
Expert Opinion

“Natural” or Alternative Medications for Migraine Prevention

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Key words: fever few, petasites, magnesium, riboflavin, coenzyme Q10, melatonin

(*Headache* 2006;46:1012-1018)

Many migraineurs are quite concerned about the toxicity of prescription medications and prefer alternative treatments regarded by them to be “natural” and thus relatively free of any side effects. If you are knowledgeable about these treatments, patients are likely to perceive you to be an enlightened physician who understands and is sympathetic to their concerns and preferences.

CLINICAL HISTORY

A medical school statistician/epidemiologist has frequent migraines. She is interested in the possibility of a preventative medication. From her research, she concludes that the usual preventative medications reduce headache frequency by about 50% in about 50% of patients, but she is concerned about the potential for side-effects and wonders about the efficacy of alternative treatments. She is also curious about the scientific validity of the studies.

Question: What is the efficacy of alternative treatments such as feverfew, petasites, magnesium, ri-

boflavin, coenzyme Q10, and melatonin? Are there any safety concerns?

EXPERT OPINION

This is a patient frequently encountered in clinical headache practice. Her interest in prevention should be honored with an adequate response, regardless of the number of days of headache she is experiencing or associated disability. Given the general interest in this area and the fact that complementary and alternative medicine (CAM) is often perceived by the public to be more helpful than conventional care for the treatment of headache and neck and back conditions, CAM for headache prevention should be considered early in care.^{1,2} According to Rossi et al, physicians should be aware of patient-driven interests in CAM so as to prevent misuse of healthcare resources and to be better equipped to meet patients' needs.¹ Approximately 25% of modern prescription drugs are plant-derived, but rarely have “herbal remedies” undergone the same scientific scrutiny devoted to conventional drugs; Peta-dolex, a notable exception, may be approaching the conventional standard for drug investigation. Despite the unknowns regarding safety and the lack of proven efficacy, however, a myriad of such remedies are used.

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Many migraineurs suffer significant functional disability, and individuals with episodic migraine are at risk for possible progression to chronic headache. Scher et al report that progression to greater than 15 headache days per month occurs at a rate of 3% per year, with an additional 6% progressing to more than 2 days per week.³ Aggravating migraine's natural drift toward chronicity is the overuse of symptomatic medication(s). This increasing pervasiveness may have a rather grim biological basis and implications. Kruit et al have reported brain MRI findings consistent with stroke in a surprisingly high proportion of individuals with more severe forms of migraine; and Rome hypothesizes that inadequately treated migraine may lead to "limbically" augmented pain (affective distress/stress) creating daily headache.⁴⁻⁷ John Edmeads speaks of the imperative need to keep the frequency and disability of attacks down and emphasizes the need to initiate "pre-emptive" prophylaxis when attack frequency increases (even if the increase is less than dramatic) when the requirement for "acute medications" increases (even if medication overuse *per se* is not yet evident), and in anticipation of situations or provoking factors known to increase frequency of attack (eg, stress) (personal communication).

For preemptive prophylactic therapy, CAM is not only a viable option, but should be a major consideration. Patients often balk at the use of daily drugs due to the perception such treatment may frequently cause side-effects. So, why not a "natural" agent, mineral, vitamin, or bodily substance? The modern equivalent to the "wild, wild, west" (ie, the Internet) informs us that petasites "reduces inflammation and spasms in blood vessel walls," that coenzyme Q10 (CoQ10) enhances energy through "sparkling" energy production within cells, and that melatonin is a natural brain (pineal gland) secretion that is found in lower levels in migraineurs. The Internet, however, fails to inform our patients that these CAM therapies are not as strictly regulated by the Food and Drug Administration of the United States as are prescription therapies and devices; they are classified as dietary supplements and not drugs. Interestingly, this is not true for Canada, where the Health Protection Branch of Health Canada regulates herbal medications, and herbals such as brand Petadolex, a petasites extract,

is regulated by the German Health Authority's Commission E.

Also of concern is the lack of industry standardization as regards the contents and purity of herbals, along with batch-to-batch consistency.⁸ For example, to determine the actual parthenolide content and appropriate dosage of feverfew in OTC products currently available is a daunting proposition. Finally, one should recall that the total number of subjects involved in studies evaluating "herbals" for headache treatment typically is small. Thus, the admonition: "consumers beware."

FEVERFEW

Feverfew (*Tanacetum parthenium*) is species-specific dried chrysanthemum leaves. According to 1 peer reviewed report, preparations of feverfew have shown a >400% variation in dosage strength of the known active ingredient parthenolide.⁹ Additionally, because feverfew also contains melatonin, some uncertainty exists as to whether parthenolide is even the major active ingredient in feverfew, although the MIG-99 trials of parthenolide might provide some insight into this issue.¹⁰ Despite a very recent positive MIG-99 trial, the totality of evidence, including systematic reviews, does not support feverfew as representing a "definitely effective" therapy for migraine, nor has its safety with long-term use been established. In short, there is Grade B evidence of feverfew's utility as a migraine therapy. Should another successful trial of MIG-99 6.25 mg pass peer review and be reported, then Grade A evidence would exist (albeit with what might prove to be a rather small therapeutic gain [TG] over placebo).

In a systematic review, Vogler et al reported on randomized controlled trials (RCTs) involving feverfew for migraine prophylaxis conducted prior to 1998.¹¹⁻¹⁶ Five studies qualified by Jadad score as adequate; 1 has been published in abstract form only, and only 216 subjects in total have been studied.¹⁷ Vogler et al concluded, "In view of the popularity of feverfew, perhaps the most striking finding was the paucity and low average quality of the existing RCTs on the subject." Three studies, including two-thirds of the total patients, showed greater benefit from feverfew than from placebo, but the study by De Weerd

et al, with the highest Jadad score and use of a standardized and constant concentration of parthenolides, showed no benefit.¹⁵ Perhaps, this was due to the latter's use of an alcoholic extract, as 2 of the positive studies (totaling 67 patients) involved a powdered extract, while the active agent used in negative studies was an ethanolic extract.^{12,13} With this "evidence" that the feverfew extraction technique might be critical to the agent's efficacy, work commenced on a supercritical CO₂ extraction method which produced a highly stable, "highly enriched" parthenolide extract named MIG-99. In 2002, Pfaffenrath et al reported the results of a dose-finding prospective RCT, involving 147 subjects treated with this extraction.¹⁸ The investigators studied three doses of MIG-99, and none was significant for the primary endpoint relative to placebo. A subset of subjects with episodic migraine of high frequency did seem to benefit, and the researchers consequently called for more study. In a 2004 Cochrane Database Systematic Review, Pittler and Ernst reviewed 5 double-blind trials with high Jadad scores involving a total of 343 patients, and noting the mixed results from the RCTs, the authors concluded that feverfew lacked convincing evidence of efficacy.¹⁹ In follow-up to the 2002 study, Diener et al performed a second multi-center RCT, wherein patients randomized to the active arm received MIG-99 6.25 mg TID.²⁰ The investigators reported reduction in headache attacks per month during the second and third recording periods (from 4.8 attacks to 2.9 with MIG-99 vs. 3.5 attacks with placebo (ie, a reduction in attacks/month of 1.9 vs. 1.3) attacks per month ($P = .0456$, and OR 3.4). Greater than 50% reduction in headache attacks per 28 days occurred in 30.3% of the feverfew group and 17.3% of the placebo group, a TG of 13% ($P = .047$). Adverse events occurred in 8.4% of subjects receiving feverfew and 10.2% of placebo controls.

From the RCT date, feverfew adverse events include sore mouth and tongue (including ulcers), swollen lips, loss of taste, abdominal pain, and GI disturbances. A "post-feverfew syndrome" of joint stiffness and aches and increasing headaches was reported in 25% of placebo subjects in the trial which randomized patients who had been using feverfew for several years to continued feverfew therapy or placebo.¹² In the MIG-99 RCTs, adverse events were similar

between all groups, with ≥ 1 adverse event occurring in 35%.¹⁹ Adequate long-term studies, including extension safety trials, appear not to have been performed as of this writing.

PETASITES

Petasites hybridus, known commonly as butterbur, is a perennial shrub which grows wild on German riverbanks. Nonextracted plant parts are carcinogenic, hepatotoxic, lung toxic, and may cause coagulopathy. The German Health Authority (Commission E) certifies the brand name Petadolex from Weber and Weber GmbH & Co as nontoxic. Petadolex is a patented, standardized CO₂ rhizome root extraction of *Petasites* marketed in Europe since 1992. Petadolex very recently has been marketed as a component in at least 1 combination product, which also contains several other ingredients discussed in this article. Despite a recent positive trial published in *Neurology*, due to the limited total number of subjects studied, neither the long-term safety nor the efficacy of Petadolex can be considered unequivocally established (Grade B evidence).

The 2 RCTs investigating Petadolex represent a thin evidence base. In the smaller study, 60 subjects were treated with placebo or Petadolex 100 mg per day for 12 weeks.^{21,22} According to investigators, "the frequency of migraine attacks decreased by a maximum of 60% compared to the baseline... and was significant ($P < .05$) compared to placebo." Due to major shortcomings of the original analysis and to comply with regulatory requirements, the data were independently reanalyzed.²³ In this reanalysis, the responder rate ($\geq 50\%$ reduction in migraine frequency) was 45% in the Petadolex group and 15% in the placebo group. In a study of 245 subjects, Lipton et al reported decreased monthly migraine frequency after 4 months and a detectable treatment effect at 1 month; a double-blind, placebo-controlled 3-arm, parallel-group dose-ranging design was used.²⁴ The migraine attack frequency in the *Petasites* (Petadolex) 75 mg bid cohort was reduced 48% versus 26% for placebo; 68% of the Petadolex subjects had $\geq 50\%$ reduction in migraine frequency compared with 49% of those on placebo. Petadolex 50 mg bid was not found to be statistically superior to placebo. The

TG for $\geq 50\%$ reduction in migraine frequency for the 150 mg Petadolex was 19%. Studies of amitriptyline, propranolol, and timolol (the latter 2, FDA approved for migraine prophylaxis) have revealed TGs of 21%, 24%, and 20%, respectively, for $\geq 50\%$ reduction in headache attacks, albeit using less rigorous methodology and analyses.^{25,26}

The Petadolex RCT adverse event profile compared favorably with placebo except for excess eructations (burping) in both active treatment arms. Long-term safety data are limited, as the average duration of use is estimated to be 3 months; shorter term safety appears to have been adequately evaluated, with an estimated more than 450,000 patients treated and >75,000 patient years of exposure as of 2003.²⁷ Although some concerns remain, it would seem fair to state that Petadolex may be the best safety tested herbal to date for the treatment of headache with CAM.^{28,29} It should be noted, however, that due to lack of data, such affirmation for other Petasites preparations currently must be withheld.

MAGNESIUM

Low brain magnesium levels have been reported in at least 8 studies involving migraineurs. At least 4 trials of magnesium as prophylactic therapy for migraine have been conducted, along with trials investigating magnesium as an acute treatment for migraine. The published trials have yielded mixed results, with favorable effects reported for acute treatment of patients with aura and, possibly, perimenstrual migraine prophylaxis. The magnesium formulation used has varied, and no study has compared different magnesium formulations with similar dosages of Mg^{++} to determine whether formulation type has clinical relevance. Magnesium's efficacy as an acute therapy may relate to ionized Mg^{++} levels, and it appears that prolonged "high dose" supplementation for a minimum of 3 to 4 months may be required to achieve any benefit from prophylactic therapy. Due to inconsistent findings from multiple trials, the evidence level for magnesium in prevention of migraine is Grade B.

Again, several reports have indicated that low levels of intracellular magnesium ion and serum ionized magnesium may correlate with the agent's efficacy, and

the conflicting results from migraine treatment of subjects either likely to respond (low levels) or unlikely to respond (normal levels).³⁰⁻³³ Even should this variable be adequately accounted for in future research, there is another that appears problematic. In a study designed to determine magnesium effects on sumatriptan non-responders (83% of whom had low ionized magnesium levels), Cady et al found that although ionized magnesium levels could be normalized intravenously, a daily dose of 250 mg of oral magnesium taurate for $5\frac{1}{2}$ months failed to maintain normal levels.³⁴ Mauskop has recommended a daily dose of 600 mg of chelated or slow-release oral magnesium for sustained supplementation.³⁵

The first RCT of magnesium for migraine prevention involved only 20 subjects and was positive; the active therapy was 360 mg Mg^{++} pyrrolidone carboxylic acid divided TID.³⁰ The second RCT, by Peikert et al, involved 81 adult women and 600 mg magnesium (trimagnesium dicitrate) daily demonstrated a 41.6% improvement with verum versus 15.8% for placebo.³⁶ The third RCT for migraine prophylaxis, published by Pfafferath et al, involved 69 patients taking 486 mg magnesium; no benefit for magnesium was found; at the end of the 3-month treatment phase, the responder rate was 28.6% in the magnesium group and 29.4% in placebo subjects, according to the primary efficacy endpoint. Diarrhea was reported in significant numbers of both patients receiving placebo (23.5%) and patients receiving magnesium (45.7%); the high rate in the active arms suggests that a poorly absorbed magnesium preparation lent to the negative outcome.^{37,38} In a last trial, Wang et al gave magnesium oxide 9 mg/kg divided TID to subjects aged 3 to 17 years.³⁹ Approximately three-quarters of eligible subjects completed the study, with a significant downward trend in headache days in the active treatment group versus placebo; the lack of any difference in the slope of treatment trends, however, was such that no significant superiority of magnesium over placebo could be documented.

Adverse events reported consequent to magnesium therapy have been mainly gastrointestinal (diarrhea predominating). There is no evidence of any short- or long-term safety issues for individuals taking magnesium in the absence of serious renal disease.

RIBOFLAVIN

Riboflavin (vitamin B2) is a water-soluble essential precursor to flavin mononucleotides necessary for electron transport within the Krebs cycle. It is essential to normal production of ATP and thus for maintaining membrane stability and for all energy-related cellular functions. RCTs involving riboflavin are extremely scarce, with no dose-ranging study involving riboflavin alone and no definite proof of efficacy (Grade B evidence, which also includes several favorable nonrandomized open-label studies).

RCTs are limited to 2 trials, 1 of which used a combination agent. In the only RCT involving riboflavin alone, Schoenen et al studied 55 patients and reported that 59% of the subjects receiving riboflavin 400 mg/day for 3 months experienced a $\geq 50\%$ reduction in migraine attacks compared with 15% for placebo.⁴⁰ Statistically significant reductions in both migraine frequency and number of headache days were reported. In the only other migraine RCT of riboflavin, Maizels et al studied 49 subjects taking 25 mg “placebo” riboflavin (to color the urine) or combination of riboflavin 400 mg, magnesium 300 mg, and feverfew 100 mg for 3 months.⁴¹ The number of migraine attacks, number of migraine days, and migraine index were lower in both groups as compared to baseline, but not statistically significant between the 2 for any endpoint. Interestingly, the “placebo” 25 mg dose produced $\geq 50\%$ reduction in the number of migraine attacks in 42%, while the combination formulation in 44%. One interpretation is that perhaps 25 mg riboflavin is an active treatment, and the other that this is a failed trial.⁸ In any case, the trials were small, and to settle the issue larger RCTs (with dose-ranging integral to the design) are required.

Adverse events reported from the studies investigating riboflavin have been limited to diarrhea and polyuria, both occurring in extremely low numbers. There is no known long-term toxicity or anticipated from supplementation provided to nonpregnant individuals; while apparently nontoxic at any dose in adults, and while fetal toxicity is unproven, riboflavin supplementation in pregnancy cannot currently be recommended. Patients should be warned against obtaining 400 mg/day from a multivitamin due to the potential for significant overdose of several toxic vitamins.

They also should be advised that riboflavin will produce fluorescent yellow urine.

COENZYME Q10

On the Internet, CoQ10 has been labeled an “energy enhancer” because, like riboflavin, it plays a role in electron transport. CoQ10 has been used in neurologic and non-neurologic conditions and is considered to have an acceptable safety and tolerance profile at all doses studied to date. Currently, only 1 RCT exists, which was not dose-ranging, and while statistically favorable results were recorded, this fails to make a solid evidence base for the supplement (Grade B evidence for a single RCT and another favorable open-label pilot study).

Sándor et al reported an RCT involving 42 subjects given either a noncommercially available liquid formulation of water-dispersed nanoparticles comprising a supercooled melt of CoQ10 with modified physicochemical properties taken 300 mg/day divided TID or placebo.⁴² Migraine attack frequency in month 4 was reduced $\geq 50\%$ in 47.6% of patients in the active arm as compared to 14.4% for placebo.

Adverse events in this trial were not statistically different between the 2 treatment groups. One patient withdrew and was not considered in the analysis due to “cutaneous allergy.”

MELATONIN

Melatonin is implicated in migraine in many ways, from sleep-related associations to seasonal circ-annual effects. Six studies have reported on 1 or another association of melatonin with migraine, with 4 revealing lower levels of melatonin either at baseline, during an acute attack, with insomnia, or without the normally expected increases late in the luteal phase of menstrual migraine.⁴³ Regardless, there has been no randomized, controlled treatment trial involving melatonin administered to migraineurs.

SUMMARY

What CAM can be stated to be evidence-based? There currently is at best Grade B evidence for all the agents discussed except melatonin, for which there are no data whatsoever. Grade B represents limited evidence from a single randomized trial, or

nonrandomized trials or multiple trials with inconsistent outcomes. I have restricted my discussion to RCTs or systematic reviews with individual standard evidence grade summary. Data are inadequate for meta-analysis. No firm consensus yet exists as to the relative treatment efficacy of these agents, but given the number of patients, data consistency, or lack thereof, I would tentatively suggest that the rank order may be: Petadolex \geq Magnesium > Feverfew (no commercially available MIG-99 forms known to this author) > Riboflavin > CoenzymeQ10 >> Melatonin.

Acknowledgments: Dr. Taylor would like to thank Drs. John Edmeads and Stewart Tepper for their help with the preparation of this opinion.

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