of three trials, but both positive trials were small and dropout rates were high, rendering the findings uncertain.^{41–43} Rigorous randomized controlled trial evidence does not exist to support the use of verapamil for migraine. Nimodipine, nicardipine, diltiazem, and cyclandelate, other nonselective calcium channel antagonists, have not shown superiority over placebo in well-designed clinical trials and cannot be recommended for migraine prophylaxis.

ANTICONVULSANTS

Anticonvulsants are increasingly recommended for migraine prevention because of well-conducted placebo-controlled trials. With the exception of valproic acid, topiramate, and zonisamide, anticonvulsants may substantially interfere with the efficacy of oral contraceptives.^{41,44}

Carbamazepine

The only placebo-controlled trial of carbamazepine that suggested a significant benefit had several methodologic issues (see **Table 2**).⁴² Carbamazepine, 600 to 1200 mg/d, may be effective in preventive migraine treatment but it is rarely used in clinical practice for this purpose.

Gabapentin

Gabapentin (1800–2400 mg) showed efficacy in a placebo-controlled double-blind trial only when a modified intent-to-treat analysis was used (see **Table 2**). Migraine attack frequency was reduced by 50% in approximately one third of patients.⁴³ The most common AEs were dizziness or giddiness and drowsiness.

Valproic Acid

Valproic acid is a simple 8-carbon, 2-chain fatty acid. Divalproex sodium (approved by the US Food and Drug Administration [FDA]) is a combination of valproic acid and sodium valproate. Both are effective,^{45,46} as is an extended-release form of divalproex sodium.⁴⁷ In 1992, Hering and Kuritzky⁴⁸ evaluated the efficacy of sodium valproate in migraine treatment in a double-blind, randomized, crossover study. Sodium valproate was effective in preventing migraine or reducing the frequency, severity, and duration of attacks in 86.2% of 29 patients, whose attacks were reduced from 15.6 to 8.8 a month. In 1994, Jensen and colleagues⁴⁹ studied 43 patients who had migraine without aura in a triple-blind, placebo- and dose-controlled, crossover study of slow-release sodium valproate. In the valproate group, 50% of the patients had a reduction in migraine frequency to 50% or less, compared with 18% for placebo.

Several subsequent randomized placebo-controlled studies have confirmed these results, with significant responder rates ranging between 43% and 48%^{39,49} and dosages ranging from 500–1500 mg/d. Extended-release divalproex sodium has also been shown to be effective for migraine prevention, and compliance and the side effect profile may be more favorable with this formulation.²⁹

Nausea, vomiting, and gastrointestinal distress are the AEs that occur most commonly; their incidence decreases, however, particularly after 6 months. Later, tremor and alopecia can occur. Valproate has little effect on cognitive functions and rarely causes sedation. Rare severe AEs include hepatitis and pancreatitis. The frequency varies with the number of concomitant medications used, the patient's age, the presence of genetic and metabolic disorders, and the patient's general state of health. These idiosyncratic reactions are unpredictable.⁵⁰ Valproate is teratogenic.⁵¹

Hyperandrogenism, ovarian cysts, and obesity are of concern in young women who have epilepsy and use valproate.⁵² Absolute contraindications are pregnancy and a history of pancreatitis or a hepatic disorder. Other contraindications are thrombocytopenia, pancytopenia, and bleeding disorders.

Valproic acid is available as 250-mg capsules and as syrup (250 mg per 5 mL) (Table 3). Divalproex sodium is available as 125-, 250-, and 500-mg capsules and as a sprinkle formulation. Start with 250 to 500 mg/d in divided doses, and slowly increase the dosage. Monitor serum levels if there is a question of toxicity or compliance. The maximum recommended dosage is 60 mg/kg/d.

Topiramate

Topiramate was originally synthesized as part of a research project to discover structural analogs of fructose-1, 6-diphosphate capable of inhibiting the enzyme fructose 1, 6-bisphosphatase, thereby blocking gluconeogenesis, but it has no hypoglycemic activity. Topiramate and divalproex sodium are the only two anticonvulsants that have FDA approval for migraine prevention. Topiramate is not associated with significant reductions in estrogen exposure at dosages less than 200 mg/d. At dosages greater than 200 mg/d, there may be a dose-related reduction in exposure to the estrogen component of oral contraceptives.

Two large, pivotal, multicenter, randomized, double-blind, placebo-controlled clinical trials assessed the efficacy and safety of topiramate (50, 100, and 200 mg/d) in migraine prevention. In the first trial, the responder rate (patients with $\geq 50\%$ reduction in monthly migraine frequency) was 52% with topiramate, 200 mg/d ($P < .001$); 54% with topiramate, 100 mg/d ($P < .001$); and 36% with topiramate, 50 mg/d ($P = .039$), compared with 23% with placebo.⁵³ The 200-mg dose was not significantly more effective than the 100-mg dose. The second pivotal trial⁵⁴ had significantly more patients who exhibited at least a 50% reduction in mean monthly migraines in the groups treated with topiramate at a dosage of 50 mg/d (39%; $P = .009$), 100 mg/d (49%; $P = .001$), and 200 mg/d (47%; $P = .001$).

A third randomized, double-blind, parallel-group, multicenter trial⁵⁵ compared two dosages of topiramate (100 mg/d or 200 mg/d) with placebo or propranolol (160 mg/d). Topiramate at a dosage of 100 mg/d was superior to placebo, as measured by average monthly migraine period rate, average monthly migraine days, rate of rescue medication use, and percentage of patients with a 50% or greater decrease in average monthly migraine period rate (37% responder rate). The topiramate

Table 3
Miscellaneous medication in the preventive treatment of migraine

Angiotensin-Converting Enzyme and Angiotensin Receptor Antagonists		
Agent	Daily Dose	Comment
Lisinopril	10–40 mg	Positive small controlled trial
Candesartan	16 mg	Positive small controlled trial
Others		
Feverfew	50–82 mg	Controversial evidence
Petasites	150 mg	75 bid better than placebo in one study
Riboflavin	400 mg	Positive small controlled trial
Coenzyme Q	100–300 mg	Two positive controlled trials
Magnesium	400–600 mg	Controversial evidence

Abbreviation: bid, twice daily.

(100 mg/d) and propranolol groups were similar in change from baseline to the core double-blind phase in average monthly migraine period rate and other secondary efficacy variables.

The most common AE of topiramate is paresthesia; other common AEs are fatigue, decreased appetite, nausea, diarrhea, weight decrease, taste perversion, hypoesthesia, and abdominal pain. In the migraine trials, body weight was reduced an average of 2.3% in the 50-mg group, 3.2% in the 100-mg group, and 3.8% in the 200-mg group. Patients on propranolol gained 2.3% of their baseline body weight. The most common central nervous system AEs were somnolence, insomnia, mood problems, anxiety, difficulty with memory, language problems, and difficulty with concentration. Renal calculi can occur with topiramate use. The reported incidence is approximately 1.5%, representing a two- to fourfold increase over the estimated occurrence in the general population.⁵⁶

A rare AE is acute myopia associated with secondary angle closure glaucoma. No cases of this condition were reported in the clinical studies.⁵⁷ Oligohidrosis has been reported in association with an elevation in body temperature. Most reports have involved children.

Start at a dosage of 15 to 25 mg/d given at bedtime (see **Table 3**). Increase dosage by 15 to 25 mg/wk. Do not increase the dose if bothersome AEs develop; wait until they resolve (they usually do). If they do not resolve, decrease the drug to the last tolerable dose and then increase to a lower dose more slowly. Attempt to reach a dosage of 50 to 100 mg given twice a day. It is the author's experience that patients who tolerate the lower doses with only partial improvement often have increased benefit with higher doses. The dosage can be increased to 600 mg/d or higher.

Lamotrigine

Lamotrigine blocks voltage-sensitive sodium channels, leading to inhibition of neuronal glutamate release of glutamate. Chen and colleagues⁵⁸ reported on two patients who had migraine with persistent aura-like visual phenomena for months to years. After 2 weeks of lamotrigine treatment, both had resolution of the visual symptoms.

Although open-label studies have suggested that lamotrigine may have a select role in the treatment of patients with frequent or prolonged aura, results from a placebo-controlled study in migraine were negative. Steiner and colleagues⁵⁹ compared the safety and efficacy of lamotrigine (200 mg/d) and placebo in migraine prophylaxis in a double-blind, randomized, parallel-group trial. Improvements were greater on placebo, and these changes, which were not statistically significant, indicate that lamotrigine was ineffective for migraine prophylaxis. There were more AEs on lamotrigine than on placebo, most commonly rash. With slow dose escalation, their frequency was reduced, and the rate of withdrawal attributable to AEs was similar in both treatment groups.

Open-label studies have suggested that lamotrigine may have a select role in the treatment of migraine with aura, but no placebo-controlled studies have yet been conducted in this patient population. Lamotrigine and topiramate⁶⁰ may have a special role in the treatment of migraine with aura.

OTHER DRUGS

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists

Schrader and colleagues⁶¹ conducted a double-blind, placebo-controlled, crossover study of lisinopril, an angiotensin-converting enzyme inhibitor, in migraine prophylaxis

(see **Table 3**). Days with migraine were reduced by at least 50% in 14 participants for active treatment versus placebo and in 17 patients for active treatment versus run-in period. Days with migraine were fewer by at least 50% in 14 participants for active treatment versus placebo. Tronvik and colleagues⁶² performed a randomized, double-blind, placebo-controlled, crossover study of candesartan (16 mg), an angiotensin II receptor blocker, in migraine prevention. In a period of 12 weeks, the mean number of days with headache was 18.5 with placebo versus 13.6 with candesartan ($P = .001$) in the intention-to-treat analysis ($n = 57$). The number of candesartan responders (reduction of $\geq 50\%$ compared with placebo) was 18 (31.6%) of 57 for days with headache and 23 (40.4%) of 57 for days with migraine. AEs were similar in the two periods. In this study, the angiotensin II receptor blocker candesartan was effective, with a tolerability profile comparable to that of placebo.

Botulinum Toxin Type A

The mechanism by which botulinum toxin may prevent migraine remains poorly understood, but it is unlikely to be related to relief of muscle spasticity. Developing evidence suggests that it may modulate release of neuropeptides, such as calcitonin gene-related peptide, and influence the process of central sensitization that is associated with migraine.

Botulinum toxin type A (Botox; 0, 25, or 75 U) has not been convincingly shown to be effective for the prevention of episodic migraine with or without aura. Although the results of an early placebo-controlled study were positive using a dose of 25 U, the results were confounded by no efficacy at the higher dose (75 U) used in this study.⁶³ Three recent placebo-controlled trials^{64–66} showed no difference between different doses of botulinum toxin (105–260 U) and placebo, however. Based on a significant response to botulinum toxin type A in a subgroup of patients who had chronic migraine and were not on other preventive medications,⁶⁷ two large, pivotal, placebo-controlled studies evaluating the efficacy of botulinum toxin type A for chronic migraine are currently underway.

Medicinal Herbs and Vitamins

Feverfew (*Tanacetum parthenium*) is a medicinal herb whose effectiveness has not been totally established.⁶⁸ Riboflavin (400 mg) was effective in one placebo-controlled double-blind trial. More than half of the patients responded.⁶⁹ *petasites hybridus* (butterbur) root is a perennial shrub, a standardized extract of which (75 mg administered twice daily) was effective in a double-blind placebo-controlled study.³⁰ The most common AE was belching.

Setting Treatment Priorities

The goals of preventive treatment are to reduce the frequency, duration, or severity of attacks; improve responsiveness to acute attack treatment; improve function; and reduce disability (**Box 2**). The preventive medications with the best-documented efficacy are the beta-blockers and amitriptyline, divalproex, and topiramate. Choice is made based on a drug's proved efficacy, the physician's informed belief about medications not yet evaluated in controlled trials, the drug's AEs, the patient's preferences and headache profile, and the presence or absence of coexisting disorders (see **Table 1**).²⁷ Coexistent diseases have important implications for treatment. In some instances, two or more conditions may be treated with a single drug. If individuals have more than one disease, certain categories of treatment may be relatively contraindicated.

Box 2**Preventive drugs**

High efficacy: low to moderate AEs

Propranolol, timolol, amitriptyline, valproate, topiramate, and flunarizine

Low efficacy: low to moderate AEs

Nonsteroidal anti-inflammatory drugs: aspirin, flurbiprofen, ketoprofen, and naproxen sodium

Beta-blockers: atenolol, metoprolol, and nadolol

Calcium channel blockers: verapamil

Anticonvulsants: gabapentin

Other: fenoprofen, feverfew, vitamin B₂

Pizotifen

Unproved efficacy: low to moderate AEs

Antidepressants: doxepin, nortriptyline, imipramine, protriptyline, venlafaxine, fluvoxamine, mirtazapine, paroxetine, protriptyline, sertraline, and trazodone

Proved not effective or low efficacy

Acebutolol, carbamazepine, clomipramine, clonazepam, indomethacin, lamotrigine, nabumetone, nifedipine, nifedipine, and pindolol

The presence of a second illness provides therapeutic opportunities but also imposes certain therapeutic limitations. In some instances, two or more conditions may be treated with a single drug. There are limitations to using a single medication to treat two illnesses, however. Giving a single medication may not treat two different conditions optimally; although one of the two conditions may be adequately treated, the second illness may require a higher or lower dose, and the patient is thus at risk for the second illness not being adequately treated. Therapeutic independence may be needed should monotherapy fail. Avoiding drug interactions or increased AEs is a primary concern when using polypharmacy.

For some patients, a single medication may adequately manage comorbid conditions. This is likely to be the exception rather than the rule, however. Polytherapy may enable therapeutic adjustments based on the status of each illness. TCAs are often recommended for patients who have migraine and depression.²⁸ Appropriate management of depression often requires higher doses of TCAs, however, which may be associated with more AEs. A better approach might be to treat the depression with an SSRI or SNRI and treat the migraine with an anticonvulsant. For the patient who has migraine and epilepsy,²⁹ one may achieve control of both conditions with an antiepileptic drug, such as topiramate or divalproex sodium. Divalproex and topiramate are the drugs of choice for the patient who has migraine and bipolar illness.^{31,51} When individuals have more than one disease, certain categories of treatment may be relatively contraindicated. For example, beta-blockers should be used with caution for the depressed migraineur, whereas TCAs or neuroleptics may lower the seizure threshold and should be used with caution for the epileptic migraineur.

Although monotherapy is preferred, it is often not the best choice, and it may be necessary to combine preventive medications. Antidepressants are often used with

beta-blockers or calcium channel blockers, and topiramate or divalproex sodium may be used in combination with any of these medications.

SUMMARY

Preventive therapy plays an important role in migraine management. With the addition of a preventive medication, patients may experience reduced attack frequency and improved response to acute treatment, which can result in reduced health care resource use and improved quality of life. Despite research suggesting that a large percentage of patients who have migraine are candidates for prevention, only a fraction of these patients are receiving or have ever received preventive migraine medication.

Many preventive medications are available, and guidelines for their selection and use have been established. Because comorbid medical and psychologic illnesses are prevalent in patients who have migraine, one must consider comorbidity when choosing preventive drugs. Drug therapy may be beneficial for both disorders; however, it is also a potential confounder of optimal treatment of either.

No clinical trial data exist to predict among the various therapeutic options and biologic or clinical parameters. The impact of prevention on the natural history of migraine remains to be fully investigated.

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