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Migraine Prophylaxis

Principles, goals and drug therapy

Introduction

Migraine headache is a chronic condition characterized by repeated, debilitating attacks of severe, usually unilateral, pulsatile headaches, often accompanied by nausea, vomiting, photophobia and a variety of other symptoms. Classical migraine is associated with prodromal symptoms referred to as aura; common migraine usually lacks these prodromal symptoms. It is a disorder with a prevalence of 17.6% in American females and 5.7% in American males.¹ The prevalence of migraine begins to increase starting at age 12, peaks at about age 38, and declines thereafter. It is approximately twice as common in boys as in girls at age 12, becomes 3.3 times as common in women as men between the ages of 42-44 and decreases to 2.5 times as common in women by age 70.² Although there is a common misperception that migraine is more common in those who have the time and money to seek treatment, the American Migraine Study has provided documentation that its incidence actually decreases with higher socioeconomic status.¹

Among the respondents to the American Migraine Study, 25% of the women had four or more severe attacks monthly, 35% had three severe attacks monthly and 40% had one severe attack per month or less.¹ The male respondents reported a similar frequency of attacks. Over 80% of respondents reported at least some degree of disability with their headaches, including severe disability or the need for bed rest in one-fourth of cases. Despite the degree of disability reported, 57%

of males and 68% of females had never consulted a physician for their headaches.⁴ Of those who consulted with physicians, 42% reported that they had not received a diagnosis of migraine. Only 13.6% of female migraineurs and 10.4% of males consulted with a neurologist about their headaches; fewer still, 1.6% of females and 4.7% males, consulted with a pain or headache specialist.

While the degree of disability experienced by migraineurs varies widely from patient to patient⁵, efforts have been made to estimate the cost of the disability resulting from migraine. A recently published study estimated that each year in the United States, 112 million workdays are missed and \$13 billion are lost to employers due to absenteeism and reduced productivity.⁶ There are also losses experienced in the social aspects of life that have no means of measurement.

The recent studies of migraine have shown that it is a common problem, afflicting over 10 million Americans at a high social and economic cost. At the same time, it appears to be a medical problem for which patients often do not seek help, and when they do, the diagnosis is often missed and referrals to specialists are infrequent. This is unfortunate, because there are many effective, well-tolerated methods available for the prevention and treatment of migraine. This article will address the principles and goals of migraine prophylaxis. The primary reference for the recommendations made here is the UW Hospital and Clinics Migraine Assessment and Treatment Guideline.⁷

Goals of treatment

According to the University of Wisconsin Hospital and Clinics Migraine Treatment Guideline, the goals of treatment are to reduce the frequency and severity of migraine attacks; a secondary goal may include improving the responsiveness of attacks to abortive therapy.⁷ A good response may be defined as a 50% reduction in the frequency or severity of the attacks. The lowest effective dose of medication should be used in order to minimize side effects. Patients should not expect that they will become completely free of migraines; rather, they should expect that they will have less disability. Rescue medications should still be available to the patient.

Non-pharmacologic measures

All prophylactic treatment plans should include some non-pharmacologic treatment strategies intended to reduce the patient's exposure to triggers that may cause a migraine attack to start. Common triggers are missed meals; too little sleep; excessive heat and humidity; certain foods such as chocolate, hard cheeses, alcoholic beverages, citrus fruits, nuts, excessive caffeine, and caffeine withdrawal; medication such as oral contraceptives, overuse of analgesics, sympathomimetic street drugs; strong sensory stimuli such as bright lights, glare, flickering lights, odors, smoke and prolonged exposure to heat or cold. Patients should be encouraged to keep a headache diary in an effort to identify triggers.

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Indications for pharmacologic prophylaxis

Any one of the following indications is sufficient to warrant a trial of prophylactic medications.⁷⁻⁹ Some published guidelines may recommend a minimum threshold number of attacks per month, but such thresholds are in fact arbitrary and any patient who wishes to reduce the number or intensity of attacks should be considered as a candidate for prophylactic therapy.

1. Occurrence of 2-3 attacks/month *OR* recurring attacks that patients feel are interfering with their daily activities even with acute treatment
2. Attacks lasting 48 hours or more
3. Extreme headache severity or prolonged aura
4. Presence of uncommon migraine conditions such as hemiplegic migraine, basilar migraine, or migrainous infarction
5. Inadequate relief from or overuse of acute therapies
6. Contraindication to or intolerable adverse effects from acute therapies
7. Intolerable cost of acute therapies
8. Patient demand

Guiding principles of drug therapy

There are a number of helpful principles that can be used to maximize the likelihood of successful results in migraine prophylaxis.^{7,8,10} Careful consideration of these principles can be useful in selecting the appropriate drug with which to begin a prophylactic trial. Additionally, it is important to explain the principles relating to commitment, compliance, trial duration and elimination of confounding medications to patients so they are able to participate fully in the process. Their input is essential to successful prophylaxis.

1. Recognize that a plan of prophylactic therapy requires a major commitment on the part of the patient and the physician.
2. Educate patients about the importance of compliance. Once an effective dose is determined, use of a long-acting, once-daily dosage form may encourage compliance.
3. Give each medication an adequate trial of two to three months before evaluating its efficacy.
4. Reduce or eliminate the use of medications that exacerbate migraine or interfere or interact with the prophylactic drug.
5. Use the lowest effective dose. Start with a very low dose of the selected medication and titrate upward until a satisfactory benefit is obtained without side effects or until the dosage is limited by side effects. The doses

required to effectively treat migraine are often lower than the doses required to treat other conditions such as epilepsy, hypertension or depression.

6. While many patients may require combinations of drugs for effective prophylaxis, it is important to add the drugs one at a time in order to keep track of their respective efficacies and to sort out side effect profiles.
7. Consider comorbid conditions when choosing a prophylactic agent. For example, in a patient with hypertension, it may be possible to choose drugs like beta-blockers or verapamil that will control hypertension and also reduce migraine recurrence. Choice of a multifunctional agent can decrease possible adverse effects, increase compliance and improve cost-effectiveness of therapy. Avoid medications that could compromise patient care, like beta-blockers in patients with asthma.
8. Consider also the side effect profile of the prophylactic drugs and whether some of the side effects might be beneficial in some patients. For example, the drowsiness caused by the tricyclic antidepressants might be a beneficial side effect in a patient who is also suffering from insomnia.

Migraine guidelines

The University of Wisconsin Hospital and Clinics has developed a Migraine Prophylaxis Guideline (on next page) based on drugs that have proven efficacy for this indication.⁷ The guideline is arranged by drug class, with drugs within that class listed in the second column. Minimum and maximum dosages are recommended, and contraindications and comments for each drug are included in the third column. The section immediately following the guideline outlines the clinical evidence for efficacy of each agent listed in the guideline.

Clinical evidence for efficacy

Propranolol has been demonstrated in a number of clinical trials to be significantly more effective than placebo in reducing the number of migraine attacks.¹¹⁻¹⁴ In addition, it has been reported as effective in case series.^{15,16} Typical doses range from 80 mg/day up to 320 mg/day. Good results were obtained with the long-acting formulation which is convenient for patients, and the drug was well-tolerated by most patients.

Other beta-blockers have been studied for migraine prophylaxis. Metoprolol, in doses of 100-200 mg/day, was significantly better than placebo in reducing the number of attacks and number of migraine days, although its effect on pain severity scores and analgesic tablet consumption was significant only at the higher dose.^{17,18} Metoprolol has been directly compared to propranolol in double-blind, cross-over studies; 100-200 mg/day of metoprolol was found to be as effective as 80 mg/day of propranolol in reducing headache frequency,

UWHC Migraine Prophylaxis Recommendations

Drug Class	Drug/Dose	Contraindications/Comments
Beta Blockers	<ul style="list-style-type: none"> • Propranolol 40-240 mg/day PO • Atenolol 50-150 mg/day PO • Metoprolol 100-200 mg/day PO • Nadolol 20-60 mg/day PO 	<ul style="list-style-type: none"> • Propranolol and nadolol are contraindicated in bronchial asthma or COPD • All beta-blockers are contraindicated in overt cardiac failure, 2nd or 3rd degree AV block or severe sinus bradycardia • Caution in CHF, diabetes mellitus, hyperthyroidism/thyrotoxicosis, peripheral vascular disease • Do not withdraw abruptly; taper over 1-2 weeks
Calcium Channel Blockers	<ul style="list-style-type: none"> • Verapamil 240-320 mg/day PO • Diltiazem 90-360 mg/day PO • Nimodipine 120-360 mg/day PO 	<ul style="list-style-type: none"> • Diltiazem and verapamil are contraindicated with atrial fibrillation or flutter, accessory bypass tracts, short PR syndromes, hypotension (≤ 90 mm Hg systolic), 2nd or 3rd degree AV block without functioning artificial pacemaker, sick sinus syndrome, wide-complex ventricular tachycardia ($QRS \geq 0.12$) • Verapamil is contraindicated in CHF, digital ischemia, ulceration or gangrene, idiopathic hypertrophic cardiomyopathy, severe left ventricular dysfunction • Diltiazem and verapamil are contraindicated with impaired renal function • Avoid extended-release dosage forms of diltiazem and verapamil with GI hypermotility or GI obstruction
Serotonin Receptor Antagonists	<ul style="list-style-type: none"> • Methysergide 2 mg every night, gradually increased to TID (maximum 8 mg/day if needed); usual dose is 4-8 mg/day 	<ul style="list-style-type: none"> • Contraindicated in pregnancy, peripheral vascular or coronary artery disease, lower limb phlebitis, pulmonary disease, collagen diseases or fibrotic disease, impaired liver or renal function or valvular disease; "drug holidays" of 3-4 weeks every 6 months are needed to prevent serious drug toxicity
Tricyclic Antidepressants	<ul style="list-style-type: none"> • Amitriptyline 10-150 mg every night • Nortriptyline 10-150 mg every night (start with 10 mg and increase as tolerated until adequate response or intolerable side effects) 	<ul style="list-style-type: none"> • TCAs are contraindicated in the acute recovery phase following myocardial infarction, and with concomitant use of monamine oxidase inhibitors (MAOIs) • Use with caution in seizure disorders; history of urinary retention, glaucoma or increased ocular pressure; hyperthyroidism; schizophrenia and cardiovascular disease • Nortriptyline should not be used concomitantly with reserpine
Anti-epileptics	<ul style="list-style-type: none"> • Divalproex 500-1500 mg/day • Valproic acid 500-1500 mg/day 	<ul style="list-style-type: none"> • Valproic acid and divalproex are contraindicated in pregnancy or with liver disease • Use with caution with drugs that affect platelet function, or with concomitant use of other CNS depressants

migraine days, analgesic consumption and ergotamine consumption.^{19,20} In the Olsson study, 100 mg metoprolol/day was effective in reducing headache pain severity scores statistically significantly from baseline.

Atenolol was evaluated in a small trial of 24 patients in a double-blind, cross-over, placebo-controlled study.²¹ Doses of 100 mg/day were significantly better than placebo in reducing migraine frequency and in its effect on headache overall. Eleven of 20 patients included in the final analysis had a 50% reduction in headache severity and two patients had no headaches during the study period while on atenolol.

A fourth beta-blocker that has been studied for migraine

prophylaxis is nadolol. In a study of 80 patients taking 0, 80, 160 or 240 mg/day, patients taking 160 or 240 mg/day had a reduction in the frequency and severity of their migraines.²² Nadolol 80 and 160 mg/day have also been compared to propranolol 160 mg/day in migraine prophylaxis.^{23,24} In the Sudilovsky study, the higher dose of nadolol produced superior results to propranolol in headache frequency, intensity, pain days and use of relief medications by the end of the first month of treatment. In the Ryan study, the lower dose of nadolol produced the greatest improvements but the difference between the groups was not statistically significant.

Verapamil is a calcium channel blocker that has been used

prophylactically for migraine, although there has been little clinical study of it. A review of three double-blind clinical trials indicates that verapamil, in doses of 240-320 mg/day, is significantly more effective than placebo in preventing migraine, with the 320 mg dose being more effective than the 240 mg dose.²⁵ Forty-five percent of the 133 patients in the trials reported greater than 50% improvement in migraine frequency. Diltiazem has also been used successfully in migraine prophylaxis, although it, too, has been little studied.²⁶

Nimodipine has been found to be superior to placebo in migraine prevention in a double-blind, cross-over trial of 33 patients.²⁷ Statistically significant improvements were attained in headache frequency, duration and headache index (pain severity X migraine days/28 days). Studies comparing nimodipine to flunarizine and pizotifen as well as placebo found nimodipine to be superior to placebo and equivalent in efficacy to the comparator drugs.^{28,29} Two other studies have shown a strong placebo response in addition to a good response to nimodipine; a superior benefit from nimodipine could not be established in these studies.^{30,31} The usual dose of nimodipine administered in the studies was 40 mg three times daily.

A fourth calcium channel blocker, nifedipine, was compared to propranolol for migraine prophylaxis.³² In this small, open-label study, nifedipine was less effective than propranolol and had a much higher incidence of side effects; 45% of the 20 patients on nifedipine withdrew from the study within two weeks. A second study found no difference between nifedipine and placebo in the frequency of headaches, although side effects were frequent among nifedipine users.³³ Based on the lack of significant benefit and the frequency of side effects, nifedipine is generally not used for migraine prophylaxis.

Methysergide is a serotonin receptor antagonist that has been used for migraine prophylaxis for many years. It has unique and serious toxicities, however, that limit its use to the most severe and refractory cases and require drug holidays of 3-4 weeks every six months. Its efficacy has been demonstrated in several clinical trials.³⁴⁻³⁷ In the Pedersen trial, 60 of 102 patients completed the trial; 57% had a 50% response to methysergide and methysergide was superior to placebo.³⁴ In the Whewell trial, 50 of 74 patients completed the trial. Patients achieved a small decrease in the number of attacks, a small decline in the duration of attacks and a larger decrease in the duration of severe headaches.³⁵ Use of methysergide resulted in a statistically significant decline in the number of attacks per week and in headache index in the Forssman trial; decreases in duration and intensity were not statistically significant.³⁶ In the Lance trial, methysergide produced the best results among six different serotonin antagonists including cyproheptadine and methdilazine; 64% of patients on methysergide had a 50% or greater improvement in their headaches.³⁷

Amitriptyline has been used widely and effectively for migraine prophylaxis, although there are not many clinical trials available. A placebo-controlled trial in 100 patients found that amitriptyline in doses of up to 100 mg/day was more effective than placebo in preventing migraine.³⁸ Over 55% of patients receiving amitriptyline had a 50% improvement in their headaches, compared to 34% of patients taking placebo. Amitriptyline was most effective in non-depressed patients with severe migraine and depressed patients with less severe migraine; depressed patients with severe migraine did not respond as well. A second trial compared amitriptyline in doses of 50 to 150 mg/day to propranolol 80 to 240 mg/day.³⁹ Both drugs were superior to placebo and there was no difference in efficacy between them. Amitriptyline has been compared to fluvoxamine for migraine prophylaxis in a study of 70 patients.⁴⁰ Both drugs reduced the headache index to a statistically significant degree. Drowsiness was more common among patients receiving amitriptyline; a larger number of patients taking amitriptyline dropped out of the study (9 compared with 2 for fluvoxamine). Nortriptyline is sometimes used as an alternative to amitriptyline. It is often better tolerated than amitriptyline and it appears to be effective, but clinical trials demonstrating its efficacy are lacking.

Divalproex sodium was evaluated for migraine prophylaxis in a placebo-controlled, dose-ranging study.⁴¹ Patients received either placebo, divalproex 500 mg/day, 1000 mg/day or 1500 mg/day. The three treatment groups had statistically significant improvements in headache frequency and severity, although there was no significant difference among the doses in degree of improvement. A second trial compared divalproex sodium to placebo in 107 patients.⁴² Headache frequency and severity were significantly decreased while patients were taking divalproex. Side effects, mainly nausea and drowsiness, were generally mild to moderate. There was no significant difference between the treatment and placebo groups in the number of patients withdrawing due to intolerance. A review of studies of sodium valproate and divalproex sodium for migraine and chronic daily headache found that patients improved on these drugs in 10 of 11 studies.⁴³ Doses from 500 to 2000 mg/day were evaluated and were well-tolerated. Divalproex has become one of the mainstays in the treatment of migraine, although its use is associated with the undesirable side effect of weight gain. Patients should be counseled about this effect and monitored for weight gain during treatment.

Emerging treatments

There are a number of drugs that are currently being used for migraine prophylaxis that have scant published evidence for efficacy or only anecdotal evidence. For most of these drugs, there is not yet enough experience with them to offer firm recommendations for dosing. However, their use may prove beneficial in refractory patients and are mentioned here

for informational purposes.

Fluoxetine and its *s*-enantiomer, *s*-fluoxetine, have been studied for migraine prophylaxis with mixed results.⁴⁴⁻⁴⁶ A double-blind, placebo-controlled trial in 32 patients evaluated fluoxetine over an 8-week period.⁴⁴ Headache scores in the active group decreased significantly beginning in the third and fourth weeks of treatment; no change was observed in the placebo group. No changes in depression scores were observed in either group. A second trial evaluated fluoxetine vs. placebo in 122 patients with migraine or chronic daily headache.⁴⁵ Fluoxetine was not significantly effective for migraine in this study but was moderately effective in reducing chronic daily headache. *S*-fluoxetine was evaluated in a placebo-controlled trial in 53 patients.⁴⁶ The active treatment resulted in a statistically significant decrease in the number of attacks, although the decreases in secondary efficacy measures, such as migraine days, attack severity and medication use, did not reach statistical significance.

Lamotrigine is a newer anticonvulsant that has been explored for migraine prophylaxis. A study in 15 patients found that lamotrigine reduced the frequency and duration of aura symptoms to a statistically significant degree, but this study did not measure the effect on headaches.⁴⁷ A second study evaluated lamotrigine for prevention of migraine with aura in 18 patients.⁴⁸ Doses of 100 mg/day decreased the number of attacks per month significantly. This study also treated five patients who had migraine without aura; they had no reduction

in the number of attacks while on lamotrigine. A third study of lamotrigine in patients with migraine with and without aura showed a tendency toward reductions in migraine days and severity scores for the active treatment group, but no statistically significant benefits were shown.⁴⁹

A recent case series on the use of gabapentin in centrally and peripherally mediated pain, migraine and tremor reported on 14 patients with migraine and cluster headache who were treated with gabapentin in doses of 900-2700 mg/day. Ten of the 14 patients reported moderate to excellent reduction in headache frequency, duration and severity.⁵⁰

Other agents currently in use or under investigation for migraine prevention are riboflavin⁵¹, magnesium⁵², montelukast⁵³ and sumatriptan (taken intermittently for menstrual migraine).⁵⁴ The anticonvulsant topiramate has been used successfully in refractory patients, although there is very little published data available. Anecdotal reports have indicated excellent response rates with very little toxicity.

Summary

While there are many apparently effective options available for the preventive treatment of migraine headache, there is good supporting data for some and relatively little clinical data supporting the use of others among these agents. Nevertheless, having a wide variety of drug classes to choose from affords more opportunities to find a drug that will be effective and well-tolerated in a given patient. It is unfortunate that so many migraine sufferers are not receiving adequate medical management of their condition, because substantial relief is available with prophylactic treatment. Many of the treatments are very affordable — some costing less per month than a single dose of the migraine abortive agent sumatriptan. Patients who are frequent users of abortive medications should be encouraged to ask their physicians about prophylactic treatment, and if they are not seeing a physician with expertise in this area, they should be encouraged to seek a referral to one. The potential gains for patients in reduction of migraine frequency, pain severity and disability are tremendous.

References available on request. ■

Costs: Estimated Average Wholesale Prices for a One-Month Supply

DRUG	DOSE RANGE	AWP/MONTH
Amitriptyline	10-150 mg/day	\$2.72-14.64
Propranolol	40-240 mg/day	\$3.90-44.55
Nortriptyline	10-150 mg/day	\$10.26-35.55
Metoprolol	100-200 mg/day	\$18.63-37.27
Atenolol	50-150 mg/day	\$21.60-64.80
Nadolol	20-60 mg/day	\$25.64-76.94
Valproic acid	500-1500 mg/day	\$49.04-147.15
Diltiazem	90-360 mg/day	\$35.27-64.20
Verapamil	240-360 mg/day	\$36.30-66.60
Divalproex sodium	500-1500 mg/day	\$49.04-147.15
Lamotrigine	100 mg/day	\$65.60
Methysergide	2-8 mg/day	\$69.59-278.35
Fluoxetine	20-40 mg	\$81.30-162.60
Gabapentin	900-2700 mg/day	\$104.40-313.20
Topiramate	200 mg/day	\$177.19
Nimodipine	120-360 mg/day	\$803.00-2411.00

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