



## INFORMATION FOR HEALTH CARE PROFESSIONALS



### **Evidence-based Basics on Nutraceuticals: Herbs, Minerals, Vitamins, and Supplements in Migraine Management**

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Is there a place for nutraceuticals in the management of migraine? This document reviews the randomized, controlled trials (RCT) for migraine for various minerals, herbs, vitamins and supplements, and gives therapeutic recommendations for the interested clinician.

#### **Rationale for Use**

There are two basic potential mechanisms for the usually tried supplements for migraine prevention, 1) to reduce migraine brain neuronal hyperexcitability, or 2) to improve energy metabolism. Low ionized magnesium levels, abnormal neuronal membrane ion channels (channelopathies) with resultant increased excitatory glutamatergic activity, and mitochondrial dysfunction with abnormal energy metabolism are linked to the genesis of migraine. Low magnesium and channelopathies are related; riboflavin or coenzyme Q10 can be used to treat mitochondriopathy; petasites may decrease the meningeal inflammatory mechanisms of migraine pain.

#### **Magnesium**

Low magnesium is linked to influx of calcium into neurons, with resultant glutamate release into the synapse. Low magnesium at the synapse causes post-synaptic neuronal excitation. Multiple studies demonstrate low magnesium in migraine patients. Trials with magnesium supplementation for migraine prophylaxis have yielded mixed results, with the positive studies in patients with aura and with perimenstrual migraine. Parenteral magnesium (1 gram IV) can terminate migraine in patients with low ionized magnesium levels, and in those with aura. The recommended dose is 400–600 mg/day of chelated magnesium (taurate, glycinate, oxide, etc) for at least 3 to 4 months. Diarrhea limits oral magnesium supplementation clinically. Although magnesium is quite safe for use most of the time, as of May 2013, magnesium sulfate has been rated Category D for use in pregnancy, meaning “positive evidence of risk to humans from human studies or post-marketing data”, due to studies showing bone problems for the developing fetus.

#### **Riboflavin (Vitamin B2)**

Riboflavin is a cofactor in the Krebs cycle during respiration, and several studies suggest mitochondrial dysfunction in some migraine patients, with abnormal phosphorylation of ADP to ATP. Thus, giving B2 could theoretically improve energy metabolism. There are four RCTs on B2 for migraine prevention. In the first, in adults, 400 mg riboflavin taken daily for 3 months was superior to placebo for reduction of migraine frequency and headache days. Two patients had diarrhea and polyuria. In the second, also in adults, 400 mg of B2 (combined with feverfew and low dose

magnesium) was no different than 25 mg of B2, which was selected as a placebo dose. In both dose groups and both studies, > 40% of patients had  $\geq$  50% reduction in migraine frequency. Thus, it was unclear whether 25 mg B2 is an active dose, or whether B2 was no more effective than placebo. Two pediatric RCTs were both negative. Thus, 3 of 4 RCTs with B2 weigh against effectiveness. On additional study suggested B2 might work in those with a mitochondrial haplotype associated with low mitochondrial function. The Canadian Headache Society Guidelines strongly recommend B2 for migraine prevention, which they base on the favorable adverse event profile, despite the conflicting and low quality evidence for its use.

### **Coenzyme Q10 (CoQ10)**

CoQ10 transfers electrons in the electron transport chain, so it can theoretically treat mitochondriopathy. One RCT of 42 patients found 100 mg TID of CoQ10 for 3 months superior to placebo; 48% of subjects had  $\geq$  50% reduction in attack frequency. In another study of 1,478 migraine patients from 3-22 years old, low CoQ10 levels occurred in 33%. Repleted CoQ10 with daily supplementation was linked to reduced migraine frequency.

CoQ10 is generally well tolerated. Side effects at high doses are uncommon, including nausea, anorexia, dyspepsia, diarrhea, and rash.

Again, the Canadian Headache Society guidelines strongly recommend use of CoQ10 for the same reasons and with the same caveats as for riboflavin.

### **Feverfew**

Feverfew is sold as capsules of the dried leaves of the weed plant *tanacetum parthenium* in the US. A meta-analysis of all of the RCTs up to 1998 concluded that data were of too low quality and too varied in results to be sure whether feverfew works in migraine prevention. Two recent RCTs of a purified stable extract of feverfew, MIG-99, suggest once again that feverfew is ineffective in migraine prevention, or has so low a clinical effect as to be close to useless. A more recent meta-analysis of five RCTs on feverfew found a suggestion of effect for migraine with aura, but otherwise the studies were negative, and concluded that feverfew is no better than placebo. Methodologic problems with the studies make meta-analysis of limited or no utility. The potential complications of arthralgias, gastrointestinal disturbances, and mouth ulcers, and the wide variety of potency in dried leaves, preclude a strong recommendation for migraine prevention.

### **Petasites (Butterbur root)**

A root extract of the butterbur plant *Petasites hybridus* is sold in various countries around the world. Two RCTs were positive for the brand name Petadolex™: a small study of 100 mg/day, and a larger study of 150 mg/day vs. placebo. The only side effect reported from those studies was burping.

However, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) in 2012 removed all butterbur/Petasites products from the UK market, and their website states, "Butterbur products have been associated with [40] cases of liver toxicity [in the literature]. Of these cases, nine were of acute hepatitis and two of the nine cases resulted in liver failure requiring transplantation." The brand name Petadolex manufacturing technique was also changed and the Swiss and German regulatory agencies also banned Petasites products. In view of these issues, the American Headache Society/American Academy of Neurology withdrew their Evidence-based guidelines for NSAIDs and other complementary treatments for episodic migraine

prevention in adults. As of January 2017, no recommendations for the use of Petasites can be made.

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