CONTINUING EDUCATION CREDIT

The Pharmacological Management Of Migraine, Part 2

Preventative Therapy

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Educational Objectives

After reviewing this article, readers should be able to:

- Define preventative (prophylactic) pharmacotherapy and specify when it may be necessary in the treatment of migraine.
- List the various preventative pharmacotherapies and their role in migraine management.
- Describe the role of the various migraine pharmacotherapies for special populations, including children, pregnant women, and the elderly.
- Describe the general pharmacological treatment pathway for the management of migraine.

This is part 2 of a two-part series.

Introduction

Migraine, its pathophysiology, and abortive (acute) pharmacotherapy were described in Part 1 of this two-part series in the July issue of *P&T.* Part 2 discusses the role of preventative (prophylactic) pharmacotherapy and the role of migraine treatments in special populations. It also provides an overview and guideline summary for general treatment pathways for the pharmacotherapy of migraine.

Prophylactic Therapy

Preventative migraine therapy refers to the daily administration of drug therapy for various periods, usually three to 12 months. The goals are to reduce the frequency and severity of attacks, to improve and reduce disability, and to minimize or eliminate the need for abortive drug therapy. Patients may be candidates for preventative therapy if they are experiencing two or more migraines per week, if their attacks last more than 48 hours, or if they have ineffective responses or contraindications to abortive therapy.[1–5] Although numerous medications are used in the management of migraine (Table 1), the commonly used agents that have been studied and that have reported efficacy include the beta blockers, the tricyclic antidepressants, and some anticonvulsants.[1]

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Beta-Adrenergic Blockers

Beta blockers were first recognized in the 1960s as effective in migraine prophylaxis; by the 1970s, their use was well established, and they continue to be a treatment of choice.[1,6–10] Their mechanism of action is not completely understood, although it may involve modulation of the adrenergic nervous system and an influence on cranial blood vessels.[11–13]

Beta blockers have been reported to be effective in approximately 70% of patients, with most data available for the nonselective agents propranolol (e.g., Inderal, Wyeth), timolol maleate (e.g., Blocadren, Merck), and nadolol (Corgard, King).[14–27] Studies with propranolol reported efficacy with doses of 80 to 240 mg, with both regular-release and controlled-release formulations.[6–10,14–19] Nadolol had similar efficacy, compared with propranolol, in doses of 20 to 120 mg when administered twice daily.[20,21]

Studies with other beta blockers, including some nonselective agents (e.g., timolol and bisoprolol)[22,27] and the beta-1 selective agents (e.g., metoprolol [Toprol, AstraZeneca] and atenolol [Tenormin, AstraZeneca]) have also been reported to be effective. Beta-1 selective agents may be an appropriate option in patients with severe respiratory disease,[23–26] but agents with intrinsic sympathomimetic activity should be avoided because of a lack of reported efficacy.[11,13]

Comparison trials with beta blockers and other preventative therapies, including valproic acid (Depakene, Abbott) and topiramate (Topamax, Ortho-McNeil), reported similar efficacy, with some data suggesting improved tolerability.[28–33] Although beta blockers are usually well tolerated, reported side effects may include sedation, dizziness, vivid dreams, depression, fatigue, orthostatic hypotension, and impotence. Absolute contraindications include asthma, heart block, severe peripheral vascular disease, and Raynaud's phenomenon.[11]

Important interactions involve other cardiovascular drugs that influence heart rate or blood pressure, including numer-

Table 1 Prophylactic Pharmacotherapies for Migraine Headache

Drug Class	Agent, Dose Range	Monitoring Parameter
Beta blockers	Propranolol (Inderal)* 40–240 mg/day in divided doses or LA q.d. Nadolol (Corgard) 20–120 mg q.d. or b.i.d. Timolol (Blocadren)* 20–60 mg q.d. or b.i.d. Atenolol (Tenormin) 25–100 mg q.d. Metoprolol (Toprol) 50–200 mg b.i.d.	Side effects • Heart rate • Blood pressure • Sexual dysfunction (males) Drug interactions Efficacy
Antidepressants	Tricyclic agents • Amitriptyline 10–150 mg h.s. • Nortriptyline (Pamelor) 10–150 mg h.s. • Doxepin (Sinequan) 10–200 mg h.s. • Desipramine (Norpramin) 25–150 mg h.s. MAOIs: Phenelzine (Nardil) 15–60 mg t.i.d. SSRIs: Fluoxetine (Prozac) 10–80 mg q.d.	Side effects • Anticholinergic • Cardiac status/predose ECG in some patients • Weight gain Drug interactions Efficacy
Anticonvulsants	Valproic acid (Depakene):* start 250 mg h.s. or b.i.d., titrate dose to 1,500 daily in divided doses Divalproex sodium 1,000 mg q.d. • Depakote valproate sodium • Depakene solution Topiramate (Topamax)* 100–400 mg b.i.d.–t.i.d. daily	Side effects • Sedation/fatigue • Liver enzymes • Complete blood count Drug interactions Efficacy Cognitive effects
Calcium-channel blockers	Verapamil (Calan) 240–360 mg daily in divided doses	Side effects • Heart rate • Blood pressure • Sexual dysfunction (males) Drug interactions Efficacy
NSAIDs	Naproxen sodium (Naprosyn) 550–1,100 mg daily in divided doses Ketoprofen 150 mg daily in divided doses	Side effects • Renal function • Signs and symptoms of bleeding

*These agents are FDA-approved for migraine prophylaxis.
b.i.d. = twice daily; ECG = electrocardiogram; ER = extended-release; h.s. = at bedtime; LA = long-acting; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; q.d. = once daily; t.i.d. = three times daily.
Adapted from references 1, 2, 4, and 34.

ous antihypertensive agents. One reported drug interaction with propranolol that might be significant in migraine patients who are using triptans that are metabolized by the monoamine oxidase A (MAO-A) pathway—including sumatriptan (Imitrex, GlaxoSmithKline), almotriptan (Axert, Ortho-McNeil), and others—is propranolol's inhibition of triptan metabolism and a potentially greater risk of side effects. The concurrent use of these triptans with propranolol should be monitored carefully. Lower doses of these triptans should be used, or they should be avoided in favor of an alternative agent.[36,37]

Beta blockers are considered a drug of choice for migraine prevention, especially in patients without absolute contraindications. They offer an excellent choice for patients with other morbidities, including hypertension and coronary artery disease. Beta blockers should be initiated at low doses along with monitoring of heart rate and blood pressure. An adequate trial of 3 to 12 months with continued assessment of efficacy and tolerability is recommended.[11,13,35]

Antidepressants

Tricyclic Agents

Although various classes of antidepressants have been studied and used to prevent migraine headache, more data are available for the tricyclic antidepressants (TCAs) (Table 1).[4,38,39] Their proposed mechanism of action is thought to involve the inhibition of central cortical depression and sympathetic activity associated with migraine pathophysiology.[40,41]

Clinical trials with the TCA amitriptyline have reported a 50% to 70% reduction in the number and in intensity of migraine attacks, with doses ranging from 10 to 100 mg daily.[38,42] Trials comparing amitriptyline with the beta blocker propranolol have reported similar efficacy.[43]

The side-effect profile of the TCAs includes dry mouth, constipation, urinary retention, and weight gain along with central effects (sedation, weakness, fatigue, and tremor), which may limit their use in some patients. The secondary-amine TCAs nortriptyline (Pamelor, Mallinckrodt) and desipramine (Nor-

pramin, Sanofi-Aventis) may be better tolerated in some patients and may be an additional option. More serious adverse effects include potential cardiac events, such as sinus tachycardia, corrected QT (QTc) prolongation, and blood pressure fluctuations.

Drug interactions involve other central-acting agents, anticholinergic drugs, and serotonergic agents (Table 2). These medications are contraindicated for patients with angle-closure glaucoma, urinary retention, and orthostatic hypotension, which are seen primarily in the elderly. Monitoring in young migraine patients should include efficacy and adverse effects such as weight gain.[38–42]

Within the antidepressant class, the TCAs are considered a first-line option for preventing migraine in patients who do not have any contraindications. These agents may be an excellent choice for patients with a concurrent comorbidity such as depression, anxiety, or insomnia.[4,41,44,45]

Other Antidepressants

The selective serotonin reuptake inhibitors (SSRIs) have not shown consistent benefits in migraine prophylaxis. A few small, short-term trials with fluoxetine (Prozac, Eli Lilly) reported benefits,[46,47] although a more recent analysis that looked at the class as a whole reported a lack of efficacy in migraine.[48] Antidepressants that have been studied in small trials with some reported efficacy include venlafaxine (Effexor, Wyeth), mirtazapine (Remeron, Organon), the monoamine oxidase inhibitors (MAOIs), and nefazodone HCl.[49–58]

Anticonvulsant Medications

Valproic Acid and Topiramate

The anticonvulsants are another class of medications that have demonstrated efficacy in the prophylaxis of migraine, with valproic acid and topiramate having the strongest evidence to support this indication (see Table 1).[4,59,60] The rationale for their use is thought to be related to common mechanisms shared in seizure disorders and migraine involving imbalances between excitatory glutamate activity and gamma-aminobutyric acid (GABA)–mediated inhibition in the brain.[61]

Table 2 Common Drugs with Serotonergic Properties

Monoamine oxidase inhibitors	Phenelzine (Nardil) Selegiline (Zelapar, Eldepryl, Emsam) Isocarboxazid (Marplan) Tranylcypromine (Parnate)
Antidepressants	Tricyclics: amitriptyline, others SSRIs: fluoxetine (Prozac), others Miscellaneous: nefazodone (Serzone*), trazodone (Desyrel), venlafaxine (Effexor), bupropion (Wellbutrin)
Others	Buspirone (BuSpar) Dextromethorphan Lithium Amantadine (Symmetrel) Cocaine

SSRI = selective serotonin reuptake inhibitor.
* Serzone has been discontinued, but generic brands are available.
Adapted from references 49–53.

Valproic acid. Valproic acid and its derivatives were the first class of anticonvulsants approved for migraine prophylaxis. Trials dating back to the 1980s have been conducted with efficacy reported at variable doses but without a consistent correlation between effective dose and serum levels. Efficacy was described as a reduction in the severity and duration of migraine, with good tolerability reported with titration and individualized doses (see Table 1).[62–67] Compared with other preventative agents, valproic acid is similar to propranolol in terms of its efficacy and tolerability, as noted with the beta blockers.[30,31,33]

Adverse events associated with valproic acid, including central nervous system (CNS) effects (e.g., sedation, tremor, confusion, gastrointestinal problems, and weight gain) may be problematic in some patients. More serious adverse events (e.g., blood dyscrasias, pancreatitis, and liver problems) are rare, but periodic monitoring is required if they occur. Valproic acid and its derivatives should be avoided in women who are planning pregnancy or in women of childbearing age because of the significant risk of teratogenicity with this agent. Drug interactions include other central-acting agents and drugs whose metabolism may be inhibited by valproic acid.[44,45,68]

Topiramate. The other anticonvulsant that has been studied extensively and has reported efficacy in migraine prophylaxis is topiramate (Topamax) (see Table 1).[69–78] The drug's proposed mechanism of action in migraine is probably similar to that of valproic acid, involving GABA-mediated inhibition in the CNS. Although serious adverse effects (kidney stones, myopia with angle-closure glaucoma, sedation, and cognitive changes) can occur,[44,45,79] clinical trials reported good tolerability in most patients, especially with lower daily doses.[69–74] Drug interactions may include other central-acting drugs, antidepressants, and oral contraceptives.[44,45,79]

In comparison trials, topiramate was similar to valproic acid[80,81] and propranolol[32] in terms of efficacy and tolerability. Because of concerns about potential dose-related effects on cognition, patients who are taking topiramate must be monitored regularly, although the drug has excellent clinical utility and can be an option, especially if weight gain is a concern.[1,79,82]

Migraine patients who take topiramate should be apprised of the drug's potential for visual and cognitive changes and their need to ensure adequate hydration.[79]

Summary. Valproic acid and topiramate provide an additional option in the prophylactic treatment of migraine headaches, but adverse effects may limit their use in some patients. Although they are probably considered second-line agents in many cases, they may be excellent choices for patients with a history of seizures disorders; obese patients (especially because of topiramate's weight-loss benefits); or patients for whom beta blockers or antidepressants may be contraindicated.[44,45,68,79]

Other Anticonvulsant Agents

Small trials with additional anticonvulsant agents reported some benefit with gabapentin (Neurontin, Pfizer) and levetiracetam (Keppra, UCB Pharma), inconsistent findings with zonisamide (Zonegran, Eisai), and a lack of efficacy with lamotrigine (Lamictal, GlaxoSmithKline). Before these agents can be recommended for migraine prophylaxis, additional studies are needed.[83–89]

Additional Migraine-Prophylactic Agents

Other agents have also been used to prevent migraine; however, many of these therapies are less effective than those discussed earlier, or they need further study. Calcium-channel blockers have had mixed success in migraine prevention,[90–94] with a few small trials suggesting modest benefits with verapamil (e.g., Calan, Pfizer) (see Table 1).[90–92]

Although primarily used in the abortive management of migraine, the nonsteroidal anti-inflammatory agents (NSAIDs) have also demonstrated modest benefits in migraine prophylaxis. Trials with naproxen (Naprosyn, Roche), fenoprofen (Nalfon, Pedinol), tolfenamic acid (e.g., Clotam, Provalis), and ketoprofen reported decreases in duration and severity of migraine. Short-term prophylaxis with NSAIDs in menstrual migraine is discussed in the next column (Special Populations).[95–102]

Skeletal muscle relaxants, including baclofen (e.g., Lioresal, Novartis) and tizanidine (Zanaflex, Acorda), have been used in the prophylaxis of migraine, but the data are limited. One controlled trial and an open-label trial with tizanidine reported reduced headache frequency, duration, and intensity.[103–105]

Although more trials are needed, the angiotensin-converting enzyme (ACE)–inhibitors and the angiotensin II receptor blockers (ARBs) have been effective for migraine prevention and may have a future role, especially in patients with cardiovascular comorbidities.[106–109]

The leukotriene receptor antagonist montelukast (Singulair, Merck) was studied in migraine prevention with mixed results, suggesting that more trials may be needed to clarify its role.[110,111] The association of migraine headaches and psychiatric disorders has prompted the consideration of antipsychotic agents for migraine, and some data have shown benefits with aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka) and olanzapine (Zyprexa, Eli Lilly).[112,113]

One of the more recent products to be studied in migraine prevention is botulinum toxin type A. Although numerous trials have been conducted, inconsistent findings have been reported, perhaps because of variable trial designs, treatment regimens, or the types of patients studied.[114–120]

Agents that might also be beneficial for migraine prophylaxis include antihistamines, salmon calcitonin (Miacalcin, Novartis, simvastatin (Zocor, Merck) and clonidine (Catapres, Boehringer Ingelheim).[1,4,121] Other potential options include herbal products and supplements such as feverfew *(Tanacetum parthenium)*, butterbur root (*Petasites hybridus*), coenzyme Q10, melatonin, riboflavin, and magnesium.[122–130]

Combination Therapies

Various combinations of prophylactic agents have been used in patients who have not responded to monotherapy. The importance of careful and slow titration of additive agents is essential because of additive side effects, potential toxicities, and drug interactions.

Special Populations

Women. The link between female sex hormones and migraine has been studied extensively. A phenomenon known as menstrual migraine refers to migraine associated with or occurring around a woman's menstrual cycle. This type of migraine appears to be associated with fluctuations in estrogen levels and the resultant biochemical effects of increased prostaglandins, enhanced prolactin release, and other physiological dysregulation.

Treatment has included a variety of agents, including hormonal manipulation and other therapies administered in conjunction with the menstrual cycle.[131–135] The newest concept of treating menstrual migraine is the use of short-term prophylaxis with NSAIDs or triptans starting a few days before the cycle and continuing for about five to seven days.[136–140] Refractory cases may respond to estrogen alone or to a combination of progesterone or testosterone in addition to the use of other hormonal manipulations.[141–146]

Migraine headaches usually improve during pregnancy, but treatment may be required in some patients. Simple analgesics like acetaminophen alone are the drugs of choice. Other therapies can be used with caution and in consideration of the risk–benefit ratio.[147–152]

Children and adolescents. The prevalence of migraine ranges from 3% to 11% in children younger than 15 years of age. Although more controlled trials are needed for evidence-based treatment of migraine in children and adolescents, the American Academy of Neurology offers some guidance. Options for abortive treatments are simple analgesics alone or triptans. The triptans, including sumatriptan (Imitrex, GlaxoSmithKline), rizatriptan (Maxalt, Merck), and zolmitriptan (Zomig, AstraZeneca), were reported to be safe but not superior to placebo. Fewer data are available for prophylactic treatment in children, although several agents have been proposed.[153–159]

Elderly Patients. New-onset headache in the elderly is considered a secondary disorder, and a comprehensive evaluation is warranted. As with pediatric patients, the safest agent for the abortive management in older adults is acetaminophen, and the use of the ergots and triptans may be limited if patients have cardiovascular or cerebrovascular disease. The selection of preventative therapies can be determined by concurrent comorbidities or contraindications.[160–162]

Treatment Plans and Guidelines for Care

As the choices for the pharmacotherapy of migraine expand, clinicians have multiple options to use for both abortive and preventative management. Various guidelines, including those of the U.S. Headache Consortium,[4] have recently been revised, although updates are not yet in print.[1,2,4,163–165]

The available guidelines support the utility of the various pharmacological agents in migraine using a stepped-care approach, with simple analgesics or NSAIDs as first-line choices and stepping up to specific migraine therapies if the response is not sufficient. With the stratified-care approach,

treatment choices are based on the severity of the headache.

The Disability in Strategies of Care (DISC) Study provided evidence that using a stratified-care approach might be able to improve headache response and disability time. In this multicenter study, which was conducted in 13 countries, the Migraine Disability Assessment Scale (MIDAS) was used to compare the stratified-care and stepped-care approaches.[166] Patients receiving stratified care were treated according to their MIDAS scores and initially received either aspirin plus metoclopramide (Reglan, Schwarz) or zolmitriptan (Zomig). For the stepped-care group, initial attacks were treated with aspirin and metoclopramide; patients could use a stepped-care strategy during an attack and zolmitriptan therapy with set parameters. Even though the study suggested that the stratified-care approach resulted in improved clinical outcomes, the study's limitations included an open-label design, a small number of pharmacotherapies, different methods of selecting therapies for the stratified group, and concerns about whether rapid escalation of therapy was comparable to that in clinical practice.

Investigators conducting future trials of stratification might consider other factors, such as symptom profiles, genetics, and biological markers.[166] The present guidelines suggest the use of simple analgesics or NSAIDs for aborting mild-to-moderate migraine and the triptans or possibly the ergots for aborting moderate-to-severe migraines. Considerations for preventive therapy are usually based on the frequency and severity of migraine and other comorbidities, and these approaches may include beta blockers, TCAs, and anticonvulsants.[1,163–165]

Conclusion

The pharmacotherapy of migraine is complex. The appropriate use of preventative medications requires an understanding of the various agents available and when they are best used. Part 1, in the July 2008 issue of *P&T*, reviewed the abortive pharmacotherapy for migraine, the role of these agents, and especially their frequency, which affects the use of preventative therapy.

The management of migraine requires a multidisciplinary approach and calls for physicians experienced in headache management along with nurses, social workers, and pharmacists. The large number of patients experiencing migraine results in significant medication usage and the potential for drug-related problems. Although all health care professionals constitute an important part of the care of the migraine patient, pharmacists can also play a major role by monitoring medication usage, evaluating patients' responses to therapy, and assessing adverse effects and drug interactions. Pharmacists should also play a prominent part in educating patients about their medications and in providing information on appropriate use.

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Conflict of Interest (COI) Statement

Dr. DeMaagd has no relationships to disclose. This article contains discussions of off-label use. The content of this article has been reviewed under Jefferson's Continuing Medical Education COI policy.