Update on the Prophylaxis of Migraine

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Opinion statement

Migraine prophylaxis is a stepwise procedure with lifestyle advice followed by consideration of medications. Patients should be advised to try to maintain a regular lifestyle, with regular sleep, meals, exercise, and management of stress, perhaps through relaxation techniques or other ways that are sensible for them. If this regimen does not adequately control their migraines, preventatives are indicated. Patients can choose between evidence-based nutraceuticals such as riboflavin, feverfew, butterbur, or coenzyme Q10, or more traditional pharmacotherapeutics. Medicine choices are somewhat limited by what is available in each country, but from the full range, the medicines of first choice are beta-adrenoceptor blockers, flunarizine, topiramate, and valproic acid. Beta-adrenoceptor blockers are particularly useful in patients also suffering from hypertension or tachycardia. Following recent studies, topiramate has become a first choice for episodic as well as chronic migraine. It is the only prophylactic drug that may lead to weight loss, but it is sometimes associated with adverse cognitive effects. Valproic acid and flunarizine also have very good prophylactic properties. However, valproic acid is often associated with adverse effects, and flunarizine is unavailable in many countries, including the United States. If sequential monotherapies are ineffective, combinations of first-line drugs should be tried before advancing to drugs of second choice, which are associated with more adverse effects or have less well-established prophylactic properties. Amitriptyline should be used carefully because of its anticholinergic effects, although it is useful in comorbid tension-type headache, depression, and sleep disorders. Methysergide is very effective, but it has been supplanted or even made unavailable in many countries because of its well-described association with retroperitoneal fibrosis. Pizotifen has a slightly better safety profile but is unavailable in the United States. Aspirin is particularly useful in patients needing platelet inhibitors for other medical conditions, but the risk of gastrointestinal bleeding must be considered. The prophylactic properties of magnesium, riboflavin, and coenzyme Q10 are low at best, but their lack of severe adverse effects makes them good treatment options. Magnesium may be particularly useful during pregnancy. Lisinopril and candesartan were shown to be effective in single trials and are preferable in patients with hypertension. Acupuncture may be another alternative; although controlled trials have failed to differentiate its effect from placebo, it is at least innocuous. Botulinum toxin A is not effective in the prophylaxis of episodic migraine.

Introduction

Migraine is a central nervous system disorder involving disabling attacks of headache associated with sensitivity to afferent inputs: gastrointestinal inputs (nausea), light (photophobia), sound (phonophobia), and head movement. The 1-year prevalence is highest between the ages of 25 and 55 years, affecting about 18% of women and 6% of men. The lifetime prevalence, however, is almost 33% in women and 13% in men. Migraine usually occurs in cyclical patterns; patients may have periods of spontaneous remission of variable length. A recent article reporting on the disease burden of migraine in the United States clearly sketched the need for intensified preventive therapy [1]: 25.7% of migraineurs were candidates for preventive therapy, and preventive medication should be considered in another 13.1%. Only 13% reported current use of daily preventive medicine. The authors concluded that a substantial number of patients who might benefit from prevention do not receive it.

MIGRAINE PROPHYLAXIS

General aspects

In about 70% of patients, migraine attacks can be effectively terminated with the available acute medications. Limitations occur in nonresponders and in sudden and fast onset of migraine attacks, severe attacks associated with neurologic symptoms, and frequent attacks. These cases call for prophylactic treatment. A prerequisite for successful migraine prophylaxis is the treating physician's attitude toward the patient. Interest and compassion about the patient's headache can have a significant positive therapeutic effect, but physician disinterest and unwillingness to deal with the patient's migraine may reduce the effect of medical prophylaxis. The goal of completely abolishing migraine attacks, although appealing, has been unattainable; few drugs are more than 50% effective and patients still require acute treatment. Efficacy is assumed if the migraine frequency is reduced by at least 50%. The mode of action of most drugs used in migraine prophylaxis is only now being investigated, and our understanding of migraine pathophysiology is incomplete, hampering new medicine development. Clinical studies are made more difficult by a powerful placebo effect, which can decrease migraine frequency by up to 40%.

If pharmacologic prophylaxis is needed, it is preferable to start with a single drug and implement polypharmacy only if multiple single-drug attempts are ineffective. Compliance with migraine prophylaxis can be low. One reason is that adverse effects appear quickly while beneficial effects occur after a delay of several weeks. Another reason for the failure of prophylactic medications is that many patients do not want to take daily medications on a long-term basis, or they forget to take them.

The following sections first address pharmacologic options for migraine prophylaxis and then present practical treatment considerations for particular clinical settings. Space limitations prevent this review from addressing clinical conditions such menstrual migraine, hormone therapy, and pediatric migraine.

Beta-adrenoceptor blockers

The migraine prophylactic properties of beta-adrenoceptor blockers were incidentally detected in patients being treated for hypertension or cardiac disorders who also suffered from migraine headaches. The mode of action remains unclear, however. Both propranolol and metoprolol [2, Class I] have been convincingly shown to have migraine prophylactic activity. Atenolol [2, Class I], timolol [2, Class I], nadolol [2, Class I], and bisoprolol [2, Class I] also have a prophylactic effect, but are less well studied. No migraine prophylactic activity has been shown for acebutolol, alprenolol, oxprenolol, or pindolol [2]. A meta-analysis of propranolol migraine prophylaxis included 53 studies with a total of 2403 patients who were treated with either propranolol (160 mg) or a reference substance or placebo [3, Class I]. On average, propranolol yielded a 44% reduction in migraine activity when daily headache recordings were used to assess treatment outcome, and a 65% reduction when clinical ratings of improvement and global patient reports were used. The dropout rate due to adverse effects was 5.3%. Fatigue or loss of energy or desire are among the adverse effects patients most frequently complain about.

Calcium channel blockers

Flunarizine was developed as a calcium channel blocker to treat brain hypoxia, but when applied to migraine, it is certainly effective. It has a number of adverse effects: antiserotonergic effects (sedation, weight gain), antinoradrenergic effects such as depression, and antidopaminergic effects on the extrapyramidal motor system. Flunarizine is not approved for migraine prophylaxis in many countries even though it has shown its efficacy in many controlled trials [2, Class I]. Other calcium antagonists are only marginally effective (verapamil) [4, Class II] or ineffective (nifedipine [2, Class I] and nimodipine [2, Class I]). Verapamil is frequently used in countries where flunarizine is not available. Cyclandelate is another calcium channel blocker that is ineffective in migraine prophylaxis [2, Class I].

Anticonvulsant drugs

Based on the pathophysiologic concept of a general neuronal hyperexcitability in migraine, anticonvulsant drugs are increasingly being used in the prophylactic management of migraine.

Valproic acid has been shown in placebo-controlled trials to be effective in migraine prophylaxis [2, Class I]. Valproic acid reduces the frequency of migraine attacks

but not their severity and duration. Doses as low as 500 to 600 mg/d seem to be as effective as higher doses, although some patients benefit from doses of up to 1500 mg/d. The most frequent adverse effects include nausea, alopecia, tremor, dyspepsia, and weight gain. Valproic acid also may cause polycystic ovary syndrome in adolescents and young women. It is contraindicated in women who are pregnant or may become pregnant because of its potential to cause neural tube defects. Women need to use contraceptive measures during the reproductive years while taking valproic acid. Additional contraindications include a history of pancreatitis and hepatic and hematologic disorders.

Topiramate is a novel anticonvulsant with multiple pharmacologic mechanisms including GABA-agonist and glutamate antagonist actions, as well as inhibition of Na^+ and Ca^{2+} channels and carbonic anhydrase. Three large clinical trials have unequivocally established its effectiveness at doses from 50 mg to 200 mg daily [5–7, Class I]. Its major limitations include potential adverse cognitive effects, which can be minimized by slow titration. It should not be used in patients with renal stones or a history of renal stones. A rare effect is acute glaucoma with rapid onset of vision loss. Chronic use may be associated with sleep loss, excessive excitability, and irritability in some patients. Recent large, well-designed studies have established further novel features of topiramate. It has the potential to prevent the development of chronic migraine in episodic migraineurs [8, Class II], and can be successfully used in chronic migraine, even in the presence of medication overuse, to reduce headache days per month [9•, Class I]. Topiramate's proven efficacy, safety, and tolerability in chronic migraine [10•, Class I], and its cost-effectiveness in long-term treatment [11, Class II] have further underlined its position as an important medicine in migraine prophylaxis.

Lamotrigine was not shown to be effective in migraine headache prophylaxis [12], but it may reduce the frequency and severity of aura symptoms [13, Class III].

Gabapentin was superior to placebo in migraine prophylaxis in a recent clinical trial [14, Class II], but the analysis was less than optimal and the result awaits replication.

Zonisamide is another anticonvulsant drug that may be effective for refractory adult [15, Class III] and pediatric [16, Class III] migraine, according to open-label studies. A retrospective chart review of 33 patients with refractory migraine did not find a beneficial effect, however [17].

Serotonin receptor antagonists

Methysergide [18, Class I], a 5-HT_2 receptor antagonist and 5-$HT_{1B/D}$ receptor agonist, and pizotifen [19, Class I], a 5-HT_2 receptor antagonist, are clearly effective in migraine prophylaxis, but the rate of adverse effects is high. Methysergide can (rarely) lead to retroperitoneal, pulmonary, and endocardial fibrosis and therefore should not be given for longer than 6 months. It raises the mean blood pressure and constricts peripheral vessels (eg, coronary arteries) and is therefore contraindicated in patients with cardiovascular risk factors. Further adverse events are sedation, dizziness, edema, and weight gain. Few cases of cardiac valvular lesions have been reported with the use of methysergide. Its use should now be restricted to patients with cluster headache and to migraine patients who do not respond to other prophylactics. Apart from fibrosis and vasoconstrictive effects, pizotifen shares the same spectrum of adverse events as methysergide and should be considered only for patients refractory to other prophylactic drugs.

Aspirin and NSAIDs

Following initial reports from the Physicians' Health Study about a prophylactic effect of aspirin, a recent study compared 300 mg of aspirin with 200 mg of metoprolol in 270 migraine patients. Aspirin was less effective than metoprolol (responder rate 42.7% vs 56.9%) but had fewer adverse effects [20, Class I]. A smaller number of studies have shown that naproxen [21], ketoprofen, and other NSAIDs possess migraine prophylactic properties, but clinical experiences teach that the effect is small and gastrointestinal adverse effects limit use. Furthermore, the potential to induce medication-overuse headache should be considered.

Antidepressants

Amitriptyline, a tricyclic antidepressant, is the pharmacologic treatment of choice in chronic tension-type headache, and it has also proved effective in migraine prophylaxis [22,23, Class I]. The trials were small, however, and not adequately powered. An inherent problem is the numerous adverse effects, especially anticholinergic effects and weight gain. Also, amitriptyline lowers the seizure threshold and should not be used in patients with a history of seizures who are no longer taking anticonvulsants. A history of cardiac disease is another contraindication because amitriptyline and other tricyclic antidepressants have been associated with arrhythmias and sudden death in this population. Amitriptyline is indicated particularly for patients who suffer from depression, those refractory to drugs of first choice, or those with primary headache (either tension-type headache or chronic migraine) on 15 days or more per month.

Venlafaxine, a serotonin-noradrenaline reuptake inhibitor, was more effective than placebo in one small study [24, Class II], but this result awaits replication in larger clinical studies. Other antidepressants (eg, monoamine reuptake inhibitors [25] and selective serotonin reuptake inhibitors [26]) have not been effective in migraine prophylaxis.

Inhibitors of the renin angiotensin system

Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to be prophylactically effective at a dose of 10 mg twice daily in a small, double-blind,

Table 1. Indications for prophylactic pharmacotherapy in migraine

More than 3–4 migraine attacks per month
Migraine attacks with no satisfactory response to acute therapy (eg, with triptans)
Intolerable adverse effects with acute attack treatment
Migraine attacks lasting longer than 48 hours and regularly leading to headache recurrence after triptan administration
Migraine attacks that are perceived as intolerable by the patient
Complicated migraine attacks (persistent neurologic deficits lasting > 7 days)
History of migrainous infarct
Ineffectiveness of nonpharmacologic prophylactic strategies (regular sleep-wake cycle, stress reduction, regular meals, regular moderate exercise, avoiding alcohol if associated with attacks)

placebo-controlled crossover trial [27, Class I]. Adverse effects to be considered include arterial hypotension, dry cough, and fatigue. Candesartan, an angiotensin II receptor antagonist, was shown to effectively reduce headache days per month at a dose of 16 mg/d [28, Class I]. Furthermore, an open study of olmesartan in migraineurs with comorbid hypertension resulted in a significant decrease of monthly attacks [29, Class III]. However, the effectiveness of inhibitors of the renin angiotensin system in migraine prophylaxis awaits confirmation in larger studies before they can be classified as first-choice treatment options.

Other drugs and treatments

Petasites (butterbur), an extract from *Petasites hybridus*, has been investigated in a few clinical trials, which suggest a small prophylactic effect [30–32, Class II]. Some patients prefer this drug because of its perceived "natural" origin, but liver damage is a potential adverse effect. Our clinical experience is not very favorable, so larger multicenter studies are needed before recommendations regarding its regular use can be given.

Feverfew (*Tanacetum parthenium*) is an extract from dried chrysanthemum leaves. Early results investigating the effect of feverfew in migraine prophylaxis were criticized for variations in dosage of the active ingredient parthenolide in the available preparations. Two recent randomized controlled trials have demonstrated a prophylactic effect [33,34] at a dose of 3 × 6.25 mg. There has been one other positive study [35] and two further negative studies [36,37], so more data and more experience are necessary to make firm conclusions.

Magnesium is the subject of controversial study results regarding its prophylactic potential. A randomized controlled trial in 81 women was positive [38]; another in 69 patients was negative [39]. Although the evidence is not strong in favor of magnesium, it is a good alternative or add-on treatment option owing to its favorable safety profile.

Substances involved in the Krebs cycle have been investigated for migraine prophylaxis because mitochondrial disorders have been thought to be associated with migraine. Riboflavin was effective in one single-center, placebo-controlled trial [40, Class II]. In another study of 42 migraineurs, coenzyme Q10 was reported to be effective [41, Class II]. A third study in 54 migraineurs investigated thioctic acid and did not find a favorable effect [42]. The reports on riboflavin and coenzyme Q10 need to be confirmed in larger, multicenter trials before the drugs can be recommended as first-choice or second-choice treatments.

Botulinum toxin A has long been postulated to have a prophylactic effect in migraine, but there is considerable debate. However, all available randomized, double-blind, placebo-controlled trials [43•,44,45,46•, Class I] except one [47], using different preparations and dosages, have shown no reduction of headache frequency when injecting in either predefined areas or trigger points. Thus, botulinum toxin A cannot be recommended for the prophylaxis of episodic migraine. Trials in chronic migraine are under way.

Acupuncture is the subject of recently published reports of randomized, sham-controlled trials specifically investigating its use in migraine prophylaxis [48•–50•, Class I]. The results show equal efficacy for "classic" acupuncture, sham acupuncture, and standard preventive drug therapy; all kinds of therapies led to a significant reduction of headache days compared with baseline. We thus have to conclude that although acupuncture can significantly improve migraine headache, this effect is not specific for "classic" acupuncture.

Homeopathy has clearly been shown to be ineffective in migraine prevention [51, Class I].

RECOMMENDATIONS AND PRACTICAL CONSIDERATIONS

Having established the migraine diagnosis, the first step is to educate the patient. Patients with migraine need to know about possible trigger factors such as alcohol and the impact of lifestyle on migraine attack frequency. A regular sleeping pattern, regular meals, and avoidance of excessive stress should be mandatory for every patient. The first "treatment recommendations" comprise nonpharmacologic methods such as relaxation techniques [52, Class I] and regular exercise [53, Class III]. If these methods are insufficient, a pharmacologic approach is indicated (Table 1). The approvals of the regulatory

agency of each country need to be considered; only propranolol, timolol, topiramate, and valproic acid are approved for migraine prophylaxis by the US Food and Drug Administration (FDA).

Beta-adrenoceptor blockers should be considered first [2, Class I]. Hypotension is often feared but usually does not occur in young patients who exercise regularly; in elderly patients with comorbid hypertension, this effect may be appreciated. Topiramate has advanced into the group of drugs of first choice following the studies of 2004 [5–7, Class I]. Many patients are attracted by the potential weight loss, a unique feature among migraine prophylactic drugs, but they need to be informed about the potential adverse effects, most notably cognitive impairment and paresthesias. Valproic acid is another drug with excellent antimigraine properties [2, Class I]. Like topiramate, it should particularly be considered in patients with comorbid epilepsy. Unfortunately, adverse effects are more frequent, most notably weight gain, tremor, and hair loss. Flunarizine has a very good prophylactic effect [2, Class I], but it is not available in many countries, including the United States. If multiple monotherapies are ineffective, combination therapies should be tried before advancing to drugs of second choice, which are associated with more adverse effects or whose prophylactic effect is less well-established. There are no controlled trials showing the superiority of combination therapy over monotherapy, however.

Amitriptyline is particularly suitable in patients with comorbid chronic tension-type headache or chronic migraine, sleep disorders, or depression [22,23, Class I]. However, the known anticholinergic effects preclude its use, for example, in patients with glaucoma, urinary retention, and cardiac arrhythmias. Methysergide [18, Class I] and pizotifen [19, Class I] are effective migraine prophylactic agents in migraineurs with resistant headache and a high migraine frequency. Neither is currently available in the United States. The vasoconstrictive properties of methysergide cause it to be contraindicated for patients with coronary heart disease, myocardial infarction, ischemic stroke, and other vascular disorders. Moreover, concomitant use of triptans is not recommended. Methysergide must not be used longer than 6 months because of its potential to cause retroperitoneal, pulmonary, or cardiac fibrosis. Low-dose aspirin [20, Class I] may be particularly suited to patients who need a platelet inhibitor because of other medical conditions like ischemic vascular events. However, the net effect is not pronounced and the potential for gastrointestinal bleeding with long-term use should be considered. Although study results are controversial, the virtual lack of adverse effects always allows the use of magnesium, which is also safe during pregnancy. Lisinopril [27, Class I] and candesartan [28, Class I] interact with the renin-angiotensin system and may be considered, particularly in patients with hypertension.

Alternatives should be considered only if these drugs are not effective. Acupuncture is of particular interest because it clearly has prophylactic properties [48•–50•, Class I]. However, these properties are not a particular feature of the "classic" technique, as sham acupuncture is also effective. The results regarding the effect of feverfew are controversial [33–37], and its use in clinical practice is limited because of a lack of adequate preparations. Commercially available preparations vary widely in the amount of the active ingredient, parthenolide. Lamotrigine does not reduce migraine headaches but may reduce the frequency of auras [13, Class III]. Other alternatives include gabapentin, zonisamide, and riboflavin.

Treatment

Diet and lifestyle

- Clinical experience teaches that a regular lifestyle can improve migraine headaches. Patients should adhere to a regular sleeping pattern (including weekends), regular meals, and avoidance of excessive stress.

Pharmacologic treatment

- Pharmacologic prophylaxis (Table 2) has the following aims: 1) reducing the number of migraine days per month, 2) reducing headache pain and associated symptoms, 3) shortening individual attacks, 4) improving the effect of acute medication, and 5) preventing medication-overuse headache.
- Preventive therapy is considered effective if the number of headache days per month is reduced by at least 50%. Response or nonresponse can only be established if the drug has been taken for at least 3 months, standard dosages have been used, and the drug was not stopped prematurely because of adverse effects. To minimize adverse effects, titration must be performed slowly.

Table 2. Drugs in migraine prophylaxis

Drugs of first choice
Propranolol, metoprolol, bisoprolol
Flunarizine*
Topiramate
Valproic acid
Drugs of second choice
Amitriptyline
Methysergide*
Pizotifen*
Low-dose aspirin
Magnesium
Lisinopril
Candesartan
Alternative therapies (drugs of third choice)
Acupuncture
Lamotrigine (only with severe aura symptoms)
Gabapentin
Zonisamide
Venlafaxine
Riboflavin
Feverfew

*Unavailable in the United States.

Drugs of first choice

Beta-adrenoceptor blockers

Standard dosage	Metoprolol 50–200 mg, propranolol 40–240 mg, bisoprolol 5–10 mg [2, Class I].
Contraindications	AV block, bradycardia, sick sinus syndrome, cardiac failure, asthma, diabetes mellitus, orthostatic dysregulation, depression.
Main drug interactions	Drugs inhibiting cardiac conductance (eg, verapamil, cardiac glycosides, other antiarrhythmics). Propranolol inhibits metabolism of rizatriptan, so only 5 mg of rizatriptan may be used for treatment of attacks.
Main side effects	Bradycardia, hypotension, fatigue, dizziness, hypoglycemia, bronchospasm, sleep disorders.
Special points	Consider use with comorbid hypertension, tachycardia.
Cost	Propranolol: 60 80-mg tablets cost $13.99; metoprolol: 60 100-mg tablets cost $17.99; bisoprolol: 30 10-mg tablets cost $32.99.

Flunarizine

Standard dosage	5–15 mg [2, Class I].
Contraindications	Focal dystonia, pregnancy, breastfeeding, depression, familial Parkinson's disease.
Main drug interactions	Increased sleepiness with concomitant use of sedatives and alcohol.
Main side effects	Fatigue, weight gain, gastrointestinal symptoms, depression, hyperkinesias, tremor, Parkinson-like symptoms.
Special points	Should not be used longer than 6 months. Unavailable in the United States.
Cost	100 5-mg capsules cost 34.60 euros (Germany).

Valproic acid

Standard dosage	500–1200 mg [2, Class I].
Contraindications	Liver disease, pregnancy (neural tube defects), alcohol abuse, pancreatitis.
Main drug interactions	Accelerated degradation with concomitant use of enzyme inductors such as carbamazepine; prolonged degradation with concomitant use of lamotrigine.
Main side effects	Fatigue, dizziness, tremor, weight gain, hair loss, liver dysfunction.
Special points	Consider use with comorbid epilepsy.
Cost	120 250-mg capsules cost $48.99.

Topiramate

Standard dosage	25–200 mg [5–7, Class I].
Contraindications	Renal or hepatic insufficiency, kidney stones, narrow angle glaucoma, pregnancy.
Main drug interactions	May worsen metabolic acidosis. Induces cytochrome P450 enzymes in doses greater than 200 mg and inactivates oral contraceptives.
Main side effects	Fatigue, word-finding difficulties, memory disturbances, weight loss, metabolic acidosis, renal stones, paresthesias, taste alterations, psychosis, narrow-angle glaucoma.
Special points	Multiple mechanisms of action (blocks currency-dependent Na^+ and Ca^{2+} channels, aggravates gamma-aminobutyric acid [GABA] effect, inhibits glutamate effect at AMPA receptors, inhibits carbonic anhydrase). Renal elimination. Cognitive adverse effects can be minimized by very slow titration. Consider use with comorbid epilepsy.
Cost	60 25-mg tablets cost $139.99.

Drugs of second choice

Amitriptyline

Standard dosage	25–150 mg [22,23, Class I].
Contraindications	Cardiac arrhythmias, narrow angle glaucoma, prostate adenoma with urinary retention, pregnancy.
Main drug interactions	Sedative effects increased with concomitant use of tranquilizers or alcohol.
Main side effects	Dry mouth, fatigue, dizziness, hypotension, sweating, urinary retention, inner unrest, impotence.
Special points	Consider with comorbid tension-type headache, depression, or sleep disorders. Not FDA-approved.
Cost	30 25-mg tablets cost $9.99.

Methysergide

Standard dosage	2–8 mg [18, Class I].
Contraindications	Hypertension, coronary heart disease, myocardial infarction, pregnancy, breastfeeding.
Main drug interactions	Triptans may not be used for attack treatment owing to potential additive vasoconstrictive effects.
Main side effects	Fatigue, weight gain, hypertension, muscle pain, nausea, gastrointestinal pain.
Special points	Treatment period should be confined to 6 months. Unavailable in the United States.
Cost	100 2-mg tablets cost $129.00 (Canada).

Pizotifen

Standard dosage	0.5–4 mg [19, Class I].
Contraindications	Glaucoma, urinary retention, cardiac arrhythmias, pregnancy.
Main drug interactions	Avoid other anticholinergic drugs such as tricyclic antidepressants.
Main side effects	Fatigue, weight gain, increased appetite, dry mouth, constipation.
Special points	Slowly taper off the drug after treatment period to avoid rebound headaches. Unavailable in the United States.
Cost/cost-effectiveness	28 0.5-mg tablets cost £2.82 (United Kingdom).

Acetylsalicylic acid

Standard dosage	100–300 mg [20, Class I].
Contraindications	Gastrointestinal ulcers, bleeding disorder, anticoagulation therapy, asthma, pregnancy.
Main drug interactions	Anticoagulants, corticosteroids.
Main side effects	Abdominal pain, gastrointestinal ulcers, prolonged bleeding time.
Special points	Consider in patients after myocardial infarction, ischemic stroke, or migrainous stroke. Not FDA-approved.
Cost	Many different brands and generics; 300 325-mg tablets cost about $4.50.

Magnesium

Standard dosage	2 × 300 mg [38,39, Class III].
Contraindications	None.
Main drug interactions	None.
Main side effects	Diarrhea.
Special points	Consider during pregnancy if pharmacologic prophylaxis is needed. Not FDA-approved.
Cost	Many brands; 100 250-mg tablets cost about $2.99.

Lisinopril

Standard dosage	5–20 mg [27, Class I].
Contraindications	Pregnancy, breastfeeding, renal impairment.
Main drug interactions	Other antihypertensives.
Main side effects	Hypotension, fatigue, dry cough, rash.
Special points	Consider with comorbid hypertension. Not FDA-approved.
Cost	60 5-mg tablets cost $31.99.

Candesartan

Standard dosage	4–16 mg [28, Class I].
Contraindications	Pregnancy, breastfeeding, renal impairment.
Main drug interactions	Other antihypertensives.
Main side effects	Hypotension, fatigue.
Special points	Consider with comorbid hypertension. Not FDA-approved.
Cost	30 8-mg tablets cost $64.99.

Physical/speech therapy and exercise

- A small, open, uncontrolled study has shown that regular aerobic exercise reduces migraine attack frequency [53, Class III].
- Relaxation training (Jacobson training) and biofeedback are effective in the prevention of migraine [52, Class I].

Other treatments

- Acupuncture has been shown to be effective in migraine prophylaxis. This is not a specific effect of "classic" acupuncture; sham acupuncture yields the same results [48•–50•, Class I].

Emerging therapies

- There are preliminary results regarding the effectiveness of zonisamide [15–17, Class III], but clinical trials are needed before a recommendation regarding its use can be given.

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Lipton RB, Bigal ME, Diamond M, et al.: **Migraine prevalence, disease burden, and the need for preventive therapy.** *Neurology* 2007, **68:**343–349.
2. Limmroth V, Michel MC: **The prevention of migraine: a critical review with special emphasis on beta-adrenoceptor blockers.** *Br J Clin Pharmacol* 2001, **52:**237–243.
3. Holroyd KA, Penzien DB, Cordingley GE: **Propranolol in the management of recurrent migraine: a meta-analytic review.** *Headache* 1991, **31:**333–340.
4. Solomon GD, Steel JG, Spaccavento LJ: **Verapamil prophylaxis of migraine: a double-blind, placebo-controlled study.** *JAMA* 1983, **250:**2500–2502.
5. Brandes J, Saper J, Diamond M, et al.: **Topiramate for migraine prevention: a randomized controlled trial.** *JAMA* 2004, **291:**965–973.
6. Diener HC, Tfelt-Hansen P, Dahlöf C, et al.: **Topiramate in migraine prophylaxis: results from a placebo-controlled trial with propranolol as an active control.** *J Neurol* 2004, **251:**943–950.
7. Silberstein SD, Neto W, Schmitt J, et al.: **Topiramate in migraine prevention: results of a large controlled trial.** *Arch Neurol* 2004, **61:**490–495.
8. Limmroth V, Biondi D, Pfeil J, Schwalen S: **Topiramate in patients with episodic migraine: reducing the risk for chronic forms of headache.** *Headache* 2007, **47:**13–21.
9.• Diener HC, Bussone G, Van Oene J, et al.: **Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study.** *Cephalalgia* 2007, **27:**814–823.
Clinical trial that establishes topiramate as effectively reducing migraine days in chronic migraine, even with medication overuse.
10.• Silberstein SD, Lipton RB, Dodick DW, et al.: **Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial.** *Headache* 2007, **47:**170–180.
Second clinical trial that shows the effectiveness of topiramate in chronic migraine.
11. Silberstein SD, Feliu AL, Rupnow MF, et al.: **Topiramate in migraine prophylaxis: long-term impact on resource utilization and cost.** *Headache* 2007, **47:**500–510.
12. Steiner TJ, Findley LJ, Yuen AWC: **Lamotrigine versus placebo in the prophylaxis of migraine with and without aura.** *Cephalalgia* 1997, **17:**109–112.
13. Lampl C, Katsarava Z, Diener HC, Limmroth V: **Lamotrigine reduces migraine aura and migraine attacks in patients with migraine with aura.** *J Neurol Neurosurg Psychiatry* 2005, **76:**1730–1732.
14. Mathew NT, Rapoport A, Saper J, et al.: **Efficacy of gabapentin in migraine prophylaxis.** *Headache* 2001, **41:**119–128.
15. Drake ME Jr, Greathouse NI, Renner JB, Armentbright AD: **Open-label zonisamide for refractory migraine.** *Clin Neuropharmacol* 2004, **27:**278–280.
16. Pakalnis A, Kring D: **Zonisamide prophylaxis in refractory pediatric headache.** *Headache* 2006, **46:**804–807.
17. Ashkenazi A, Benlifer A, Korenblit J, Silberstein SD: **Zonisamide for migraine prophylaxis in refractory patients.** *Cephalalgia* 2006, **26:**1199–1202.
18. Silberstein SD: **Methysergide.** *Cephalalgia* 1998, **18:**421–435.
19. Cerbo R, Casacchia M, Formisano R, et al.: **Flunarizine-pizotifen single-dose double-blind cross-over trial in migraine prophylaxis.** *Cephalalgia* 1986, **6:**15–18.

20. Diener HC, Hartung E, Chrubasik J, et al.: **A comparative study of acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomised, controlled, double-blind, parallel group phase III study.** *Cephalalgia* 2001, **21:**140–144.
21. Welch KMA: **Naproxen sodium in the treatment of migraine.** *Cephalalgia* 1986, **6:**85–92.
22. Couch JR, Hassanein RS: **Amitriptyline in migraine prophylaxis.** *Arch Neurol* 1979, **36:**695–699.
23. Ziegler DK, Hurwitz A, Hassanein RS, et al.: **Migraine prophylaxis. A comparison of propranolol and amitriptyline.** *Arch Neurol* 1987, **44:**486–489.
24. Ozyalcin SN, Talu GK, Kiziltan E, et al.: **The efficacy and safety of venlafaxine in the prophylaxis of migraine.** *Headache* 2005, **45:**144–152.
25. Kuritzky A, Zoldan Y, Melamed E: **Selegeline, a MAO B inhibitor, is not effective in the prophylaxis of migraine without aura—an open study.** *Headache* 1992, **32:**416.
26. Moja PL, Cusi C, Sterzi RR, Canepari C: **Selective serotonin re-uptake inhibitors (SSRIs) for preventing migraine and tension-type headaches.** *Cochrane Database Syst Rev* 2005:CD002919.
27. Schrader H, Stovner LJ, Helde G, et al.: **Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study.** *BMJ* 2001, **322:**19–22.
28. Tronvik E, Stovner L, Helde G, et al.: **Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial.** *JAMA* 2003, **289:**65–69.
29. Charles JA, Jotkowitz S, Byrd LH: **Prevention of migraine with olmesartan in patients with hypertension/prehypertension.** *Headache* 2006, **46:**503–507.
30. Grossmann M, Schmidramsl H: **An extract of *Petasites hybridus* is effective in the prophylaxis of migraine.** *Inter J Clin Pharmacol Therapeutics* 2000, **38:**430–435.
31. Diener HC, Rahlfs VW, Danesch U: **The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria.** *Eur Neurol* 2004, **51:**89–97.
32. Lipton RB, Gobel H, Einhaupl KM, et al.: ***Petasites hybridus* root (butterbur) is an effective preventive treatment for migraine.** *Neurology* 2004, **63:**2240–2244.
33. Diener HC, Pfaffenrath V, Schnitker J, et al.: **Efficacy and safety of 6.25 mg t.i.d. feverfew CO2-extract (MIG-99) in migraine prevention—a randomized, double-blind, multicentre, placebo-controlled study.** *Cephalalgia* 2005, **25:**1031–1041.
34. Pfaffenrath V, Diener HC, Fischer M, et al.: on behalf of the Investigators. **The efficacy and safety of *Tanacetum parthenium* (feverfew) in migraine prophylaxis—a double-blind, multicentre, randomized placebo-controlled dose-response study.** *Cephalalgia* 2002, **22:**523–532.
35. Palevitch D, Earon G, Carasso R. **Feverfew *(Tanacetum parthenium)* as a prophylactic treatment for migraine—a double-blind placebo-controlled study.** *Phytother Res* 1997, **11:**508–511.
36. Murphy JJ, Heptinstall S, Mitchell JRA: **Randomized double-blind placebo-controlled trial of feverfew in migraine prevention.** *Lancet* 1988, **2:**189–192.
37. Johnson ES, Kadam NP, Hylands DM, Hylands PJ: **Efficacy of feverfew as a prophylactic treatment of migraine.** *BMJ* 1985, **291:**569–573.
38. Peikert A, Wilimzig C, Köhne-Volland R: **Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study.** *Cephalalgia* 1996, **16:**257–263.
39. Pfaffenrath V, Wessely P, Mener C, et al.: **Magnesium in the prophylaxis of migraine—a double-blind placebo-controlled study.** *Cephalalgia* 1996, **16:**436–440.
40. Schoenen J, Jacquy J, Lenaerts M: **Effectiveness of high-dose riboflavin in migraine prophylaxis—a randomized controlled trial.** *Neurology* 1998, **50:**466–470.
41. Sandor PS, Di Clemente L, Coppola G, et al.: **Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial.** *Neurology* 2005, **64:**713–715.
42. Magis D, Ambrosini A, Sandor P, et al.: **A randomized double-blind placebo-controlled trial of thioctic acid in migraine prophylaxis.** *Headache* 2007, **47:**52–57.
43.• Aurora SK, Gawel M, Brandes JL, et al.: **Botulinum toxin type A prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study.** *Headache* 2007, **47:**486–499.

One in a series of clinical trials that have shown that botulinum toxin A is not effective in migraine prophylaxis.

44.• Elkind AH, O'Carroll P, Blumenfeld A, et al.: **A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis.** *J Pain* 2006, **7:**688–696.

One in a series of clinical trials that have shown that botulinum toxin A is not effective in migraine prophylaxis.

45. Evers S, Vollmer-Haase J, Schwaag S, et al.: **Botulinum toxin A in the prophylactic treatment of migraine—a randomized, double-blind, placebo-controlled study.** *Cephalalgia* 2004, **24:**838–843.
46.• Relja M, Poole AC, Schoenen J, et al.: **A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches.** *Cephalalgia* 2007, **27:**492–503.

One in a series of clinical trials that have shown that botulinum toxin A is not effective in migraine prophylaxis.

47. Silberstein S, Mathew N, Saper J, Jenkins S: **Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group.** *Headache* 2000, **40:**445–450.
48.• Diener HC, Kronfeld K, Boewing G, et al.: **Efficacy of acupuncture for the prophylaxis of migraine: a multicentre randomised controlled clinical trial.** *Lancet Neurol* 2006, **5:**310–316.

One in a series of studies showing the effectiveness of acupuncture in migraine prophylaxis. However, the effect is not specific for "classic" acupuncture and is also seen with sham procedures.

49.• Linde K, Streng A, Jurgens S, et al.: **Acupuncture for patients with migraine: a randomized controlled trial.** *JAMA* 2005, **293:**2118–2125.

One in a series of studies showing the effectiveness of acupuncture in migraine prophylaxis. However, the effect is not specific for "classic" acupuncture and is also seen with sham procedures.

50.• Alecrim-Andrade J, Maciel-Junior JA, Cladellas XC, et al.: **Acupuncture in migraine prophylaxis: a randomized sham-controlled trial.** *Cephalalgia* 2006, **26:**520–529.

One in a series of studies showing the effectiveness of acupuncture in migraine prophylaxis. However, the effect is not specific for "classic" acupuncture and is also seen with sham procedures.

51. Ernst E: **Homeopathic prophylaxis of headaches and migraine? A systematic review.** *J Pain Symptom Manage* 1999, **18:**353–357.
52. Campbell J, Penzien DB, Wall EM: **Evidence-based guidelines for migraine headache: behavioral and physical therapy.** Available at http://www.aan.com/professionals/practice/pdfs/gl0089.pdf. Accessed July 2007.
53. Köseoglu E, Akboyraz A, Soyuer A, Ersoy AO: **Aerobic exercise and plasma beta endorphin levels in patients with migrainous headache without aura.** *Cephalalgia* 2003, **23:**972–976.