

Nutraceuticals in the Treatment of Headache: Evidence-based Approaches



W. J. Becker
University of Calgary



Objectives

After attendance at this session, participants will be able to:

- discuss the evidence supporting the use magnesium, butterbur, riboflavin, coenzyme Q10, and feverfew in the prophylaxis of migraine.
- describe what is known of the mode of action of the commonly used nutraceuticals in the prophylaxis of migraine.
- utilize the commonly used nutraceuticals appropriately for the prophylactic treatment of migraine, based upon the patient's clinical features.

Definition: Nutraceutical

- From “nutrient” and “pharmaceutical”.
- Any product derived from food with extra health benefits in addition to its basic nutritional value.
- It includes isolated nutrients, dietary supplements and herbal products.
- Nutraceutical has no meaning in US law. Depending on its ingredients and the claims made, it may be regulated as a drug, dietary supplement, or food.
- The worldwide nutraceuticals market has been projected to reach US \$250 billion by 2018.

“Let food be thy medicine”



Hippocrates of Kos c. 460 – c. 370 BC)
Wikipedia

Nutraceuticals Used in Migraine Prophylaxis

- Butterbur
- Magnesium
- Riboflavin
- Coenzyme Q10
- Feverfew
- Omega-3 Fatty Acids

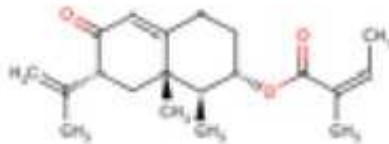
Cases: Which of the following would be appropriate for prophylaxis with a nutraceutical?

- Case 1. A 25 year old woman presents with 4 migraine attacks per month. They respond well to sumatriptan, and she is not missing any work. She uses sumatriptan on 4 days a month. She has never taken a prophylactic.
- Case 2. A 35 year old woman is experiencing 4 migraine attacks per month, which last about 2 days each. She responds to sumatriptan, but not all that well, and is missing two days of work per month. She is very frustrated because of her migraine-related disability. She has never taken a prophylactic.

Butterbur

(*Petasites hybridus*)

its large leaves were used to wrap butter during warm weather in the UK

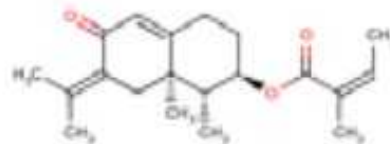


Petasin

Active ingredients: Have anti-inflammatory and smooth muscle relaxant properties (inhibit COX-2, PGE2, and leukotriene synthesis, and affect calcium channels)

Pyrrolizidine alkaloids

Hepatotoxic and carcinogenic



Isopetasin



Giles M et al
Journal of Herbal
Pharmacotherapy,
Vol. 5(3) 2005

Clinical information review document
National Institutes of Health, Nov 2009

Butterbur (*Petasites hybridus*)

- Used for medicinal purposes for centuries
- 2 RCTs of Butterbur in migraine prophylaxis using Petadolex formulation

Lipton 2004

- Good/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

- Good/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

Butterbur and the Future

- Is it **Bye-bye, butterbur** because of toxicological issues?
- Its efficacy in migraine prophylaxis is reasonably well established.

American Academy of Neurology Guideline
Level A Recommendation
Is effective and should be offered
for migraine prevention

Canadian Headache Society Guideline
Strong recommendation for use,
moderate quality evidence

EFNS Guideline: Prophylactic of second
choice, Level B (probably effective)
recommendation

But, safety concerns may result in these recommendations being re-evaluated.

Holland S et al, Neurology
2012; 78: 1346-1353

Pringsheim, I et al
Can J Neurol Sci. 2012;39(2 Suppl 2):S1-59.

Evers S et al Eur J Neurol 2009;
16: 968-981

Is Butterbur safe?

- Only if all the pyrrolizidine alkaloids are removed
- Lack of stringent regulations for marketing of natural products is a major problem for patients who would like to use butterbur.
- When 21 butterbur-containing dietary supplements were analyzed:
 - Only 7 contained the active ingredients (petasins) in the amount claimed by the label.
 - 6 contained no active ingredients, and 4 more contained only traces
 - Seven contained detectable toxic pyrrolizidine alkaloids
- Only Petadolex based products consistently met standards (Prieto)

Prieto JM Botanicals: Targets and Therapy 2014; 4: 1-9, Avula B et al Journal of Pharmaceutical and Biomedical Analysis 2012; 70: 53-63

Is Butterbur Safe?

- In the UK, regulatory authorities have asked patients not to take butterbur, and have asked businesses to voluntarily withdraw it from the market. It is not banned or prohibited. There have been no serious side effects reported in the UK or the USA.
- Because of new regulations, butterbur cannot be produced in Germany, but it can be prescribed and imported from abroad. The two clinical trials done with the new manufacturing method were not considered sufficient to prove safety.
- Butterbur was banned in Switzerland, but one brand appealed and is currently available.
- Of 9 reported cases of liver toxicity in Germany, only one was considered as “probably related” by a panel of experts.



Magnesium



Magnesium

- Magnesium plays a role in multiple physiological processes, including reducing excitability of NMDA receptors, and influencing mitochondrial metabolism.
- Multiple studies suggest a relationship between magnesium deficiency and migraine.
- Nearly 50 % of Americans have a Mg deficient diet (processed foods and refined grains are low in Mg)
- Proton pump inhibitors reduce Mg absorption.
- Caffeine, alcohol, and stress increase Mg excretion.
- 3 studies of magnesium for migraine prophylaxis

Peikert 1996

- Fair/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

- Fair/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
- ? Poor absorption?

Magnesium

- AAN/AHS

- Level B: Probably effective and should be considered for migraine prevention

- CHS

- Strong Recommendation, low quality evidence. There is some evidence for benefit and side effects are minimal. Due to contrary evidence in trials, recommend that magnesium citrate 600 mg be used.

- EFNS

- Level C (possibly effective); third choice prophylactic

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Riboflavin

- Vitamin B2
- Component of enzymes that are cofactors in the electron transport chain of the Krebs cycle
- Plays a role in membrane stability and maintenance of energy-related cellular functions
- Recommended daily nutritional dose: 1.2 mg
- 2 RCTs of riboflavin for migraine prophylaxis (400 mg)



Schoenen 1998

- Good/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

Maizels 2004

- Fair/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?

Riboflavin: Negative Pediatric Studies

- MacLennan SC et al J, Child Neurol. 2008 Nov;23(11):1300-4.
- Riboflavin 200 mg vs placebo double-blind, n = 48
- No difference from placebo

- Bruijn J et al Cephalalgia 2010; 30: 1426-1434
- Riboflavin 50 mg vs placebo double-blind crossover, n = 42
- No difference from placebo for migraine prophylaxis

Riboflavin

- AAN/AHS
 - Level B: Probably effective and should be considered for migraine prevention
- CHS
 - Strong recommendation, low quality evidence: some evidence for benefit and side effects are minimal
- EFNS
 - Level C: possibly effective, third choice prophylactic

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Coenzyme Q10

- Enzyme cofactor involved in the mitochondrial electron transport chain, ATP production
 - Synthesized in the body – biosynthesis requires at least 12 genes
 - Inhibits warfarin
 - Some marketed products contain no Q10, others have more than the label indicates.
-
- 1 RCT of coenzyme Q10 as a migraine preventive



Sandor 2005

- Fair/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
- Responder rate
 - Coenzyme Q10 47.6% vs. placebo 14.3%
 - Few reports of gastrointestinal disturbances and cutaneous allergy as side effects

Coenzyme Q10

- AAN/AHS
 - Level C: Possibly effective and may be considered for migraine prevention
- CHS
 - Strong recommendation, low quality evidence
- EFNS
 - Level C: possibly effective, 3rd choice prophylactic

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Conclusions

- Targeted manipulation of Omega-3 fatty acids improved pain and improved quality of life in patients with chronic daily headache of unspecified diagnosis
- Hit-6 decreased by 7.5 in the high 3 plus low 6 group versus a reduction of only 2.1 in the low 6 group. ($p < 0.001$)

Ramsden CE et al Pain 2013; 154: 2441 - 2451

Nutraceuticals for Migraine Prevention

- There is evidence to support the use of several nutraceuticals for migraine prevention, although the evidence is modest
- The amount of benefit with nutraceuticals may be modest for most patients
- Worth trying in individuals who wish to avoid side-effects

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Cases: Which of the following would be appropriate for prophylaxis with a nutraceutical?

- Case 1. A 25 year old woman presents with 4 migraine attacks per month. They respond well to sumatriptan, and she is not missing any work. She uses sumatriptan on 4 days a month. She has never taken a prophylactic.

Opinion: Not very disabled, could be appropriate

- Case 2. A 35 year old woman is experiencing 4 migraine attacks per month, which last about 2 days each. She responds to sumatriptan, but not all that well, and is missing two days of work per month. She is very frustrated because of her migraine-related disability. She has never taken a prophylactic.

Opinion: Quite disabled. She should have a drug unless she insists on a "non-drug" approach.

Case 3

- A 37 year old woman has tried multiple prophylactics in the past without success. She is quite disabled by her frequent migraines, and is having 12 headache days a month. She has had a tubal ligation in the past.
- It is decided to try divalproex sodium which she has not tried in the past.
- Because of the refractory nature of her migraine, ***would it be appropriate for her to also take magnesium citrate 300 mg twice a day, and riboflavin 400 mg daily?***

When Should Nutraceuticals be Used?

- Consider:
 1. For patients without marked disability who are trying prophylaxis for the first time.
 2. For patients for whom avoiding side-effects is more important than efficacy
 3. For patients who have intolerable side-effects on conventional drug prophylactics.
 4. As a baseline (riboflavin, magnesium) to which drug prophylactics can be added if necessary.

