SELECT NUTRITIONAL COMPONENTS TO SUPPORT MIGRAINE HEADACHES

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A migraine headache is classified as one of the primary inherited headache disorders. It is estimated that thirty-six million Americans, or about 12% of the population, suffer from migraine headaches.[1] "Over excitability of specific areas of the brain"[1] is specifically noted in migraine headaches. Common migraine triggers include: specific foods and beverages, such as aged cheese, alcoholic beverages, food additives such as nitrates (in pepperoni, hot dogs, luncheon meats), and monosodium glutamate (MSG), commonly found in Chinese food. These triggers are thought to be responsible for up to 30% of migraines.[2] Other triggers include: excessive caffeine, menstrual period, excessive fatigue, missing meals, or changes in normal sleep patterns. The primary symptom is intense throbbing in an area of the head. Other common associated symptoms include: sensitivity to light, noise, odors, nausea and vomiting, stomach upset or abdominal pain, loss of appetite, fatigue, dizziness, and blurred vision.[2] Rare symptoms include fever and diarrhea.

According to the World Health Organization, migraine is one of the 20 most disabling medical illnesses. Although there is no cure for migraines, recognized treatment options are available. Nutritional supplementation can also be of benefit; as certain compounds have demonstrated benefits in mitigating vascular effects, thus aiding to control migraine headaches. These compounds will be discussed below.

Riboflavin referred to as vitamin B_2 (vitamin G), is a water-soluble B-vitamin involved in the formation of flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Both FAD and FMN function in oxidation-reduction reactions, and act as coenzymes in the mitochondrial respiratory chain, as well as in numerous other pathways. There are also numerous other FAD and FMN-linked enzymes, including xanthine oxidase, cytochrome reductase, glutathione reductase, and lactate dehydrogenase, all of which play important roles in the body. Riboflavin also functions in the redox cycle of glutathione. Glutathione is a major antioxidant, and plays an important role as a participant in protecting organisms from reactive oxygen species, such as hydroperoxides.

Riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of hemoglobin.[3] Riboflavin is also essential for metabolism regulation. In relation to headaches, Boehnke, C, et al. noted a significant reduction in the frequency of headaches with riboflavin intake. Prophylactic treatment with riboflavin (400mg/day) was demonstrated to both reduce migraine attack frequency, and to attenuate the use of abortive anti-migraine therapy. [4]

Butterbur (*Petastis hybridus*) is a perennial shrub that has lilac-pink flowers and can grow up to three feet high. It is found throughout Europe, as well as in parts of Asia and North America. The genus name, *Petasites*, is derived from the Greek word "petasos", which is the felt hat worn by shepherds. Its botanical and common names are attributed to its broad leaves, up to three feet in diameter. Its common name is attributed to the large leaves being used to wrap butter during warm weather.[5] Its habitat is typically wet, marshy ground, damp forests, or adjacent to rivers or streams.

Butterbur has been used for hundreds of years to treat aches and pains, including headache.[6] There are numerous studies outlining the benefits of butterbur for migraine prophylaxis. In a study comparing Butterbur root extract and music therapy in pediatric migraines, both were demonstrated to cause greater headache reduction as compared to placebo. Butterbur root extract and music therapy might also be superior to placebo and may represent promising treatment approaches in the prophylaxis of pediatric migraine.[7] In another study group daily consumption of *Petasites* extract at a dose of 75mg, bid was demonstrated to decrease the frequency of migraine attacks by 48%, compared to the placebo group ($p = 0.00102$).[8] In a separate study migraine frequency improved in $\geq$50% in 45% in the Butterbur group, while improvement in the placebo group was only 15%[9] Butterbur has also been demonstrated to reduce smooth muscle spasm. It is believed that Butterbur likely acts through calcium channel regulation and inhibition of peptide leukotriene biosynthesis, thus influencing the inflammatory cascade associated with migraine.[10]

Importantly, Butterbur from differing manufacturers varies in the quantity of the targeted active phytochemical group called petasins. A high quality Butterbur will possess distinguishable quantities of the six different petasins, including: 3-desoxy-neopetasol, isoperasin, neo-petasin, petasin,[11] neo-S-petasin and S-petasin. In examining different sources of Butterbur, a Chinese extract evaluated did not show the presence of sesquiterpenes, suggesting the absence of petasins. This demonstrates the importance of supplier evaluation, which allows product formulation with the raw materials possessing the most activity.

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Contraindications:

- Butterbur is not recommended for those with dermatologic conditions, as butterbur may cause skin discoloration, pruritus, rash, and/or hot flushes.[12,13]
- Butterbur is not recommended for those with gastrointestinal diseases, as discoloration of stools, dysphagia, vomiting, burping, upset stomach, pain, nausea, diarrhea, indigestion, bitter taste, flatulence, and constipation have been reported.[12,13,14,15,16,17,18,19,20,21]
- Butterbur is not recommended in patients with somatoform disorders.[13,20]
- Caution is advised when used in patients with certain musculoskeletal conditions, as arthralgia, limb pain, and other pain complaints have occurred in some patients treated with butterbur.[21]
- Butterbur is not recommended in patients with eye conditions, as according to secondary sources, butterbur may cause itchy eyes. [22]
- Butterbur is not recommended in patients with respiratory conditions as butterbur may cause respiratory problems such as difficulty breathing and wheezing.[12, 13, 20]
- Butterbur is not recommended in patients with hepatic disorders or those taking anticholinergic agents, as butterbur may increase liver enzyme levels, particularly when administered in high doses.[12, 21, 23]

Feverfew (*Tanacetum parthenium*) Feverfew is a daisy-like perennial, herbaceous herb. The name feverfew is derived from the Latin word febrifugia, meaning "fever reducer," and was traditionally used as an antipyretic. It is noted to possess aperient (constipation relief), carminative, and bitter properties, and is also useful as an emmenagogue (stimulates blood flow in the pelvic area and uterus areas). It is also said to, "allay any distressing sensitiveness to pain".[24] The 17th Century English herbalist Culpeper wrote of the effectiveness of this herb for headache and uterine disorders.[25]

The active principles are noted to include one or more of the sesquiterpene lactones, including parthenolide, which is the main sesquiterpene lactone in feverfew.[26] Other potentially active constituents include flavonoid, glycosides and pinenes. Noted pharmacology properties include: anticancer, anti-inflammatory, cardiotonic, anti-spasmodic, an emmenagogue, as well as an enema for worms. Parthenolide comprises up to 85% of the total sesquiterpene content and is found primarily in the superficial leaf glands (0.2%–0.5%), but not in the stems.[27,28,29]

Feverfew also possesses anti-inflammatory activity. Extracts of the above ground parts and leaf extracts have been noted to suppress prostaglandin production, with leaf extracts inhibiting to a lesser extent. It is assumed that the lipophilic compounds other than parthenolide may be associated with its anti-inflammatory activity, particularly with reducing human neutrophil oxidative burst activity, as indicated by some studies.[30,31,32]

Contraindications:

- Feverfew is contraindicated in patients allergic to other members of the Asteraceae family, such as aster, chamomile, chrysanthemum, ragweed, sunflower, tansy, and yarrow. Due to its potential antiplatelet effects, it is not recommended for use in patients undergoing surgery. Patients with blood-clotting disorders should consult their health care provider prior to using products containing feverfew.
- Pregnant women should not use the plant because the leaves possess emmenagogue activity (ejection of the placenta and fetal membranes) and may induce abortion. It is also not recommended for breast-feeding mothers or for use in children younger than 2 years of age.

Coenzyme Q_{10} (emulsified). Migraine due to mitochondrial impairment has been theorized in certain individuals.[34,35] As a component of the electron transport chain Coenzyme Q_{10} (CoQ_{10}) participates in aerobic cellular respiration, generating energy as ATP, and thus functions as a necessary component in cellular energy production. Ninety-five percent of the body's energy is produced in this manner. In addition to CoQ_{10}'s assistance in cellular energy production, it also functions as an antioxidant. Low levels of CoQ_{10} have been reported in numerous disease states as well as in the ageing.[36,37,38,39] Several factors have an effect on the serum and/or tissue concentrations of CoQ_{10}. These factors include genetic mutations, ageing, cancer, as well as therapy from certain drugs, most notably the statin medications used in the management of cholesterol.

CoQ_{10} has been proposed as a prophylaxis for migraines, especially in children and women of childbearing age.[40] Magnetic resonance spectroscopy (MRS) studies suggest an impaired energy metabolism in the brain and skeletal muscle of migraine patients.[41] Since CoQ_{10} plays an essential role in the mitochondrial respiratory chain via its function as a redox carrier, permitting the "transfer of reducing equivalents from complex I and complex II to complex III"[42], a deficiency in CoQ_{10} results in insufficient transfer of protons across the inner mitochondrial membrane.[43] This, in turn, affects the "generation of adenosine triphosphate and all adenosine triphosphate–dependent metabolic processes."[43] Additionally, "a defect of reduced nicotinamide adenine dinucleotide (NADH) dehydrogenase, citrate synthase, and cytochrome-c-oxidase platelet activities in migraine patients" has also been noted.[44] According to Bianchi, A, et al., "if a decreased energy state characterizes the migraineur's brain, compounds such as CoQ_{10}, which improves mitochondrial function, could theoretically be used in migraine prophylaxis."[45] In an open label investigation (non-blinded) Rozen TD, et al. demonstrated that $CoQ_{10,}$ at a dose of 150mg/day, was effective as a migraine preventive.[46] In addition, Barbiroli, B., et al. demonstrated improvements in both muscle and energy metabolism with CoQ_{10} administration in patients with "mitochondrial cytopathies".[47]

Polyphenolic-Like Compounds (derived from ***Lens esculenta*** extract) (**Phytolens**®). Migraine as well as headache duration has been correlated to oxidative/

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antioxidative parameters, thus, antioxidants are proposed as beneficial adjuncts in migraine physiology. Polyphenolic-like compounds (from Phytolens®) possess numerous antioxidant characteristics, including the ability to quench both organic free radicals, and superoxide anions. They have also been demonstrated to prevent the oxidation of ascorbic acid in solution, and prevent the autoxidation of linoleic acid *in vitro*, more effectively than BHT and alpha tocopherol. Specifically, these compounds were noted to "have beneficial effects on inflammation via the attenuation of peroxynitrite-induced apoptosis and macrophage-dependent immunity."[48] Distinctively defined, these compounds are "a water-soluble extract of polyphenolic antioxidants from non-soy legumes."[48]

Polyphenols are noted as compounds that possess antioxidant properties both *in vivo* and *in vitro*.[49] They have also been associated with an inhibition of epidermal lipid peroxidation, with the degree inhibition dependent upon the polymerization in polyphenol structure. Also noted was the greater degree of polymerization in the polyphenol structure, the greater inhibitory potential towards lipid peroxidation.[50]

Procyanidins are known to possess many beneficial properties. Specifically, the procyanidins from grape seed "are known to exert anti-inflammatory, anti-arthritic and anti-allergic activities, prevent skin aging, scavenge oxygen free radicals and inhibit UV radiation-induced peroxidation activity."[50]

The combination of the above noted nutrients (MygranX™) were utilized as part of a small clinical evaluation to determine its effect on migraines in select patients.[51] Preliminary data indicated that it reduced headache severity in four of the six patients, while five out of six patients reported reduction in frequency. Other noted experiences included an improvement in mental sharpness, and an increased interest in participation in outside activities. Side effects noted were mild, and included nausea and some gastrointestinal disturbances.

As a consequence of the many harmful oxidative reactions that take place in the body, as part of the metabolic and physiological processes that occur, the generation of reactive oxygen species, which include: superoxide radical anions, hydroxyl radicals, and hydrogen peroxides, results in oxidative reactions, and in turn oxidative stress. These oxidative reactions may be harmful to the body, thus, the need for antioxidant support. For that reason, "the hypothesis of oxidative stress in migraine is supported by various studies."[52,53,54,55] Nutritional compounds, specifically antioxidant compounds, may assist in mitigating the effects that stress may play in migraine pathology.

References:

1. http://www.americanmigrainefoundation.org/about-migraine/.
2. http://my.clevelandclinic.org
3. Powers HJ, Weaver LT, Austin S, Beresford JK. A proposed intestinal mechanism for the effect of riboflavin deficiency on iron loss in the rat. Br J Nutr. 1993;69(2):553-561
4. Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhaüpl KM, Arnold G. High-dose riboflavin treatment is efficacious in migraine prophylaxis: an open study in a tertiary care centre. European Journal of Neurology. 2004 11:475–477.
5. http://www.naturalstandard.com/databases/herbssupplements/butterbur.asp#undefined
6. Anon. Monograph. Petasites hybridus. Altern.Med.Rev. 2001;6(2):207-209.
7. Rieke Oelkers-Ax, Anne Leins, Peter Parzer, Thomas Hillecke, Hans V. Bolay, Jochen Fischer, Stephan Bender, Uta Hermanns, Franz Resch. Butterbur root extract and music therapy in the prevention of childhood migraine: An explorative study. Eur J of Pain. April 2008 12(3):301–313.
8. Lipton RB, Göbel H, Einhäupl KM, Wilks K, Mauskop A. Petasites hybridus root (butterbur) is an effective preventive treatment for migraine. *Neurology*. December 28, 2004 63(12): 2240-2244.
9. Diener HC, Rahlfs VW, Danesch U. The first placebo-controlled trial of a special butterbur root extract for the prevention of migraine: reanalysis of efficacy criteria. *Eur Neurol*. 2004 51:89–97.
10. Eaton J. Butterbur, herbal help for migraine. *Nat Pharm*. 1998;2:23-24.
11. Muanza D. Biotics Research Corporation. Personal communication, January 2014.
12. Schapowal A1; Petasites Study Group. Butterbur Ze339 for the treatment of intermittent allergic rhinitis: dose-dependent efficacy in a prospective, randomized, double-blind, placebo-controlled study. *Arch Otolaryngol Head Neck Surg*. 2004 Dec. 130(12):1381-6.
13. Guo R, Pittler MH, Ernst E. Herbal medicines for the treatment of allergic rhinitis: a systematic review. *Ann Allergy Asthma Immunol*. 2007 Dec 99(6):483-95.
14. Sun-Edelstein C, Mauskop A. Alternative headache treatments: nutraceuticals, behavioral and physical treatments. *Headache*. 2011 Mar 51(3):469-83.
15. Pringsheim T1, Davenport W, Mackie G, Worthington I, Aubé M, Christie SN, Gladstone J, Becker WJ; Canadian Headache Society Prophylactic Guidelines Development Group. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci*. 2012 Mar;39(2 Suppl 2):S1-59.
16. Holland S1, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E; Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012 Apr 24;78(17):1346-53.
17. Tepper SJ. Complementary and alternative treatments for childhood headaches. *Curr Pain Headache Rep*. 2008 Oct;12(5):379-83.
18. Pothmann R1, Danesch U. Migraine prevention in children and adolescents: results of an open study with a special butterbur root extract. *Headache*. 2005 Mar;45(3):196-203.
19. Käufeler R1, Polasek W, Brattström A, Koetter U. Efficacy and safety of butterbur herbal extract Ze 339 in seasonal allergic rhinitis: postmarketing surveillance study. *Adv Ther*. 2006 Mar-Apr;23(2):373-84.
20. Melzer J1, Schrader E, Brattström A, Schellenberg R, Saller R. Fixed herbal drug combination with and without butterbur (Ze 185) for the treatment of patients with somatoform disorders: randomized, placebo-controlled pharmaco-clinical trial. *Phytother Res*. 2009 September 23(9):1303-8.
21. Oelkers-Ax R1, Leins A, Parzer P, Hillecke T, Bolay HV,

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Fischer J, Bender S, Hermanns U, Resch F. Butterbur root extract and music therapy in the prevention of childhood migraine: an explorative study. *Eur J Pain*. 2008 Apr;12(3):301-13. Epub 2007 Jul 30.
22. https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/b/butterbur/professional. aspx.
23. Anderson N, Meier T, Borlak J. Toxicogenomics applied to cultures of human hepatocytes enabled an identification of novel petasites hybridus extracts for the treatment of migraine with improved hepatobiliary safety. *Toxicol Sci*. 2009 Dec;112(2):507-20.
24. Grieve M. **A Modern Herbal**. https://www.botanical.com/botanical/mgmh/f/feverf10.html
25. http://loadbalanced.naturalstandard.com/index-abstract.asp?create-abstract=feverfew.asp&title=Feverfew.
26. Majdi M1, Liu Q, Karimzadeh G, Malboobi MA, Beekwilder J, Cankar K, Vos Rd, Todorović S, Simonović A, Bouwmeester H. Biosynthesis and localization of parthenolide in glandular trichomes of feverfew (Tanacetum parthenium L. Schulz Bip.). *Phytochemistry*. 2011 Oct 72(14-15):1739-50.
27. Chavez M, Chavez P. Feverfew. *Hosp Pharm*. 1999 34:436–61.
28. Heptinstall S, Awang DW, Dawson BA, Kindack D, Knight DW. Parthenolide Content and Bioactivity of Feverfew (Tanacetum parthenium (L.) Schultz-Bip.). Estimation of Commercial and Authenticated Feverfew Products. *J Pharm Pharmacol*. 1992 44:391–5.
29. Bohlmann F, Zdero C. Sesquiterpene Lactones and Other Constituents from Tanacetum parthenium. *Phytochemistry*. 1982 21:2543–9.
30. Sumner H, Salan U, Knight DW, Hoult JR. Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew.Involvement of sesquiterpene lactones and other components. *Biochem Pharmacol*. 1992 43:2313–20.
31. Collier HO, Butt NM, McDonald WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. *Lancet*. 1980 2:922–3.
32. Brown AM, Edwards CM, Davey MR, Power JB, Lowe KC. Pharmacological activity of feverfew (Tanacetum parthenium [L.] Schultz-Bip.): Assessment by inhibition of human polymorphonuclear leukocyte chemiluminescence in vitro. *J Pharm Pharmacol*. 1997 49:558–61.
33. Freeman LW. **Mosby's Complementary & Alternative Medicine: A Research-Based Approach**. 3rd ed. St. Louis, MO: Mosby Elsevier; 2009:422-424.
34. Bresolin N, Martinelli P, Barbiroli B, Zaniol P, Ausenda C, Montagna P, Gallanti A, Comi GP, Scarlato G, Lugaresi E. Muscle mitochondrial DNA deletion and 31P-NMR spectroscopy alterations in a migraine patient. *J. Neurol. Sci*. 1991 104:182–189.
35. Koo B, Becker LE, Chuang S, Merante F, Robinson BH, MacGregor D, Tein I, Ho V.B., McGreal D.A., Wherrett J. R., et al. Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS): Clinical, radiological, pathological, and genetic observations. *Ann. Neurol*. 1993 34:25–32.
36. Hoppe U, Bergemann J, Diembech W, Ennen J, Gohla S, Harris I, Jacob J, Kielholz J, Mei W, Pollet D, Schachtschabel D, Suermann G, Schreiner V, Stab F, Steckel F: Coenzyme Q, a cutaneous antioxidant and energizer. *Biofactors*. 1999 9:371–378.
37. Rosenfeldt FL, Pepe S, Ou R, Mariani JA, Rowland MA, Nagley P, Linnane AW: Coenzyme Q10 improves the tolerance of the senescent myocardium to aerobic and ischemic stress. *Biofactors*. 1999 9:291–300.
38. Willis R, Anthony M, Sun L, House Y, Qiao G: Clinical implications of the correlation between coenzyme Q10 and vitamin B6 status. *Biofactors*. 1999 9:359–363.
39. Hodges S, Hertz N, Lockwood K, Lister R: CoQ10: could it have a role in cancer management. *Biofactors*. 1999 9:365–370.
40. Sándor PS, Di Clemente L, Coppola G, Saenger U, Fumal A, Magis D, Seidel L, Agosti RM, Schoenen J. Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. *Neurology*. 2005 64:713–715.
41. Lodi R, Kemp GJ, Montagna P, Pierangeli G, Cortelli P, Iotti S, Radda GK, Barbiroli B. Quantitative analysis of skeletal muscle bioenergetics and proton eZux in migraine and cluster headache. *J. Neurol. Sci*. 1997 27:73–80.
42. Ernster L, Dallner G. Biochemical, physiological and medical aspects of ubiquinone function. *Biochim Biophys Acta*. 1995 1271:195-204.
43. Lalani SR, Vladutiu GD, Plunkett, K, Lotze TE, Adesina AM, Scaglia F. Isolated mitochondrial myopathy associated with muscle coenzyme Q10 deficiency. *Arch Neurol*. 2005 62:317-320.
44. Sangiorgi S, Mochi M, Riva, R, Cortelli P, Monari L, Pierangeli G, Montagna P. Abnormal platelet mitochondrial function in patients affected by migraine with and without aura. *Cephalalgia*. 1994 14:21–23.
45. Bianchi A, Salomone S, Caraci F, Pizza V, Bernardini R, Cesare Colucci D'Amatox CC. Role of Magnesium,Coenzyme Q10, Riboflavin, and Vitamin B12 in Migraine Prophylaxis. **Vitamins & Hormones.** Elsevier Inc. 2004 Vol. 69. Chapter 11 p. 301.
46. Rozen TD, Oshinsky ML, Gebeline CA, Bradley KC, Young WB, Shechter AL, Silberstein SD. Open label trial of coenzyme Q10 as a migraine preventive. *Cephalalgia*. 2002 Mar;22(2):137-41.
47. Barbiroli B, Iotti S, Lodi R. Improved brain and muscle mitochondrial respiration with CoQ. An in vivo study by 31P-MR spectroscopy in patients with mitochondrial cytopathies. *Biofactors*. 1999 9:253–260.
48. Sandoval M, Ronzio RA, Muanza DN, Clark DA, Miller MA. Peroxynitrite-Induced Apoptosis in epithelial (T84) and macrophage (Raw 264.7) cell lines: effect of legume-derived polyphenols (Phytolens™). *Nitric Oxide*. 1997 1(6):476-483.
49. Stoner GD, Mukhtar H. Polyphenols as cancer chemopreventative agents. *J. Cell. Biochem*. 1995 22:169-180.
50. Zhao J, Wang J, Chen Y, Agarwal R. Anti-tumor-promoting activity of a polyphenolic fraction isolated from grape seeds in the mouse skin two-stage initiation-promotion protocol and identification of procyanidin B5-3'-gallate as the most effective antioxidant constituent. *Carcinogenesis*. 1999 Sep;20(9):1737-45.
51. Vreeland, Court. The Vreeland Clinic. Norwich, VT. Personal correspondence 10/30/14.
52. Shulka R, Barthwal MK, Srivastava N, Srivastava N, Sharma P, Raghavan SA, Nag D, Srimal RC, Seth PK, Dikshit M. Neutrophil-free radical generation and enzymatic antioxidants in migraine patients. *Cephalalgia*. 2004 24:37-43.
53. Tozzi-Ciancarelli MG, De Matteis G, Di Massimo C, Marini C, Ciancarelli I, Carolei A. Oxidative stress and platelet responsiveness in migraine. *Cephalalgia*. 1997 17:580-584.
54. Shimomura T, Kowa H, Nakano T, Kitano A, Marukawa H, Urakami K, Takahashi K. Platelet superoxide dismutase in migraine and tension-type headache. *Cephalalgia*. 1994 14:215-218.
55. Ciancarelli I, Tozzi-Ciancarelli MG, Di Massimo C, Marini C, Carolei A. Urinary nitric oxide metabolites and lipid peroxidation by products in migraine. *Cephalalgia*. 2003 23:39-42. ◆