Evidence Basis Behind the Use of Supplements

Tamara Pringsheim, MD FRCPC FAAN
Associate Professor, University of Calgary
Evidence Based Medicine Methodologist, American Academy of Neurology

I have no disclosures

Objectives

- List the supplements for which there are clinical trials evaluating efficacy for migraine headache prevention
- Describe the level of evidence for each supplement used for the prevention of migraine headache
- Prescribe supplements using a safe and evidence-based approach to care

Riboflavin

- Vitamin B2
- Essential component of two major coenzymes which play roles in energy production, cellular function, growth and development, and metabolism of fats, drugs and steroids
- 1 RCT of riboflavin vs placebo
- AAN/AHS
  - Level B: Probably effective and should be considered for migraine prevention

Schoenen 1998

- Class I
  - Riboflavin 400 mg/day vs. placebo for 12 weeks, after baseline 1 month placebo phase
  - N=55
- Primary outcome: Change in attack frequency in month 4 vs. month 1
  - Riboflavin 2 fewer attacks per month vs. no change in placebo (p=0.0001)
- Responder rate: percentage of patients achieving a 50% decrease in migraine frequency
  - Riboflavin 56% vs. Placebo 19%
  - 2 minor adverse reactions reported in riboflavin group-diarrhea and polyuria

Riboflavin: National Institutes of Health

- Recommended dietary allowance (RDA) in adults
  - 1.3 mg male, 1.1 mg female
- Intakes of riboflavin from food that are many times the RDA have no observable toxicity, possibly because riboflavin's solubility and capacity to be absorbed in the gastrointestinal tract are limited
- Because adverse effects from high riboflavin intakes from foods or supplements have not been reported, the Food and Nutrition Board (FNB) did not establish tolerable upper intake levels for riboflavin
- Riboflavin is not known to have any clinically relevant interactions with medications.

Coenzyme Q10

- Activity in mitochondrial function and as an antioxidant
- 2 RCT of coenzyme Q10 as a migraine preventive
- AAN/AHS (based on results of 1 RCT)
  - Level C: Possibly effective and may be considered for migraine prevention

Sandor 2005

- Class II
  - Coenzyme Q10 100 mg 3 times daily vs. placebo for 3 months, after 1 month placebo baseline
  - N=43
- Primary outcome: change from baseline to month 4 in attack frequency
  - Coenzyme Q10 -1.19 vs. placebo -0.09 (p=0.05)
- Responder rate
  - Coenzyme Q10 47.6% vs. placebo 14.3% (p=0.02)
  - Few reports of gastrointestinal disturbances and cutaneous allergy as side effects

Dahri 2017

- Class II
  - Coenzyme Q10 200 mg twice daily vs. placebo for 12 weeks, after one month baseline
  - All patients also started on tricyclic or anticonvulsant for migraine prevention at first visit
  - N=84
- Primary outcome: not stated
- Responder rate
  - Coenzyme Q10 53.8% vs. placebo 31.6% (p=0.048)
- No discussion of adverse effects

Coenzyme Q10: National Institutes of Health

- No RDA
- Studies have not reported serious side effects related to CoQ10 use
- The most common side effects of CoQ10 include insomnia, increased liver enzymes, rashes, nausea, upper abdominal pain, dizziness, sensitivity to light, irritability, headaches, heartburn, and fatigue
- CoQ10 should not be used by women who are pregnant or breastfeeding.
- Statins may lower the levels of CoQ10 in the blood
- CoQ10 may make warfarin less effective.

Oral Magnesium

- Magnesium plays a role in multiple physiological processes
- Co-factor in more than 300 en zyme systems that regulate protein synthesis, muscle and nerve function, blood glucose control and blood pressure
- Multiple studies suggest a relationship between magnesium deficiency and migraine
- 3 studies of magnesium for migraine prophylaxis
- AAN/AHS
  - Level B: Probably effective and should be considered for migraine prevention

Peikert 1996

- Class II
  - Trimagnesium dicitrate 600 mg vs. placebo for 12 weeks
  - N=81
- Reduction in attack frequency (final month vs. baseline)
  - Magnesium 1.51 Placebo 0.58, p=0.03
- Responder Rate
  - Magnesium 52.8% Placebo 34.4%, p=0.15
- Soft stool diarrhea in 8; treatment related discontinuation in 2

Pfaffenrath 1996

- Class III
- Magnesium aspartate 243 mg twice daily vs. placebo for 12 weeks following 4 week baseline
- N=69
- No significant difference between groups in duration of migraine or intensity of migraine
- High rate of soft stools/diarrhea in magnesium treated group

Koseoglu 2008

- Class III
  - Magnesium citrate 600 mg vs. placebo for 12 weeks after 4 week baseline
  - N=40
- Reduction in monthly attack frequency, final month of treatment vs. baseline
  - Magnesium -1, Placebo -0.5, p=0.005

Oral Magnesium: National Institutes of Health

- RDA in adults
  - 400-420 mg in males, 310-360 mg in females (depending on age, pregnancy and lactation)
- Dietary surveys of people in the United States consistently show that intakes of magnesium are lower than recommended amounts.
- The Supplement Facts panel on a dietary supplement label declares the amount of elemental magnesium in the product, not the weight of the entire magnesium-containing compound.
- Absorption of magnesium from different kinds of magnesium supplements varies
- Magnesium in the aspartate, citrate, lactate, and chloride forms is absorbed more completely and is more bioavailable than magnesium oxide and magnesium sulfate
- Very high doses of zinc from supplements (142 mg/day) can interfere with magnesium absorption

Oral Magnesium: National Institutes of Health

- Too much magnesium from food does not pose a health risk in healthy individuals because the kidneys eliminate excess amounts in the urine
- High doses of magnesium from dietary supplements often result in diarrhea
  - Most commonly reported with magnesium carbonate, chloride, gluconate, and oxide
- Very large doses of magnesium-containing laxatives and antacids (providing more than 5,000 mg/day magnesium) have been associated with magnesium toxicity
- The risk of magnesium toxicity increases with impaired renal function
- Tolerable upper intake levels for supplemental magnesium by FNB 350 mg in adults
- Drug interactions with bisphosphonates, tetracyclines, quinolones, diuretics and proton pump inhibitors

Feverfew/Tanacetum Parthenium/MIG-99

- May act as an anti-inflammatory through inhibition of prostaglandin synthesis
- AAN/AHS
  - Level B; probably effective and should be considered for migraine prevention

Cochrane Review 2015: Feverfew for preventing migraine

- Six trials with 561 patients; sample size ranged from 17 to 218
- Pooled analysis not possible due to lack of common outcome measures and heterogeneity between studies
- Feverfew self-administered orally one to three times daily in capsule form
- Study duration ranged from 2-8 months

Feverfew for preventing migraine

- Results of the six trials are mixed
  - 4 positive trials, 2 negative trials
- Diener 2005
  - Most recent and largest study
  - Feverfew CO2 extract (MIG-99) vs placebo three times daily for 16 weeks
  - N=218
  - Primary outcome: total number of migraine attacks within 28 days during 2nd and 3rd 28 day treatment period compared with baseline
  - Feverfew -1.9 attacks per month
  - Placebo -1.3 attacks per month ($p<0.05$)

Feverfew for preventing migraine

- Adverse events mild and reversible
  - Gastrointestinal problems most common
  - Mouth ulceration

Feverfew: National Institutes of Health

- No serious side effects have been reported from feverfew
- Side effects can include nausea, digestive problems, and bloating; if the fresh leaves are chewed, sores and irritation of the mouth may occur
- People who take feverfew for a long time and then stop taking it may have difficulty sleeping, headaches, anxiety, and stiff and painful muscles
- Do not take feverfew while pregnant because it may affect uterine contractions
- Handling the plant may cause skin irritation

Butterbur (Petasites hybridus)

- Shrub used for medicinal purposes for centuries
- Main pharmacologically active component are petasin and isopetasin
- Anti-inflammatory properties; inhibits cyclooxygenase 2 and leukotriene biosynthesis
- Calcium channel regulation
- 2 RCTs of Butterbur using Petadolex formulation
- AAN
  - Level A Recommendation
  - Established as effective and should be offered for migraine prevention

Butterbur and Pyrrolizidine Alkaloids (PAs)

- Butterbur contains PAs which are hepatotoxic
- These toxins are removed in the Petadolex formulation by a proprietary treatment but may be present in other butterbur extracts
- Safety concerns regarding Butterbur preparations have arisen in recent years
- Petadolex taken off the market in UK and Switzerland because of safety concerns and in Germany because of changes in the purification process (requires re-registration)

Review Article

Cephalalgia Reports

Cephalalgia Reports
Volume 1: 1–8

DOI: 10.1177/2515816318759304
journals.sagepub.com/home/rep
SAGE

Safety profile of a special butterbur extract from *Petasites hybridus* in migraine prevention with emphasis on the liver

HC Diener[1], FG Freitag[2], and U Danesch[3]

Analysis of Available Butterbur Products

- European Food Safety Authority considers a threshold of 0.007 micrograms per kilogram PA daily intake as acceptable exposure (0.35 micrograms in 50 kg person)
- National Center for Natural Products Research analyzed 21 commercial butterbur products available in the US for petasins (active ingredient) and PAs (toxin)
- 7/21 products had a petasin amount within the limits of the label claim and no detectable PAs (3/7 were Petadolex formulation)
- 6/21 had no detectable amounts of petasin!
- 7/21 had PA levels between 0.1 and 4.48 micrograms per tablet

Adverse Drug Reactions of the Hepatobiliary System

- 12 reports of increased liver enzymes from two RCTs of Petadolex including a total of 397 patients
- Adverse drug reactions involving the hepatobiliary system reported outside of RCTs between 1972 and 2015
- 50 non-serious
  - 2 cases of reversible liver enzyme elevation rated as probably related to Petadolex
- 10 serious
- Germany, UK and Austria
  - 10 cases evaluated by the Roussel Uclaf Causality Assessment Method (RUCAM) test
  - 2 cases possibly related, 5 cases unlikely related, 3 cases not related

Butterbur: National Institutes of Health

- Only butterbur products that have been processed to remove PAs and are labeled or certified as PA-free should be used.
- Several studies, including a few studies of children and adolescents, have reported that PA-free butterbur products are safe and well tolerated when taken by mouth in recommended doses for up to 16 weeks. The safety of longer-term use has not been established.
- Butterbur is usually well tolerated but can cause side effects such as belching, headache, itchy eyes, diarrhea, breathing difficulties, fatigue, and drowsiness.
- Butterbur may cause allergic reactions in people who are sensitive to plants such as ragweed, chrysanthemums, marigolds, and daisies.

Lipton 2004

- Class I
  - Petadolex 50 mg BID, Petadolex 75 mg BID vs. placebo for 16 weeks
  - N=233
- Percent change from baseline in migraine frequency
  - Placebo -28%
  - 50 mg -32%
  - 75 mg -45% (p=0.005)
- Responder rate
  - Placebo 49%
  - 50 mg 56%
  - 75 mg 68% (p<0.05)
  - Mild gastrointestinal side effects- burping

Grossman 2000/Diener 2004

- Class I
  - Petadolex 50 mg BID vs. placebo for 12 weeks
  - N=33
- Number of migraine attacks per month
  - Petadolex Baseline 3.4; 12 weeks 1.8 (p=0.0024)
  - Placebo Baseline 2.9; 12 weeks 2.6
- Responder Rate
  - Petadolex 45%
  - Placebo 15%
  - Nonsignificant

Combining nutraceuticals

Less is better than more?

Maizels 2004

- Class II study
  - Combination treatment of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg vs. riboflavin 25 mg for three months, after one month baseline run-in
  - N=52
- No significant difference between groups in primary outcome, responder rate
  - 44% vs. 42%
  - Active comparator? (RDA for riboflavin 1.3 mg males, 1.1 mg females)
  - High placebo response?

Gaul 2015

- Class II study
- Combination tablet (Dolovent) containing 400 mg riboflavin, 600 mg magnesium, 150 mg coenzyme Q10 and multivitamins/trace elements per 4 capsules
- Compared to placebo for three months, after one month baseline period
- N=130
- No significant difference between groups in the primary outcome, days with migraine
  - Combination tablet 6.2 (SD 1.95) at baseline, 4.4 (SD 2.99) at 3 months
  - Placebo 6.5 (SD 1.78) at baseline, 5.2 (SD 3.22) at 3 months
- Significantly greater reduction in maximal pain per migraine day with combination tablet vs placebo (p=0.03)
- Most frequent adverse effect was diarrhea

Other supplements

- Omega-3
  - 1 negative RCT
- Folic acid, B6 and B12 combination
  - 1 negative RCT
- Lavender essential oil
  - 1 positive RCT

Conclusions

- Some evidence to support the use of supplements for migraine prevention
- Conflicting results
- Choice of preparation is important