

How to Choose a Preventive Treatment for Migraine

Alan M. Rapoport, M.D.

Clinical Professor of Neurology, The David Geffen School of Medicine at UCLA, Los Angeles, California

Principles of Preventive Treatment

Daily preventive migraine therapy is indicated for patients with frequent migraine attacks (1-2 headache days per week or more), significant disability associated with individual attacks, poor response to acute care medications, migraine with brainstem aura, hemiplegic migraine, contraindications to triptans and other vasoactive medications, significant triptan side effects, use of acute care treatment more than 2-3 days per week or patient preference. Preventive medications are often chosen based on co-existing medical conditions, as the optimal medication may improve both the migraine and the medical condition (a therapeutic “two-fer”). Other considerations include desirable and undesirable effects/side effects, as well as potential drug interactions with existing medications.

General principles of management :

- Establish a therapeutic partnership with the your patient and explain that they have to do most of the work, but you will guide and support them
- Start treating with preventive medications at a low dose and gradually increase over an extended period of time, to minimize adverse effects
- Continue well-tolerated medications for at least 2-3 months at a therapeutic level before deciding on effectiveness
- Polypharmacy is sometimes necessary and lower doses of two medications may cause fewer adverse effects than a higher dose of one
- Communicate clear expectations to the patient regarding the timing and magnitude of their expected clinical benefit
- Warn patients of the most frequent side effects and explain when and how to contact you
- Establish a comprehensive migraine management plan that includes long-term goals, appropriate use of acute care treatments, tips on when the medication needs to be changed, a regular office visit schedule, and guidelines for contacting the office

There are only five FDA-approved medications for episodic migraine prevention and one of them, methysergide, is unavailable worldwide. The others are **propranolol**, **timolol**, **divalproex sodium** and **topiramate**. It is best to stay on-label with these four medications when instituting migraine preventive therapy if possible. However, other off-label medications approved for other conditions have evidence of effectiveness in clinical studies, including angiotensin II receptor blockers (candesartan), angiotensin-converting enzyme (ACE) inhibitors (Lisinopril) and NMDA receptor blockers (memantine). [Refer to supplemental slides with evidence guidelines and selection suggestions.]

Current Headache Consortium Preventive Guidelines [[Link to supplemental slides](#)]

The various categories of preventive medication are:

β-Blockers

Propranolol, nadolol, atenolol, metoprolol and *timolol* are effective for migraine prevention. Common side effects are lethargy, exercise intolerance, hypotension, depression, and sleep disorders. Avoid their use in patients with asthma, diabetes, bradycardia and congestive heart failure. Patients on propranolol who take eletriptan acutely to stop a migraine attack, must be given only 5 mg (half of the usual dose).

Antidepressants

Four major types of antidepressants are available: monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). All have been used extensively for prevention of migraine, although SSRIs occasionally cause headaches to worsen. Tricyclic antidepressants, such as amitriptyline or nortriptyline, given before bedtime may benefit patients with migraine and insomnia. Initiating therapy with the lowest dose is prudent as TCAs may be quite sedating. Antidepressants are useful in patients with co-existing depression, anxiety, tension-type headache or primary stabbing headache. Serotonin syndrome occurring with serotonin reuptake inhibitors and triptans is rare; the incidence is approximately 0.03%. There is less experience using *bupropion* and *trazodone* for migraine prevention, but they are useful in some patients. .

Membrane Stabilizers (Anticonvulsants)

Membrane stabilizers frequently used in the prevention of migraine include *divalproex sodium* (available and approved in the ER or extended release form, which is given only once per day), sodium valproate and topiramate. Gabapentin does not have the same strength of evidence but it is effective in many patients.. Several other medications in this category, such as *levetiracetam* and *zonisamide*, have shown promise as migraine preventive medications in open trials. *Valproate* is contraindicated in pregnancy, and should not even be prescribed for women of childbearing potential and never for those intending to become pregnant. Potential neural tube defects, which occur very early in gestation, should be discussed with all women of childbearing potential taking *valproate*. *Topiramate* is also contraindicated during pregnancy, as well as in patients with a history of calcium phosphate kidney stones. Topiramate is the best studied and probably the most effective migraine preventive but is associated with many possible adverse events such as paresthesias, word finding difficulty, weight loss, depression and, rarely, angle closure glaucoma and kidney stones.

Nonsteroidal Anti-inflammatory Drugs

NSAIDs, often used in acute migraine treatment, can also prevent migraine. A meta-analysis of seven placebo-controlled studies of naproxen (500 mg/day) or naproxen sodium (1100 mg/day) suggest a modest but clinically significant improvement in headache index and reduction in frequency. However, daily use of NSAIDs, although helpful in the short term, may cause Medication Overuse (Rebound) Headache if used many days per week long term. They can also cause GI bleeding and renal dysfunction so should close monitoring is needed with daily use. .

Vitamins, Minerals, Supplements and Herbs

Several over-the-counter preparations have been shown in randomized trials to be effective in migraine prevention in some patients. They are feverfew (*Tanacetum parthenium*), butterbur (*Petasites hybridus*), magnesium 400 mg pr day, vitamin B2 (riboflavin) 400 mg per day, coenzyme Q 10 300 mg per day and melatonin (0.5-12 mg at night). Petasites is under scrutiny for reports of liver toxicity. (See Fact Sheet on Nutraceuticals).

Calcium Channel Antagonists

Although not FDA-approved for migraine, over 45 clinical studies report on the efficacy of several different agents including: *verapamil*, *flunarizine* (not available in the United States), *nimodipine*, *nifedipine*, *cyclandelate*, and *nicardipine*. The most common side effects are constipation and edema. Verapamil is often used for cluster headache prevention in higher doses than migraine and may cause heart block even with a stable, normal EKG. Headache is an infrequent side effect. Calcium channel antagonists may be useful for migraine with brainstem aura, hemiplegic migraine and monocular aura related to vasospasm.

The antihistamine *cyproheptadine* has calcium channel blocking properties. Although its clinical efficacy has not been proven in double-blind, randomized studies, clinical experience suggests that it may confer some benefit in the prevention of migraine in children (off-label). It is not well tolerated by adults due to drowsiness and weight gain.

Chronic Migraine Preventive Treatments

Chronic migraine is defined as a patient with migraine with or without aura who has 15 days or more of headache per month, 8 of which are migraine days or would have been without acute treatment with a triptan or ergot. The ICHD criteria (ICHD-3 beta) now permit the diagnosis of Chronic Migraine in patients who also have Medication Overuse.

OnabotulinumtoxinA is the only treatment approved in the US for Chronic Migraine. Most insurers require pre-authorization for coverage and patients have to fail 2 or 3 different categories of migraine prevention which are not even approved for Chronic Migraine before *onabotulinumtoxinA* is covered. There is clinical trial evidence that patients with medication overuse can improve when given *onabotulinumtoxinA* but concomitant tapering and discontinuation of the overused medication(s) is also recommended.

Topiramate has been shown in clinical trials to be helpful in Chronic Migraine as have other agents, but it and they are not FDA approved for this indication.

Behavioral Therapy

Biofeedback training and cognitive restructuring have been shown to be effective in clinical trials and there are no adverse events. Biofeedback training is an excellent preventive therapy especially in children and may obviate the need for pharmacologic treatment. (see Fact Sheets on Behavioral Management and Pediatric Headaches)

Devices

The supraorbital nerve stimulator (Cefaly) was approved based on a small study. While supporting evidence of effectiveness is not strong, some patients benefit from its use, particularly those who prefer a non-pharmacologic option or in whom standard preventive agents are poorly tolerated or contraindicated. (See Fact Sheet on Devices)

Can Preventive Medications Ever Be Discontinued?

Although some patients prefer to continue taking effective preventive medications long-term, assuring reluctant patients that preventive medications are not necessarily a lifelong commitment helps encourage them to try the therapies. When migraines are controlled for 6 months, preventive medication(s) may be gradually discontinued, one at a time, over a period of months. *OnabotulinumtoxinA* injections can be given at longer intervals to see if the benefit is maintained.

Summary

Consider migraine prevention for frequent attacks or long attacks with disability when acute care medications do not work. The five on-label medications are good but many others can be used. Start low and go slow. Behavioral and alternative treatments as well as new devices may be helpful.

References

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