



## INFORMATION FOR HEALTH CARE PROFESSIONALS



### How to Choose a Preventive Medication for Migraine

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#### **Principles of Preventive Treatment**

Daily preventive migraine therapy is indicated for patients with frequent migraine attacks (1-2 per week or more), significant disability associated with individual attacks, poor response to acute care medications, contraindications to triptans and other vasoactive medications, significant triptan side effects, or use of symptomatic treatment more than 3 days per week. Preventive medications should be chosen based on co-existing medical conditions, as the optimal medication may improve both the migraine and the medical condition. For example, consider a beta blocker or calcium channel antagonist for a migraine patient with hypertension; a tricyclic antidepressant taken at bedtime may benefit a migraine patient who is depressed or having difficulty sleeping. 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 patient
- Always start treating with preventive medications at a low dose and gradually increase over an extended period of time, in order to minimize adverse events
- Continue well-tolerated medications for at least 2-3 months at a therapeutic level before deciding on effectiveness
- Communicate clear expectations to the patient regarding the timing and magnitude of expected clinical benefit
- Warn patients of the most frequent adverse events and explain when and how to contact you
- Establish a comprehensive migraine management plan that includes long-term goals, 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 migraine prevention and one of them, methysergide, is no longer available in the U.S. or Canada. 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. But if they are not helpful or if they are contraindicated, you may need to incorporate off-label uses of medications approved for other conditions.

The various categories of preventive medication are:

#### **$\beta$ -Blockers**

*Propranolol*, *nadolol*, *atenolol*, *metoprolol* and *timolol* are effective for migraine prevention. Common side effects are lethargy, depression, exercise intolerance, hypotension and sleep

disorders. Avoid their use in patients with asthma, diabetes, bradycardia and congestive heart failure. Patients taking propranolol who use eletriptan acutely must be given only 5 mg (half of the usual dose).

### **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. They can affect cardiac rhythm. They are useful for basilar-type migraine and isolated aura symptoms.

### **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 they occasionally cause headaches to worsen. They are useful in patients with co-existing depression, anxiety, tension-type headache or primary stabbing headache. Serotonin syndrome rarely occurs in patients taking serotonin reuptake inhibitors with triptans; the AHS has issued a position paper on this subject and the incidence is approximately 0.03% (see fact sheet on Serotonin Syndrome). There is less experience using *bupropion* and *trazodone* for migraine prevention.

### **Membrane Stabilizers (Anticonvulsants)**

Membrane stabilizers frequently used in the prevention of migraine include *divalproex sodium* (available and approved in an extended release form which is given only once per day), *sodium valproate*, *topiramate* and *gabapentin*. Several other medications in this category such as *levetiracetam* and *zonisamide* may be useful in some patients but do not have confirmed efficacy in randomized, placebo-controlled trials. *Valproate* is contraindicated in pregnancy, should not be prescribed for women of childbearing potential and should never be used in females intending to become pregnant. Potential neural tube defects should be discussed with all women of childbearing potential taking *valproate*. Similarly, *topiramate* is contraindicated during pregnancy because of cleft palate malformations, and should not be prescribed for patients with a history of kidney stones.

### **Nonsteroidal Anti-inflammatory Drugs**

NSAIDs, often used for acute treatment, also can 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.

### **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 butterbur (*Petasites hybridus*), feverfew (*Tanacetum parthenium*), magnesium, vitamin B2 (riboflavin), coenzyme Q 10 and melatonin.

### **Serotonergic Agents**

#### *Methysergide*

Methysergide (Sansert) has been used for migraine prevention for over 50 years but its use is limited due to its risk of retroperitoneal and peripleural fibrosis associated with extended use. It was discontinued from the US and Canadian markets, but it is still available elsewhere in the world.

#### *Cyproheptadine*

The antihistamine cyproheptadine is a 5-HT<sub>2</sub> antagonist with 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.

### **Miscellaneous Preventive Treatments**

#### *Botulinum toxin*

*OnabotulinumtoxinA* injections may be helpful in patients with chronic migraine and other headache types, as well as in patients who are refractory to oral agents or do not tolerate them. It is FDA-approved for prevention of chronic migraine only and many insurers require pre-authorization for coverage. Chronic migraine is defined as a patient with 15 days or more of headache per month, and a current or previous history of migraine. Medication overuse is not a contraindication but must be addressed in conjunction with onabotulinumtoxinA therapy.

In May 2012 the American Academy of Neurology and the American Headache Society issued two sets of guidelines on migraine prevention. One addressed pharmacologic therapy that has been proven effective in trials and one evaluated NSAIDs and complementary treatments that have proven effectiveness:

- Level A pharmacologic medications with established efficacy (in 2 or more Class I trials) are divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, timolol and frovatriptan for short term prevention of menstrually related migraine.
- Level B medications (with 1 Class I or 2 Class II studies) are amitriptyline, venlafaxine, atenolol, nadolol, and naratriptan and zolmitriptan for short term prevention of menstrually related migraine.
- The only complementary treatment recommended with Level A evidence was butterbur (*Petasites hybridus*).
- Level B evidence supports the use of multiple NSAIDs, magnesium, feverfew, riboflavin and histamine subcutaneous injections.

### **References**

- 1) Silberstein SD. Preventive migraine treatment. *Neurologic Clinics* 2009;27:429-43.
- 2) Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. *Neurology* 2012;78:1337-1345.
- 3) Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. *Neurology* 2012;78:1346-1353.