

Side Effects of Preventive Migraine Treatment

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According to the American Headache Society Position Statement on Integrating New Migraine Treatments Into Clinical Practice, preventive treatments should be based on the attack frequency and degree of disability. You should offer preventive treatment if a patient has:

- Six or more headache days/month whether they are disabling or not
- Four or more headache days/month with some disability
- Three or more severe headache days/month

You should consider a preventative treatment if the patient has two to three headache days/month with some disability.

Choosing a Preventive Treatment

In choosing an oral preventive medication, like with any treatment for your patient, you should select a couple of the medications and become familiar with their potential side effects. It is not necessary to be aware of all medications and treatments available. Developing a treatment plan should be

based on your experience with the medication, the patient's preference, and comorbidities. You need to also consider, if the patient is female, if she is pregnant, breastfeeding or attempting to conceive.

While the use of evidence-based treatments is important, only considering Level A evidence may keep you from considering an effective treatment for your patient. The classification of the oral preventive medications include: antiepileptic medications, beta blockers, and antidepressants.

Antiepileptic Drugs

Divalproex sodium, valproate sodium and topiramate have all established efficacy and Class A evidence. However, they all have the potential for teratogenic effects and should be avoided in patients who are contemplating pregnancy. In addition, Divalproex sodium and valproate sodium have the side effects of nausea, weight gain, tremor, hair loss, and pancreatitis. These medications may not be appropriate for your patients who are overweight or have an underlying

tremor. However, these medications have been used as mood stabilizers and can be considered in those patients they may also have bipolar disorder.

Topiramate can have adverse events including fatigue, dizziness, somnolence and mood changes. Probably the most limiting side effect is the cognitive problems associated with this medication, which include word-finding problems, slowed thinking, and concentration and memory difficulties. Because topiramate is a carbonic anhydrase inhibitor, it can cause kidney stones and should be avoided in patients who have a history of calcium kidney stones. Paresthesias are common with the medication as well as taste disturbances. It has also been associated with acute angle glaucoma and changes in vision.

In those patients that did not tolerate topiramate, zonisamide is another antiepileptic medication that is also a carbonic anhydrase inhibitor and has demonstrated some efficacy in treating migraine. It has a similar side effect profile, but may be tolerated better in some patients. Weight loss has been observed with both topiramate and zonisamide and can be considered in patients who are overweight. Topiramate has also been used for patients with alcohol use disorder.

Gabapentin has also been suggested as a preventive treatment for migraine. The studies have been mixed. However, in patients that have difficulty sleeping, associated painful neuropathies, or chronic pain syndromes, it may be a good option to help with these comorbidities. Common side effects include somnolence, dizziness, peripheral edema and weight gain.

Beta Blockers

Propranolol has the most studies and does show efficacy but also has significant side effects. Metoprolol, likewise showed efficacy as did atenolol, nadolol and timolol. These studies were smaller and had less strength of evidence. Beta blockers can lower blood pressure and heart rate which can be beneficial in some patients but can lead to exercise intolerance and hypotension which would be undesirable side effects. Metoprolol and atenolol are beta selective and may be a better choice in patients with asthma, although these medications can also worsen asthma. The beta blockers can also cause depression and impotence and should be avoided in patients with Raynaud's syndrome. There have not been any head-to-head comparisons of the beta blockers to determine that one is more effective than the other.

Antidepressants

The earliest studies used amitriptyline in the treatment of migraine and amitriptyline has been used as a comparator to other treatments. Other tricyclics have been used including nortriptyline, imipramine, desipramine, doxepin, and protriptyline. There may not be studies in the literature for all of these. However, evaluating the individual side effect profile can determine which medication may be appropriate in a particular patient. Amitriptyline and doxepin tend to be the most sedating and protriptyline the least. All of them cause

weight gain. All can help or worsen depression and anxiety and are associated with dry eyes, dry mouth and constipation due to the anticholinergic effects. Caution should be used in patients on other anticholinergics and if they have Sjogren's syndrome.

The SNRI, venlafaxine was shown to be effective in treating migraine. Duloxetine is indicated in the treatment of many painful conditions including, fibromyalgia, diabetic neuropathy, and chronic musculoskeletal pain. It has not been studied specifically in the treatment of migraine. However, there is no reason to think it wouldn't be effective in treating patients with migraine especially if they have the comorbid conditions of chronic pain, generalized anxiety disorder and/or fibromyalgia. The SNRIs can be associated with nausea, sexual dysfunction but have less problems with the sedation and weight gain as do the tricyclic antidepressants. They also have significant withdrawal symptoms, but may be a bit less for duloxetine as it has the longer half-life.

In choosing an oral preventive treatment it is best to start low and titrate slowly. The selection of a preventive treatment should be based on multiple factors: provider experience, patient preference, comorbid and coexistent conditions, physiological factors such as heart rate and blood pressure, body habitus and pregnancy.



CGRP mAbs

This treatment group is the first treatment designed specifically to treat migraine. There are four treatments approved by the FDA for the preventive treatment of migraine. Erenumab targets the receptor and the other three (fremunazemb, galcanezumab and eptinezumab) target the CGRP ligand. Erenumab, fremanezumab and galcanezumab are administered via subcutaneous injection and eptinezumab is via intravenous infusion. The primary side effect to the three subcutaneous injectables was injection site reaction for fremanezumab and galcanezumab and injection site reaction and constipation for erenumab. Hypersensitivity reactions have been reported in all three. The most common adverse reactions for the infusion, eptinezumab were nasopharyngitis and hypersensitivity reaction. These agents do not require titration and all may demonstrate rapid treatment effects over days to weeks. These treatments

are indicated for patients over the age of 18 and, presently, it is recommended that the patient has had the inability to tolerate or inadequate response to a six-week trial of at least two of the following: topiramate, divalproex sodium/valproate sodium, beta blocker, tricyclic antidepressant, SNRI.

When discussing a preventive treatment with your patient, it is imperative that they understand the medication and its side effects as well as having appropriate expectations on the

efficacy and need to have an adequate trial of the medication. Success of a treatment can be defined as any of the following: 50% reduction in headache or migraine days; significant decrease in attack duration and/or severity; better response to abortive treatment; decreased migraine related disability; improvement in health related quality of life. The success of a preventive treatment, therefore, depends on establishing realistic expectations by the patient.

Summary of Preventive Treatment for Patient Discussion

Drug	Dosage	Comments
Antiepileptic		
Divalproex/Sodium Valproate	500-1500 mg	Teratogenic effects, weight gain
Topiramate	50-200 mg	Teratogenic effects, weight loss, cognitive effects
Zonisamide	50-300 mg	Weight loss
Gabapentin	300-3600 mg	Mixed results but may be beneficial in patients with sleep disorders and pain syndromes
Beta Blockers		
<i>Should be avoided in patients with Raynaud's syndrome</i>		
Propranolol	40-240 mg	
Metoprolol	25-200mg	Use long acting preparation once daily, beta selective
Atenolol	25-100 mg	Beta selective
Nadolol	20-160 mg	
Timolol	10-30 mg BID	
Antidepressants		
Amitriptyline	10-150 mg	Most sedating, weight gain
Nortriptyline	10-150 mg	
Protriptyline	5-60 mg	Least sedating
Venlafaxine	75-225 mg	Significant withdrawal symptoms
Duloxetine	30-120 mg	Consider in patients with comorbid anxiety, depression, and chronic pain syndromes.

Recommended Reading:

The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache*. 2019;59:1-18.

Silberstein SD. Preventive migraine treatment. *Continuum (Minneapolis)*. 2015;21(4 *Headache*):973-989.