Medicine Cabinet

Migraine prophylaxis in adult patients

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Summary points

- Not all patients are candidates for prophylactic therapy for migraine; physicians must evaluate whether prophylaxis is indicated in a patient
- Prophylaxis of migraines is not a cure; abortive measures will still be necessary in most patients
- A headache diary is essential to identify and avoid triggers and to evaluate therapy
- For prophylactic drug therapy, choose the agent that has the potential for the highest benefit and lowest risk to the patient
- Although their efficacy is questionable, alternative therapies may have some role in migraine prophylaxis

INTRODUCTION

Migraine headaches can be debilitating if patients cannot control or minimize the symptoms, and they can substantially impair the quality of life. However, migraines can often be successfully controlled by the avoidance of triggers, lifestyle changes, and abortive treatment. In patients in whom these measures prove insufficient or unsatisfactory, prophylactic measures to prevent migraines may be needed.[1] A common preventive measure is the use of prophylactic drugs, which will be the focus of this article. I will briefly mention nonpharmacologic or alternative measures.

SEARCH METHODS

The information given here is based on a MEDLINE search from 1966 to the present using the terms "migraine prevention" and "migraine prophylaxis." The search was limited to English-language review articles and studies with human subjects. I also searched the Internet using the key word "migraine" to link to the Web sites of the *Journal of the American Medical Association* Migraine Information Center and the *American Academy of Neurology*.

BEFORE STARTING PROPHYLAXIS

Patients for whom prophylactic therapy is indicated have the following migraine features:

- More than 2 headaches per month, but fewer than 8 (>8 attacks per month usually indicate overuse of abortive therapy)[2]
- Headaches less frequent but more prolonged (>2 days' duration) or severe attacks leading to substantial disability[1,3]
- Migraines are refractory to abortive treatment measures
- Therapies for acute attacks are intolerable, contraindicated, or overused (>2 per week)[2-4]
- Migraines are predictable in occurrence
- The patient has other migraine conditions such as migraine with prolonged aura or hemiplegic migraine[5]

Before prophylaxis is appropriate, the physician must evaluate whether proper and adequate abortive therapies have been instituted. Some patients overuse abortive measures, leading to rebound headaches. In these patients, the drug should be withdrawn before preventive therapy is initiated.[2,6]

A headache diary is essential for all patients who suffer from migraine headaches.[7] If migraine triggers can be identified, prophylactic therapy may be unnecessary. If, however, the triggers are unavoidable or undetermined, drug therapy is indicated to try to prevent the migraines. If prophylactic therapy is initiated, a 2- to 3-month trial is generally needed to assess the efficacy of the regimen.[5] Prophylaxis may be daily on a continuous basis or scheduled according to predetermined triggers, such as the onset of menses. The physician should evaluate previous prophylactic measures, if any, for adequacy and appropriateness. Women of childbearing age should be treated with caution because of the teratogenicity of most prophylactic drugs.[2]

Patients must also understand the goals, limits, and risks of migraine prophylaxis. The goals are to reduce the duration, frequency, and severity of the attacks to improve the patient's quality of life and minimize disability.[5] Prophylactic therapy is rarely curative; therefore, abortive therapies continue to be necessary in most patients, although their effectiveness is usually increased when used with prophylactic drugs.[6] A 50% reduction in the frequency of migraines is generally deemed successful.[8] Compliance is a major issue because patients experience medication side effects before any benefit from prophylactic drugs.[3]

CHOOSING AN AGENT

Many drugs have proven efficacy in preventing migraine. Based on patient-specific indices, the agent with the highest risk-to-benefit ratio should be used. The efficacy, contraindications, precautions, side effects, concurrent disease states of the patient ("special indications"), compliance issues, and cost should all be considered.[1,5,9] Side effects must be given special consideration because migraine sufferers have an increased frequency of adverse effects compared with other patients.[2,3]

Guidelines for migraine prophylaxis

- Initiate the chosen drug at a low dose and titrate up (usually every 2-4 weeks) until benefits occur or side effects prevent any further increase in dose. Long-acting formulations may improve compliance[2,5]
- A 2- to 3-month trial is needed to assess the efficacy of a regimen
- After 1 year, try to withdraw the drug, even if it has been effective.

- Use a drug that may benefit any comorbid conditions the patient has[5]
- Prophylaxis should be monotherapy whenever possible. Combinations of drugs have not shown substantial benefit except in some patients with multiple comorbid conditions.[2]

DRUGS WITH AN ESTABLISHED ROLE IN MIGRAINE PROPHYLAXIS

First-line agents

The first-line agents with the greatest efficacy are β-blockers, tricyclic antidepressants, and divalproex sodium or valproic acid. I have not considered agents unavailable in the United States, such as flunarizine, lisuride, and pizotifen.[1] I have also excluded agents that have proved to be ineffective or for which proof of efficacy is limited.

β-Blockers

The scientific and clinical evidence supports β-blockers as the drugs of choice for the prevention of migraines.[7] The most commonly used agent is propranolol hydrochloride. Generally, if 1 agent fails, another in its class may be tried, and this change may prove to be effective. It is imperative that abrupt stoppage of therapy is avoided.[2] β-Blockers are not effective in reducing aura.[7] In general, response to these agents is gradual, and it may take at least a month to see an effect.[10] The use of β-blockers with intrinsic sympathomimetic activity (such as pindolol) should be avoided.[11] The daily dose range for β-blockers in migraine prophylaxis, together with their side effects, precautions, and special indications, are given in the first box.[5-7,10]

Tricyclic antidepressants

Tricylic antidepressants are another class of medication considered as first-line treatment in migraine prophylaxis. Even without the presence of depression, these agents are effective in preventing migraines, and the response is usually more rapid (within 4 weeks) than with β-blockers.[10,12,13] Combined use with β-blockers does not reduce the incidence of migraines, but it may reduce that of tension-type headaches.[7] Although the entire class is considered useful in prophylaxis, tertiary amines, such as amitriptyline, are more effective than the secondary amines, such as nortriptyline.[6] Amitriptyline hydrochloride is the first-line agent of choice among the tricyclic antidepressants.[5] Physicians need to consider the differences in side-effect profiles of the various drugs when deciding which one to use (second box).[5-7,10,14]

Divalproex sodium or valproic acid

Divalproex and valproic acid are also first-line agents in migraine prevention, and the former has been approved by the Food and Drug Administration (FDA) for this indication (third box).[5-7] The initial dose is usually from 250 mg daily, titrated up to 1,500 mg.[5,7] If no benefit is seen at low doses, dose escalation is usually not helpful.[15] A serum drug concentration of 50 to 120 mg/L is considered to be in the therapeutic range, but it is unclear whether such monitoring is necessary or, indeed, indicative of efficacy.[10,16,17] Other anticonvulsants either have no efficacy or have not proved effective at this time.[5]

β-Blockers in migraine prophylaxis

Daily dose range (the most effective dose or dose range is shown in parentheses)

- Propranolol hydrochloride (should be specifically considered as first-line agent)*: 40 to 320 mg (80-240 mg)
- Timolol maleate (should be specifically considered as first-line agent)*: 20 to 30 mg
- Nadolol: 40 to 240 mg
- Metoprolol tartrate: 50 to 300 mg (200 mg)
- Atenolol: 50 to 200 mg (100 mg)

Side effects

- Fatigue
- Bradycardia
- Dizziness
- Depression
- Impotence
- Bronchospasm
- Nausea (adverse effects are less frequent than with the other first-line agents)

Precautions

- Asthma
- Chronic heart failure
- Diabetes mellitus
- Peripheral vascular disease
- Conduction defects or heart block
- Depression
- Raynaud's disease
- Hypotension

Special indications

- Concurrent hypertension
- Angina
- Post myocardial infarction
- Tremor
- Anxiety or panic attacks (specifically propranolol)

*Approved by the Food and Drug Administration for migraine prevention

Second-line agents

Calcium channel blockers

Calcium channel blockers are effective second-line agents (fourth box).[5-7,10] They are usually slower in onset than

Tricyclic antidepressants in migraine prophylaxis

Daily dose range (the most effective dose range is shown in parentheses)

- Amitriptyline hydrochloride (should be specifically considered as first-line agent): 10 to 300 mg (30-150 mg)
- Doxepin hydrochloride: 10 to 200 mg (50-150 mg)
- Imipramine hydrochloride: 10 to 200 mg (50-150 mg)
- Nortriptyline hydrochloride: 10 to 150 mg (50-150 mg)
- Protriptyline hydrochloride: 15 to 40 mg

Side effects

- Anticholinergic effects (dry mouth, constipation, blurred vision)
- Sedation
- Postural hypotension
- Agitation
- Tremor
- Seizures
- Sexual dysfunction
- Weight gain

Precautions

- Arrhythmias or cardiac conduction defects
- Urinary retention
- Angle closure glaucoma
- Seizures
- Obesity
- Pregnancy
- Concurrent monoamine oxidase inhibitor use

Special indications

- Tension-type headaches
- Concurrent depression, insomnia, and chronic pain

β-blockers, and an initial increase in headache frequency may occur on starting therapy. They are a viable alternative in patients who cannot tolerate β-blockers.[6]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used daily or intermittently. When migraine triggers are identified or are predictable—such as menstruation—intermittent therapy may be used (using NSAIDs 1 week before menses and then throughout menstruation).[19-21] Naproxen sodium is the most commonly used NSAID for migraine prophylaxis (fifth box),[5-7,10] and the dose is 1,100 mg daily. Other NSAIDs that may be substituted for naproxen are mefenamic acid, flurbiprofen sodium, fenoprofen calcium, ketoprofen, and aspirin.[5] Adverse effects tend to be infrequent with short-term therapy but increase with extended treatment.[3,5]

Michael W Davidson/The Florida State University

Nifedipine, shown in this photomicrograph, is a viable alternative for patients who cannot tolerate β-blockers

Third-line agents

Two medications that have proved effective in prophylaxis but are reserved for severe or refractory cases are methysergide and phenelzine sulfate. Both should be reserved for use only by specialists in headache treatment.[2,7]

Methysergide is the fourth agent indicated and approved for migraine prophylaxis by the FDA. Because of its side-effects profile, numerous precautions, and contraindications, it has become a last-line drug. Longer than 6

Divalproex sodium and valproic acid in migraine prophylaxis

Side effects

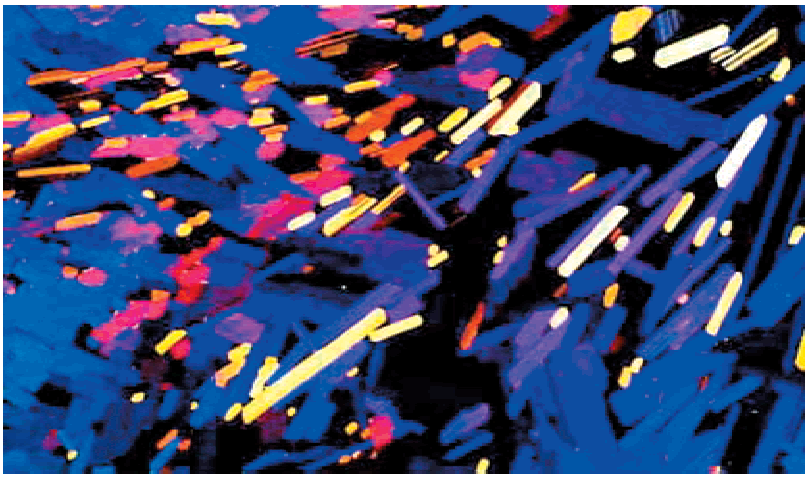
- Nausea
- Vomiting
- Tremor
- Weight gain
- Hair loss
- Drowsiness
- Ataxia
- Hepatotoxicity

Precautions

- Liver disease
- Thrombocytopenia
- Pregnancy
- Young children (high risk of hepatotoxicity)

Special indications

- Prolonged or atypical migraine aura
- Tension-type headache
- Concurrent epilepsy, mania, trigeminal neuralgia, cluster headache



Michael W. Davidson/The Florida State University

Nonsteroidal anti-inflammatory drugs, such as aspirin (shown in this photomicrograph), can be taken to prevent migraine

months of continuous use can lead to fatal retropleural, retroperitoneal, or cardiac fibrosis, and drug holidays must be instituted when methysergide is used.[3,7]

Phenelzine—a monoamine oxidase inhibitor—has numerous precautions and contraindications. It should be considered only in severe refractory cases, specifically those that are compounded by tension headaches or atypical depression,[7,22] and only in patients whose compliance can be expected. Phenelzine is difficult to use—it has several potentially dangerous interactions with other drugs, and it can cause hypertensive crises in patients who do not comply with a tyramine-free diet.[6,7]

Calcium channel blockers in migraine prophylaxis

Daily dose range (most effective dose shown in parentheses)

- Verapamil hydrochloride: 120 to 480 mg (240 mg)
- Nifedipine: 30 to 90 mg
- Diltiazem: 120 to 360 mg
- Nimodipine: 60 to 120 mg

Side effects

- Constipation (especially verapamil)
- Dizziness
- Hypotension
- Peripheral edema
- Weight gain

Precautions

- Ventricular dysfunction
- Heart block
- Hypotension
- Bradycardia
- Sick sinus syndrome
- Pregnancy

Special indications

- Prolonged or atypical aura[18]
- Concurrent angina, hypertension, and arrhythmias

NSAIDs in migraine prophylaxis

Side effects

- Dyspepsia
- Erosive gastritis
- Peptic ulceration
- Occult gastrointestinal bleeding
- Hematologic complications

Precautions

- Hypersensitivity to aspirin or other NSAIDs
- Active gastrointestinal bleeding
- Peptic ulcer
- Liver disease
- Kidney disease
- Elderly patients
- Coagulopathies

Special indications

- Concurrent arthritis, dysmenorrhea, and stroke (specifically with aspirin)

DRUGS WITH AN UNCERTAIN OR UNPROVEN ROLE IN MIGRAINE PROPHYLAXIS

The efficacy of fluoxetine hydrochloride has not been well established in prophylaxis, but some experts already consider it a viable alternative to tricyclic antidepressants.[5-7,14] Doses from 20 mg every other day to 40 mg a day have been used. Other selective serotonin-reuptake inhibitors may prove to be useful, but the evidence for their efficacy is so far weak or nonexistent.[5]

Some evidence exists that riboflavin (vitamin B_2) in high doses (400 mg daily) has some effect in migraine prophylaxis. Because of its low cost and low side-effect profile, it may prove to be a useful alternative.[23] Similarly, magnesium at doses of 400 to 600 mg daily may also be of benefit, but there is less evidence for its efficacy than that for riboflavin.[5,24,25]

NONPHARMACOLOGIC MEASURES IN PREVENTING MIGRAINE

The standard nonpharmacologic approach is the avoidance of triggers to migraines. Avoidance may lower headache frequency by 50%.[26] The following are common migraine triggers:

- Environmental or hormonal factors—noise, odors, hunger or thirst, menses, menopause
- Behavioral changes—stress, sleep deprivation, excessive sleep
- Medications—oral contraceptives, hormone replacement therapy, histamine-2 blockers
- Foods or drinks—cheese, wine, alcohol, chocolate, caffeine[27-29]

POSSIBLE ALTERNATIVE THERAPIES FOR MIGRAINE PREVENTION

Feverfew, an herbal medication (*Chrysanthemum parthenium*), is marketed as being useful in migraine prevention, at a daily dose of 125 mg. Most data support the notion that feverfew is superior to placebo. However, a systematic review failed to substantiate its efficacy.[30] Adverse effects are mild—usually gastrointestinal upset—but withdrawal may lead to increased frequency of headache, anxiety, and sleep disturbances. Its use should be avoided in pregnancy.[31]

Other alternative therapies are used by patients in migraine prevention:

- Relaxation therapy—breathing exercises and muscle relaxation
- Cognitive-behavioral therapy—identification and avoidance of behaviors or responses to migraines that may exacerbate a migraine attack
- Biofeedback techniques—these rely on the premise that patients may be able to control physiologic responses of the body, such as to migraine attacks[6]
- Homeopathy (no better than placebo in most studies)[32]
- Acupuncture
- Reflexology
- Massage
- Temperature changes (hot or cold packs)[29]

There is little evidence of the effectiveness of these therapies. However, because most do not cause any apparent harm, some patients may benefit from these options in treatment when used alone or as an adjunct to prophylactic medications.[6]

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