Chapter 59

Prioritizing Prophylactic Treatment of Migraines

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The present chapter focuses on general information necessary for the physician to advise patients about the choice of prophylactic drugs. For general recommendations on when to use prophylactic treatment, on the use of headache diaries, and on tailoring the dose to the individual patient, consult Chapter 47 on the general and pharmacologic approach to migraine management.

The first priority is to use the drug that has the highest benefit–risk ratio. At first glance, this task might seem easy based on numerous publications about pharmacologic prophylaxis of migraine. Review of these studies and clinical trials show, however, that most prophylactic drugs have an approximate 40% advantage over placebo in reducing attack frequency (see Chapters 54, 55, 56, 57, and 58). In part, this may be artifactual, as a result of publication bias occasioned by authors, industrial companies, and editors having a preference for positive results. If a trial of an active drug does not produce better results than placebo, or if the new drug has inferior benefits compared with those of an established drug, the trial often remains unpublished. In addition, comparability is seldom substantiated by narrow confidence intervals. Even in small trials with grossly inadequate power, the lack of significance is often confused with lack of difference (see Chapter 7). Side effects are often reported as infrequent for active drugs as for placebo in controlled clinical trials, probably because of either the inclusion of too few patients in the trial or an inadequate system for reporting adverse events (see Chapter 7). In clinical practice, prophylactic antimigraine drugs often have side effects that limit their use.

In addition to these limitations in transferring results from controlled trials to clinical practice, it should be kept in mind that migraine patients recruited for controlled trials are often hard-core patients from specialized clinics who have participated in multiple trials. Controlled trials are probably not a true reflection of general practice.

Our ranking of prophylactic drugs (summarized in Table 59-1) is based on a combination of our judgment of the publications and our personal experience and may differ from the experience of others. The table gives a ranking, from + to ++++ (see Table 59-1), for clinical efficacy, scientific validity of the drug trials, and potential for side effects. The table also includes side effects and contraindications. For a more extensive review of side effects and contraindications, the reader should consult the individual chapters. Drug contraindications should be known before a drug is considered for use. The potential for side effects is an important factor in the choice of prophylactic drug, because use may be prolonged over months to years. Side effects may cause noncompliance with a drug that is otherwise effective. The potential side for effects ranges from verapamil (+), candesartan (+) and clonidine (+), which have few side effects, to methysergide (++++), which potentially have serious fibrotic complications after long-term treatment. Accordingly, methysergide can never be the drug of first choice despite its effectiveness.

Physicians also should consider the scientific proof for efficacy when choosing a drug; the contemporary patient is often inquisitive. The literature is extremely varied with regard to the scientific support of drugs used in migraine prophylaxis (see Table 59-1). Some old, well-established drugs (e.g., methysergide, ranked ++) have not been evaluated using contemporary methods (see Chapter 55); for verapamil (+), results for only 41 patients in three controlled trials have been published (see Chapter 56). In contrast, the β-blockers, especially propranolol (++++), the calcium antagonist flunarizine (++++), and sodium valproate/divalproex (+++) and topiramate (++++) were evaluated extensively in controlled clinical trials and found superior to placebo (see Chapters 54, 56, and 57).

Concerning clinical efficacy, the drugs are ranked from the less efficacious drugs (+), such as verapamil and clonidine, to the most effective drugs (++++), such as

TABLE 59-1 Clinical Efficacy,[a] Scientific Proof of Efficacy,[b] and Potential for Side Effects[a] Rated on a Scale From + to ++++ for Some Drugs Used in Migraine Prophylaxis

Drug	*Clinical Efficacy*	*Scientific Proof for Efficacy*	*Side Effect Potential*	*Examples of Side Effects (Examples of Contraindications)*
β-blockers (propranolol, metoprolol, atenolol, nadolol, timolol, bisoprolol)	++++	++++	++	Tiredness, cold extremities, vivid dreams, depression (asthma, brittle diabetes, AV conduction defects)
Antiepileptics				
Sodium valproate/ divalproex	++ or +++	+++	+++	Weight gain, tremor, hair loss (thrombocytopenia, liver disease,[c] pregnancy)
Topiramate	+++	++++	+++	Sedation, paresthesia (pregnancy)
Antiserotonin drugs				
Methysergide	++++	++	++++	Chronic use: fibrotic disorders (cardiovascular disease)
Pizotifen	++	++	+++	Weight gain, sedation (obesity)
Calcium antagonists				
Flunarizine	+++	++++	+++	Sedation, weight gain (depression, Parkinson)
Verapamil	+	+	+	Constipation (bradycardia, AV conduction defects)
NSAIDs				
Naproxen	++	+++	++	Dyspepsia, peptic ulcers (active peptic ulcers)
Tolfenamic acid	++	+++	++	Dyspepsia, peptic ulcers (active peptic ulcers)
Miscellaneous				
Amitriptyline	++	++	++	Sedation, dry mouth, weight gain (glaucoma)
Lisinopril	++	++	++	Cough (hypotension)
Candesartan	++	++	+	Orthostatic hypotension (liver disease)
Clonidine	+	+	+	Dry mouth
Dihydroergotamine	++	+	++	Nausea, diarrhea (ischemic heart disease)

[a] The rating is based on a combination of the published literature and our personal experience.
[b] As judged by the authors (apparently conflicting with the overwhelming majority of comparative trials claiming equipotency of two drugs. This claim of comparability is probably because of small trials; see text).
[c] In most countries, routine hematologic screening and biochemical tests of liver function are considered necessary prior to starting and during valproate or divalproex treatment.
Abbreviations: AV, atrioventricular; DHE, dihydroergotamine; NSAIDs, nonsteroidal anti-inflammatory drugs.

β-blockers and methysergide, whereas other drugs, such as flunarizine (+++) , topiramate (+++), pizotifen (+++), sodium valproate/divalproex (++), naproxen (++), tolfenamic acid (++), amitriptyline (++), dihydroergotamine (++), candesartan (++), and lisinopril (++) are judged to be intermediate in their effectiveness (see Table 59-1). This ranking of clinical efficacy should be considered along with the ranking for potential for side effects (see Table 59-1). The options, documented outcomes, relative efficacy, and side effects always should be discussed with the patient.

In general, the drugs of first choice are the β-blockers, which are in practice the most frequently used agents. No trials have been performed to show the superiority of one of the effective β-blockers over another (see Chapter 54). When β-blockers are not effective or are contraindicated, the choice of a prophylactic drug depends to some extent on local availability (e.g., pizotifen and flunarizine are not available in United States); based on the ratios for efficacy/side effects the choice can be either pizotifen, flunarizine, sodium valproate/divalproex, topiramate, one of the nonsteroidal anti-inflammatory drugs listed, lisinopril, candesartan, or amitriptyline. Verapamil, clonidine, dihydroergotamine, and methysergide (in a specialist's hands) probably should be used only as last resort. Finally, the physician should check the patient at 2- to 3-month intervals, the patients should keep a simple headache diary for monitoring migraine attack frequency (see Fig. 1 of Chapter 47), and the efficacy/safety ratio should be discussed with the patient, who is ultimately the judge of the prophylactic treatment.