ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Integrative Medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure
Russell H. Greenfield, MD (executive editor), David Kiefer, MD (peer reviewer), Leslie Coplin (AHC Media executive editor), and Neill Kimball (managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Alternative Medicine Alert is available on-line.
For more information, go to www.ahcmedia.com/online.html or call (800) 688-2421.

Heads Up: The Integrative Approach to Migraine Prophylaxis

By Susan T. Marcolina, MD, FACP

Dr. Marcolina is an internist and geriatrician in Issaquah, WA; she reports no financial relationship to this field of study.

MIGRAINE HEADACHES AFFECT 11% OF THE WORLD'S POPULATION.[1] Since 90% of migraineurs experience moderate to severe pain and 35% are bedridden with headache episodes, the World Health Organization has listed migraine among the top 20 disability-causing diseases.[2]

In the United States, 17% of women, 6% of men, and 11% of children 5-15 years of age are affected. Although 25% of migraine patients meet criteria for prophylaxis with two or more monthly episodes of headache and 1) incomplete relief or intolerance/contraindication to acute pharmacologic treatment, 2) absence from school or work, and 3) diminished quality of life, only 3-5% receive preventive therapy.[3-5]

Since the public often perceives complementary and alternative medicine supplements to be as or more helpful than conventional care for the treatment of headache, neck and back conditions, they frequently purchase over-the-counter (OTC) supplements based on internet searches and positive anecdotal experiences of friends and family.[6] Primary care physicians can more specifically advise patients regarding evidence-based preventive treatment strategies for chronic headaches. Such prophylaxis when effective reduces medication overuse and migraine progression; specific OTC supplements can be one aspect of such treatments.[7]

Clinical Characteristics of Migraine

Migraine headaches typically begin prior to age 40, most often in childhood or teenage years. There is typically an associated family history. Table 1 summarizes the International Headache Society's (IHS) diagnostic criteria for migraine.

Application of these criteria improves the accuracy of the headache diagnosis and reserves neuroimaging for patients presenting with headache plus any of the following clinical findings, which may indicate a more serious secondary headache disorder, requiring medical and/or surgical intervention:[8]

- onset of headaches after age 40 or before age 5
- first, worst headache
- abrupt onset (thunderclap)
- progressive, changing pattern of headache
- abnormal physical examination/neurologic symptoms
- new onset of headaches with immunosuppression, cancer, trauma, pregnancy
- exacerbation of headache with valsalva, exertion, sexual activity
- syncope/seizures

A personal headache diary is often recommended because it provides information about a patient's headache history and allows patients and their doctors to understand possible environmental, dietary, and lifestyle precipitants, and to implement appropriate interventions.[9]

Pathophysiology of Migraine

Migraine headache symptoms occur as a wave of neuronal depolarization spreads across the cerebral cortex. This cortical spreading depolarization activates one or more subdivisions of trigeminal nerve afferents resulting in inflammatory changes in the pain-sensitive meninges and altered blood-brain barrier permeability. Common triggers (*see Table 2*) destabilize the nervous system and result in headaches for certain individuals.[10]

Migraines and Comorbidities

Since overuse of short-acting analgesics and other acute drugs may interfere with the efficacy of preventive drugs, patients should be educated about how to manage their headache episodes. Patients with recurrent migraine headaches often have other chronic medical conditions such as hypertension or psychiatric comorbidities (i.e., anxiety and depressive disorders) that need to be considered and comanaged as part of the chronic treatment regimen.[11]

Since migraine headaches have no cure, treatment goals are to manage and reduce the burden of pain and disability. Current FDA-approved drugs for prevention of episodic migraine include propranolol, timolol, valproate, tricyclic antidepressants, and topiramate.[11]

Different classes of antihypertensives have been studied for migraine prophylaxis. Beta-blockers, especially timolol and propanolol, may be good choices for chronic migraneurs with coexistant hypertension, though they should be avoided in patients with asthma, peripheral vascular disease, a smoking history, and Raynaud's disease, and used judiciously in patients with depression and diabetes.[12] Although the calcium channel blockers amlodipine and verapamil may be efficacious for migraine prophylaxis in hypertensive migraineurs, pedal edema is a limiting side effect.[13] Lisinipril and candesartan have been found to reduce headache frequency and severity in randomized controlled trials but cost and side effects, such as cough and angioedema, are problematic.[14,15]

For migraneurs with coexistant depression, tricyclic antidepressants such as amitriptyline have been shown in randomized controlled trials to be effective preventive headache treatment.[16] The dose of amitriptyline for migraine prophylaxis is lower than that recommended to treat depression, and its benefits for migraine headaches are independent of improvements in mood. However, dry mouth, constipation, and weight gain are significant, and for some patients, prohibitive side effects. Although SSRIs have been effective in depression treatment, they

Table 1. International Headache Society Diagnostic Criteria for Migraine Headaches[8]

1. Recurrent (at least 5 episodes fulfilling criteria 2-5)
2. Attacks last 4-72 hours
3. Possess at least two of the following characteristics:
   - Unilateral location (typically)
   - Pulsatile quality
   - Moderate to severe pain intensity
   - Aggravation with routine physical activity
4. Possess at least one of the following during headache:
   - Nausea or vomiting
   - Photophobia and phonophobia
5. Not attributable to another disorder

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin
MANAGING EDITOR: Neill Kimball
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Alternative Medicine Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices

United States
$299 per year (Student/Resident rate: $165).
Add $17.95 for shipping & handling.
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 24 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for physicians and researchers interested in complementary and alternative medicine. It is in effect for 36 months from the date of the publication.

For CME credit, add $50.

Questions & Comments

Please contact Executive Editor **Leslie Coplin**, at leslie.coplin@ahcmedia.com.

Table 2. Common Dietary/Environmental Triggers for Migraineurs[10]

- Stress
- Menses
- Excessive sensory stimuli (bright lights, loud noises, strong odors)
- Chronobiologic changes (irregularity in sleep, meals, exercise)
- Alcohol overindulgence
- Caffeine withdrawal
- Aspartame (diet soda)
- Tyramine (cheese, wine, sauerkraut)
- Nitrites (hot dogs, cured meats)
- Monosodium glutamate (MSG; frozen, canned, and processed foods; certain condiments)
- Chocolate

are not effective for migraine prophylaxis. However, one randomized controlled trial found venlafaxine (a serotonin/norepinephrine reuptake inhibitor) to be effective in the prevention of migraine.[17]

Anticonvulsants, primarily valproate and topiramate, are effective for migraine prophylaxis due to their potentiation of the neurotransmitter gamma amino butyric acid, reduction of neuronal firing in the trigeminocervical complex, and inhibition of neuronal sodium and calcium channels.[18] Valproate can also stabilize mood disorders in patients who have concomitant bipolar depression. Mulleners, in a Cochrane review, concluded that anticonvulsants double the chance of reducing chronic migraine headache by more than 50% compared to placebo.[19] However, side effects of osteomalacia, memory and language disturbances, fatigue and liver dysfunction (valproate), and dizziness, drowsiness, and nausea (topiramate) limit the use of this class of drugs, particularly in children and adolescents.

Therapeutic Lifestyle Management of Chronic Migraines

Chronic stress, excessive caffeine, alcohol, frequent and regular analgesic medication intake, and disturbances in chronobiologic rhythms such as sleep deprivation can all be barriers to successful palliation of migraine headaches and other types of chronic headaches.

Overnight headaches or headaches upon awakening reflect a sleep disturbance in 55% of patients with these complaints. It is particularly important to rule out obstructive sleep apnea syndrome with a sleep study in patients with a history of snoring, daytime somnolence, and early morning headaches because treatment results in improvement of both headaches and general medical health.[20] The Somogyi effect (rebounding high blood sugar as an exaggerated response to low blood sugar in the early morning, generally secondary to excessive exogenous long-acting evening insulin) may cause chronic morning headaches in patients with diabetes, particularly if coupled with fasting hyperglycemia.

Dietary Triggers. For certain patients, especially children and adolescents, food and food additives can be significant precipitants of migraine headaches. Such triggers are outlined in Table 2. Skipped meals and fasting were reported as migraine triggers in 40-56% of migraineurs from subspecialty headache centers. Postulated mechanisms by which skipped meals can precipitate headache include alterations in serotonin and norepinephrine in the brainstem pathways or in release of stress hormones such as cortisol.[21]

Low-fat Diet. Bic et al conducted a prospective cohort trial of 54 migraine patients and found that decreasing dietary fat from 66 to 28 grams/day resulted in a significant decrease in headache frequency, intensity, duration, and medication use ($P < 0.001$ for all measures).[22]

Exercise. Regular exercise increases plasma beta endorphin levels.[23] Koseoglu et al studied 36 migraineurs who engaged in regular home aerobic exercise three times weekly for 30 minutes over 6 weeks. The exercise significantly raised beta endorphin levels after the home exercise program ($P < 0.0001$) and had beneficial effects on all migraine parameters ($P < 0.0001$).[24] Additionally, persons who exercise regularly increase their cardiovascular and cerebrovascular health with resultant improvements in psychological states, including depression, anxiety, and stress.

Over-the-counter Supplements for the Treatment of Migraine

Consumers may prefer nutraceuticals and OTC supplements for treatment of medical conditions for any number of reasons, including avoidance of possible medication-induced adverse effects. However, per the Dietary Health and Supplements Act of 1994, no standardization is required for over-the-counter supplements that do not claim to treat specific medical conditions. Patient resources for helping to identify safe vitamins and supplements include the United States Pharmacopeia (www.usp.org/USPVerified/dietarySupplements/), the NIH Office of Dietary Supplements (http://ods.od.nih.gov/), and Consumer Lab (www.consumerlab.com), an independent, subscription-based database and laboratory that provides reliable information regarding the labeling accuracy of OTC product content, the presence of contaminants such as lead, and the absorption of the product from the gastrointestinal (GI) tract.

Magnesium. Magnesium is an essential cofactor in more than 300 enzymatic reactions in the central nervous system. For example, magnesium is involved in all reac-

tions resulting in the formation and utilization of adenosine-5'-triphosphate in energy metabolism. Such reactions are critically important to neuronal ion pump functioning, which controls membrane depolarization and neurotransmitter release, processes involved in migraine genesis. Additionally, magnesium concentration influences serotonin receptors, nitric oxide (NO) synthesis, and release of inflammatory mediators.[25]

In a small randomized, double-blind, multicenter, placebo-controlled trial, Peikert et al found that 600 mg/day of orally supplemented magnesium citrate for 12 weeks significantly decreased migraine frequency by 41.6% compared to a decrement of 15.8% with placebo ($P < 0.05$). The improvement occurred during the 9- to 12-week treatment interval.[26]

In another small, randomized, placebo-controlled trial of patients with menstrual migraines (women predisposed to migraine headaches 1-2 days before and during the initial three days of menstrual periods), Facchinetti et al found that oral supplementation with 360 mg/day of magnesium for the last 2 weeks of the menstrual cycle significantly reduced the Pain Total Index compared to subjects receiving placebo after 2 months of treatment.[27]

In a randomized, placebo-controlled, double-blind study in 86 migranous children 3-17 years of age, Wang et al found a statistically significant decrease in headache frequency for the magnesium oxide-supplemented group over placebo group ($P = 0.0037$) during a 16-week treatment period. Additionally, the magnesium treated group had significantly lower headache severity compared to the placebo group ($P = 0.0029$).[28]

Intravenous magnesium sulfate, in a 1 g dose, administered over 15 minutes in a small, single-blind, placebo-controlled study was significantly more effective (100% response rate) than placebo treatment with an intravenous normal saline infusion (6.6% response rate) for relieving moderate to severe acute migraine headaches.[29]

Magnesium is the only preventive agent with a Category A rating for pregnancy. Therefore, it is an appropriate choice for prophylaxis for women who are pregnant or trying to conceive.[30,31]

Riboflavin. Riboflavin is a critical cofactor in oxidative metabolism and energy generation within mitochondria.

Schoenen et al demonstrated in a small, randomized, placebo-controlled study of 55 patients with chronic migraines that supplementation with 400 mg/day of riboflavin (vitamin B2) resulted in a significantly greater proportion of patients with > 50% improvement in headache frequency (54% vs 19% improvement with placebo), headache days (57 vs 15), and migraine index (headache days plus mean severity; 39% vs 8%). These benefits were evident after 3 months of treatment. Riboflavin was well tolerated at this dosage.[32]

Coenzyme Q10. Coenzyme Q10 plays an essential role in electron transport and energy metabolism in the mitochondria of all cells in the body. It is also a potent free radical scavenger, and plays a role in stimulation of NO release by the vascular endothelium. Due to these vascular effects and its role in mitochondrial oxidative metabolism, coenzyme Q10 has been investigated as a treatment for migraine headache.[33]

In a randomized, controlled trial of 42 migraine patients, Sandor et al found that treatment with 100 mg three times daily of coenzyme Q10 resulted in > 50% reduction in headache frequency after 3 months of treatment compared to placebo (47.6% vs 14.4%), although it did not decrease severity nor use of acute headache (rescue) drugs.[34]

Hershey et al demonstrated that, as part of a multidisciplinary treatment program, supplementation of coenzyme Q10-deficient pediatric and adolescent migraine patients significantly decreased their headache frequency ($P < 0.0001$) and improved quality of life as assessed by their pre- and post-supplementation Pediatric Migraine Disability Questionnaire scores ($P < 0.001$).[35]

Botanical Preventive Therapy: *Petasites hybridus* (Butterbur). Butterbur is a perennial shrub in the Asteraceae or daisy family that can be found along rivers and marshy areas of Europe, Asia, and North America. Two active ingredients of the extract, petasin and isopetasin, have both calcium channel blocking and potent anti-inflammatory effects via inhibition of leukotriene synthesis.

The plant contains hepatotoxic and carcinogenic pyrrolizidine alkaloids (PA), but a proprietary PA-free root extract, Petadolex, (Weber and Weber GmbH & Co. KG, Germany) is approved by the German Commission E for the treatment of migraine headaches. Petadolex is licensed as a pharmaceutical medication under the German Health Authority regulation. It is a food supplement in the United States and therefore not under FDA scrutiny.[36]

In a double-blind, randomized, parallel group, placebo-controlled study of 229 patients aged 18-65 meeting criteria for chronic migraine headaches, Lipton et al compared Petadolex in doses of 50 mg and 75 mg twice daily to placebo. Patients were treated for 4 months preceded by a 1-month baseline evaluation. Compared to baseline, after 4 months the groups treated with 75 mg and 50 mg twice daily experienced an average 45% and 32% respective reduction in monthly headaches, both significantly different from the 28% reduction seen in the placebo group ($P = 0.005$). The higher Petadolax dosage was more effective. Long-term safety data for the use of this preparation, however, are lacking.[37]

Botanical Preventive Therapy: *Tenacetum parthenium* (Feverfew). A Cochrane review by Pittler concluded there was no evidence of efficacy for feverfew for the prophylaxis of migraine headache.[38] A critical consideration

Table 3. Dosages for Supplements Used in Migraine Prophylaxis

Supplement	Dosage	Commentary
Magnesium	360-600 mg/day	Not for use in patients with renal insufficiency Diarrhea may be a limiting adverse effect May take up to 3 months to accrue prophylaxis benefit
Coenzyme Q10	Kids: 1-3 mg/kg/day Adult: 300 mg/day	Significant reduction in risk of preeclampsia noted in pregnant migraineurs taking 100 mg orally twice daily after week 20 Soft gel formulations improve absorption Takes 3 months to accrue prophylaxis benefit May decrease the effect of warfarin
Riboflavin (vitamin B2)	400 mg/day	Dose is teratogenic; therefore contraindicated in pregnancy and lactation Diarrhea and polyuria possible adverse reactions Takes 3 months to accrue prophylaxis benefit
Petadolex (butterbur)	75 mg twice daily	Not for use in children, or pregnant or lactating patients
MIG-99 (Feverfew)	6.25 mg three times daily	Not for use in children, or pregnant or lactating patients Can potentiate effects of anticoagulants

Adapted from References 25, 26, 28, 31, 32, 35, 36, 37, 40, 41, 46.

with these studies, however, is the fact that the commercial feverfew products varied considerably with respect to stability and concentration of the presumed active constituent, parthenolide. Parthenolide has anti-inflammatory action via inhibition of prostaglandin synthesis; it also has effects on serotonin secretion and cranial vessel contractility.[39]

A double-blind, multicenter, placebo-controlled study by Diener et al using a standardized, stable feverfew extract (MIG 99) in 85 migraneurs showed a significant reduction in migraine episode frequency after 4 months of treatment compared to placebo.[40]

Table 3 summarizes dosing and the guidelines for supplements used in migraine prophylaxis.

Adverse Events

Magnesium supplements can frequently cause diarrhea, but taking them with food can mitigate this side effect. Certain forms of magnesium (such as magnesium citrate, lactate, and gluconate) are more easily absorbed and less likely to cause diarrhea.[42] Individuals with renal impairment should not be given supplemental magnesium as toxic levels can accumulate. Appropriate supplementation with magnesium in pregnancy is unlikely to be associated with adverse effects and may effectively prevent premature labor and sudden infant death syndrome.[43]

Riboflavin is extremely safe, but in high doses may cause diarrhea and polyuria.[32] Feverfew, butterbur, and the high doses of vitamin B2 recommended for migraine prophylaxis should be avoided in pregnancy and lactation because they may be teratogenic. They also should not be used in children.[44-46]

One randomized, placebo-controlled, double-blind study found that a coenzyme Q10 product (Q-Absorb, Jarrow Formulas, Los Angeles, CA) was well tolerated in pregnancy after 20 weeks' gestation without adverse maternal or fetal outcomes, and was associated with a lower incidence of preeclampsia in women at risk for this condition. Mild gastrointestinal symptoms were the most common side effects of coenzyme Q10, but they occurred with similar frequency and severity in the placebo group.[41] There have been several case reports, however, in which coenzyme Q10 supplementation has decreased the anticoagulant effects of warfarin.[47]

Formulations with enhanced solubility are more expensive. Coenzyme Q10 is best absorbed when fat or oil is present in the GI tract as during a meal. Softgels (containing oil) improve absorption.[48]

The proprietary butterbur product, PA-free Petadolex, was well tolerated by study migraineurs at a maximal dose of 75 mg twice daily for 4 months without associated abnormalities in liver function. The most common adverse effect compared to placebo was eructation.[37,49]

A randomized, double-blind, controlled trial of a standardized feverfew preparation, MIG-99, showed that it had a side effect profile no different from placebo.[40] Since feverfew extract interferes with platelet aggregation, however, it can potentiate the effects of anticoagulant therapy.[50]

Mouth ulceration, ageusia, and lip swelling may occur as side effects of feverfew use. Although allergic reactions to feverfew have rarely been reported, theoretically persons with allergies to chamomile, ragweed, or yarrow should avoid the use of feverfew-containing products due to cross reactivity.[50]

Conclusion

As with any chronic illness, a multifactorial approach, in this case guided by information from a headache diary, may help to mitigate pain, lessen disability, and avoid triggers. Identification and treatment of comorbidities such as affective disorders, alcohol and caffeine overuse, sleep disturbances, and analgesic overuse can decrease headache frequency and severity. The National Headache Foundation and the American Academy of Neurology have both identified magnesium and riboflavin as preventive therapies for migraine headaches.[51,52]

Standardized preparations of certain botanicals, such as butterbur and feverfew, may be useful in certain nonpregnant, non-lactating adult migraineurs, but larger, long-term studies are necessary to substantiate initial promising findings. Coenzyme Q10 as a softgel in a dose of 300 mg/day for adults and 1-3 mg/kg/day in children shows promise for the prophylaxis of migraine headaches. Feverfew and coenzyme Q10 should be used cautiously in persons on chronic warfarin anticoagulation.

Recommendations

Primary care physicians can utilize IHS criteria to diagnose migraine headaches; initiate therapeutic lifestyle interventions such as regular aerobic exercise, a low-fat diet, and avoidance of migraine triggers; and evaluate the need for preventive nutraceuticals such as riboflavin, magnesium, and coenzyme Q10. Comorbidities should be identified and treated. A trial of a standardized preparation of butterbur (Petadolex) or feverfew (MIG-99) may be considered in certain patients who do not respond to therapeutic lifestyle interventions, chronobiologic regulation, and first-line pharmacologic treatment; however, there is a dearth of data for long-term use of these botanical products as preventive therapy. Since feverfew and coenzyme Q10 can interfere with the effects of anticoagulant medication such as warfarin, the risk/benefit ratio for using them in patients receiving such therapy must be carefully considered. ■

References

1. Stovner L, et al. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia* 2007;27:193-210.
2. Leonardi M, et al. The global burden of migraine: Measuring disability in headache disorders with World Health Organization's classification of functioning, disability and health. *J Headache Pain* 2005;6:429-440.
3. Lipton RB, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;68:343-349.
4. Abu-Arafeh I, Russell G. Prevalence of headache and migraine in schoolchildren. *Br Med J* 1994;309:765-769.
5. Evers S, et al. European Federation of Neurological Societies (EFNS) guideline on the drug treatment of migraine-revised report of the EFNS task force. *Eur J Neurol* 2009;6:968-981.
6. Eisenberg DM, et al. Perceptions about complementary therapies relative to conventional therapies among adults who use both. Results from a national survey. *Ann Int Med* 2001;135:344-351.
7. Schmitz N, et al. Attack frequency and disease duration as indicators for brain damage in migraine. *Headache* 2008;48:1044-1055.
8. Headache Classification Subcommittee of International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004;24(Suppl 1):1-160.
9. Migraine and Headache Diary Workbook. The Health Central Network. My Migraine Connection. Available at: www.helpforheadaches.com/lwfiles/Diary_Workbook.pdf. Accessed Aug. 3, 2011.
10. Millichamp JG, et al. The diet factor in pediatric and adolescent migraine. *Pediatr Neurol* 2003;28:9-15.
11. Silberstein SD. Practice parameter: Evidence-based guidelines for standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-762.
12. Linde K, Rossnagel K. Propranolol for migraine prophylaxis. *Cochrane Database Syst Rev* 2004;2:CD003225.
13. Tfelt-Hansen P. Prophylactic pharmacotherapy of migraine. Some practical guidelines. *Neurol Clin* 1997;15:153-159.
14. Schrader H, et al. Prophylactic treatment of migraine with angiotensin convertine enzyme inhibitor (lisinopril): Randomized, placebo-controlled, crossover study. *BMJ* 2001;322:1-5.
15. Trovnik E, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker: A randomized controlled trial. *JAMA* 2003;289:65-69.
16. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. *Arch Neurol* 1979;36:695-699.
17. Buleit S, et al. Venlafaxine versus amitryptyline in the prophylaxis of migraine. A randomized, cross-over study. *Clin Neurol Neurosurg* 2004;107:44-48.
18. Artemenko AR, et al. Effects of toiramate on migraine frequency and cortical excitability in patients with frequent migraine. *Cephalalgia* 2008;28:203-208.
19. Mulleners WM, Chronicle EP. Anticonvulsants in migraine prophylaxis; a Cochrane review. *Cephalalgia* 2008;28:585-597.
20. Paiva T, et al. Chronic headaches and sleep disorders. *Arch Intern Med* 1997;157:1701-1705.
21. Scharff L, et al. Triggers of headache episodes and coping response of headache diagnostic groups. *Headache* 1995;35:397-403.
22. Bic Z, et al. The influence of a low-fat diet on incidence

and severity of migraine headaches. *J Womens Health Gend Based Med* 1999;8:623-630.
23. Goldfarb AH, Jamiertas AZ. Beta-endorphin response to exercise. An update. *Sports Med* 1997;24:8-16.
24. Koseoglu E, et al. Aerobic exercise and plasma beta endorphin levels in patients with migrainous headache without aura. *Cephalalgia* 2003;23:972-976.
25. Bianchi A, et al. Role of magnesium, coenzyme Q10, riboflavin and vitamin B12 in migraine prophylaxis. *Vitam Horm* 2004;69:297-312.
26. Peikert A, et al. Prophylaxis of migraine with oral magnesium: Results form a prospective multicenter, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996;16:257-263.
27. Fascchinetti F, et al. Magnesium prophylaxis for menstrual migraine: Effects on intracellular magnesium. *Headache* 1991;31:298-301.
28. Wang F, et al. Oral magnesium oxide prophylaxis of frequent migraine headaches in children. A randomized, double-blind, placebo-controlled trial. *Headache* 2003;43:601-610.
29. Demirkaya S, et al. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* 2001;41:171-177.
30. Drugs.com monograph on magnesium. Available at: www.drugs.com/pro/magnesium-sulfate.html. Accessed Aug 6, 2011.
31. Evers S, et al. EFNS guideline on the drug treatment of migraine-revisied report of an EFNS task force. *Eur J Neurol* 2009;16:968-981.
32. Schoenen J, et al. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. *Neurology* 1998;50:466-470.
33. Sparaco M, et al. Mitochondrial dysfunction and migraine: Evidence and hyothesis. *Cephalalgia* 2006;26:360-372.
34. Sandor PS, et al. Efficacy of coenzyme Q10 in migraine prophylaxis: A randomized controlled trial. *Neurology* 2005;64:713-715.
35. Hershey AD, et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. *Headache* 2007;47:73-80.
36. Thomet OA, et al. Role of petasin in the potential anti-inflammatory activity of a plant extract of *Petasites hybridus*. *Biochem Pharmacol* 2001;61:1041-1047.
37. Lipton RB, et al. *Petsites hybridus* root (butterbur) is an effective preventive treatment for migraine. *Neurology* 2004;63:2240-2244.
38. Pittler MH, Ernst E. Feverfew for preventing migraine. *Cochrane Database Syst Rev* 2004; DC002286.
39. Makheja AM, Bailey JM. A platelet phospholipase inhibitor from the medicinal herb feverfew. *Prostaglandins Leukotrienes Med* 1982;8:653-660.
40. Diener HC, et al. Efficacy and safety of 6.25 mg tid feverfew C02 extract (MIG-99) in migraine prevention—A randomized, double-blind, multicenter, placebo-controlled study. *Cephalalgia* 2005;25:1031-1041.
41. Teran E, et al. Coenzyme Q10 supplementation during pregnancy reduces the risk of pre-eclampsia. *Int J Gynecol Obstet* 2009;105:43-45.
42. Firoz M, Graber M. Bioavailablity of US commercial magnesium preparations. *Magnes Res* 2001;14:257-262.
43. Durlach J. New data on the importance of gestational magnesium deficiency. *J Am Col Nutr* 2004;23:69S-70S.
44. Loder E. Migraine in pregnancy. *Semin Neurol* 2007; 27:425-433.
45. Silberstein SD. Headaches in pregnancy. *Neurol Clin* 2004;22:727-756.
46. Consumer Lab on Butterbur. Available at www.consumerlab.com/tnp.asp?chunkiid=21626&docid=/tnp/pg000417. Accessed August 8, 2011.
47. Heck AM, et al. Potential interaction between alternative therapies and warfarin. *Am J Health Syst Pharm* 2000;57:1221-1227.
48. ConsumerLab. Available at: www.consumerlab.com/reviews/Review-CoQ10-Supplements-and-Ubiquinol/CoQ10/. Accessed Aug. 2, 2011.
49. Grossmann W, Schmidramsl H. An extract of *Petasites hybridus* is effective in the prophylaxis of migraine. *Alt Med Rev* 2001;6:303-309.
50. Ernst E, Pittler, MA. The efficacy and safety of feverfew (*Tanacetum parthemium* L): An update of a systematic review. *Public Health Nutr* 2000:3:509-514.
51. Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): Report of the Quality Standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-762. Available at: www.guideline.gov/summary/summary.aspx?docjd=2820. Accessed Aug. 3, 2011.
52. Mauskop A; Graff-Radford S. Special treatment situations: Alternative headache treatments. Standards of Care for Headache Diagnosis and Treatment. Chicago, IL: National Headache Foundation; 2004:115-122.

Sweet! Chocolate for Mind AND Body

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD

Synopsis: *The study authors reviewed observational data on chocolate consumption and the risk of car-*

diometabolic disease, and found strong evidence of a protective effect. The wide variety of methods employed across studies, among other issues, make cause and effect assumptions premature, though they do fall in line with previous data suggesting chocolate's health benefits.

Source: Buitrago-Lopez A, et al. Chocolate consumption and cardiometabolic disorders: Systematic review and meta-analysis. *BMJ* 2011;343:d4488.

Chocolate has, of course, long been a favored food around the globe. In recent years, data suggesting chocolate might also offer health benefits has been greeted with smiles, but in the recesses of many people's minds was the lingering concern that the high fat and sugar content of chocolate, in general, might in the long run do more harm than good. In this systematic review and meta-analysis, researchers sought to examine and better define the relationship between chocolate consumption and subsequent risk of cardiometabolic disorders (including cardiovascular disease, diabetes, and metabolic syndrome) in adults.

Medline, Embase, Cochrane Library, PubMed, CINAHL, IPA, Web of Science, Scopus, Pascal, and reference lists of relevant studies were scoured for randomized controlled trials, cohort, case-control, and cross-sectional studies where the level of chocolate consumption was related to the development of cardiometabolic disorders. There was no language restriction, and interpreters were available if translation were necessary.

Reviewers worked in pairs and initially screened the titles and abstracts, with disagreements resolved through consensus or consultation with a third reviewer. Full text articles were retrieved for the selected titles. Reference lists of the retrieved articles were searched for additional publications, and authors of the retrieved papers contacted directly for any unpublished data. The retrieved studies were assessed again by two independent authors to ensure that they satisfied inclusion criteria. Extracted data included participant characteristics, type of intervention and measurement methods, and reported outcomes. For each study, the group with highest chocolate consumption was compared to the group with the lowest consumption, and summary relative risks were calculated. Results were pooled using a random effects model. Testing for publication bias and heterogeneity was performed.

Out of the 4576 references initially considered, full text assessment of 53 articles was undertaken, and a total of seven articles (one cross-sectional study, six cohort studies), including data on more than 100,000 subjects, were considered appropriate for analysis. Many of the excluded studies did not report on levels of chocolate consumption or on outcomes relevant to the meta-analysis. The studies analyzed had no industry funding, and were deemed of adequate quality without evident bias.

Participants' ages ranged from 25-93 years, the vast majority of whom were Caucasian, and follow-up was from 8-16 years. Some studies included subjects taking prescription drugs. Although no study focused specifically on metabolic syndrome as an outcome, reported outcomes included heart attack, heart failure, diabetes and stroke, among others. One study used participant diaries of chocolate consumption to draw conclusions, while the other six employed food frequency questionnaires. Specific type (milk, dark, or white) of chocolate ingested was not reported, only overall chocolate consumption.

Five studies documented a significant inverse association between chocolate intake and development of cardiometabolic disorders after adjustment for numerous possible confounders, including coffee consumption and body mass index. With pooling of retrieved measures of association, high chocolate consumption was found to decrease the risk of cardiometabolic disorders by approximately one-third — 37% for any cardiovascular disease (RR = 0.63, 95% CI 0.44 to 0.90) and 29% for stroke (RR = 0.71, 95% CI 0.52 to 0.98). No significant association was observed in relation to heart failure. One study reported on the association between chocolate consumption and diabetes, finding a beneficial effect for both Japanese men and women (HR = 0.65 [0.43 to 0.97] and 0.73 [0.48 to 1.13], respectively).

The authors conclude that on the basis of observational evidence, higher levels of chocolate consumption may be associated with a substantial lowering of the risk of cardiometabolic disease.

■ COMMENTARY

Chocolate often falls under the category of "guilty pleasure," but data such as those just described make this classification almost anachronistic, a perspective long held now largely being proved false. That's reason to smile on many fronts.

Cardiometabolic disorders are a major source of morbidity and mortality around the world, but they are also largely preventable through diet and lifestyle measures. One might have thought that part of such a prevention program would be avoidance of chocolate. Apparently, not so, and chocolate may even be considered part of a preventive strategy. Studies suggest that chocolate provides antioxidants, and anti-inflammatory and antithrombotic effects, among others, as a result of the polyphenols present (dark chocolate contains almost three times more catechins than tea) and the specific type of fat present in high percentage cocoa.

Of course, one must consider degree of consumption — many of the products available on store shelves are

extremely high in saturated fat (primarily milk fat) and sugar, and over-indulgence of the type not uncommonly seen in today's society may negate any potential health benefits, even when the discussion turns to the apparently healthier dark varieties (cocoa content > 70%).

The authors are appropriately cautious about their results due to a number of factors: the study was observational in nature, so firm conclusions about cause and effect cannot be supported; the data come from a small number of trials, more than half of which were published in the past two years; means of determining chocolate intake were inexact; there were no randomized controlled trials to review; the majority of subjects were white, so generalizability is hampered; and in light of significant heterogeneity between studies the authors felt they could not venture a clear dose-response relationship for chocolate intake and decreased risk of cardiometabolic disease.

Beyond the possible physical benefits of a small piece of high-quality chocolate each day are the emotional benefits — chocolate has been found to acutely enhance mood in some trials. And then there is consideration of the developing world where, as the study authors point out, much of our chocolate comes from and where cardiometabolic disorders are increasing in prevalence. Their own natural resource could be a boon for public health, both locally and globally.

Yes, there are severe limitations to the conclusions that can be drawn from this study, but the results align with those of prior data and lend credence to the idea that chocolate (in moderation) is not a guilty pleasure — it's the all-too-rare pleasure that is good for us. ■

Non-specific Factors Come to the Fore in Study of Biofield Therapy

ABSTRACT & COMMENTARY

By Dónal P. O'Mathúna, PhD

Dr. O'Mathúna is Senior Lecturer in Ethics, Decision-Making & Evidence, School of Nursing, Dublin City University, Ireland; he reports no financial relationship to this field of study.

Synopsis: *This blinded, randomized, controlled trial found that a biofield therapy and a mock treatment did not differ in their effectiveness in relieving cancer-related fatigue, although they both were significantly better than control. The biofield therapy did lead to significantly greater cortisol variability, which is associated with fatigue.*

Source: Jain S, et al. Complementary medicine for fatigue and cortisol variability in breast cancer survivors: A randomized controlled trial. *Cancer* epub 5 August 2011; DOI: 10.1002/cncr.26345

Cancer-related fatigue is one of the most common and bothersome side effects of cancer and cancer treatment. One third of cancer patients experience significant fatigue 5-10 years after treatment.[1] The cause of this fatigue is unclear, but in breast cancer patients it is associated with decreased diurnal cortisol variability. The precise mechanism involved here is not known. Few effective treatments are available for cancer-related fatigue. Many breast cancer patients pursue complementary and alternative medicine (CAM), among these therapies are a group called biofield therapies. According to the National Center for Complementary and Alternative Medicine (NCCAM), biofield therapies "are intended to affect energy fields that purportedly surround and penetrate the human body. The existence of such fields has not yet been scientifically proven."[2] These include Therapeutic Touch, Reiki, and Qigong. While training is available in each, variations are commonly introduced, such as with the therapy examined in this study.

Few high-quality studies have examined the effectiveness of biofield therapies in cancer patients. Jain and colleagues designed a three-arm, double-blinded study to test the effectiveness of a hands-on energy healing technique called "energy chelation." The technique's description makes it appear very similar to Reiki, with the practitioner's hands positioned over different parts of the recipient's body. Each position was held for 5-7 minutes with the whole session lasting 45-60 minutes. During this time, the practitioner focused her intention on bringing healing to the patient.

A mock healing technique was developed for scientists who were skeptical of energy healing. Volunteers were trained in the hand positions, but kept their intention focused on their own research activities. They were also trained to answer common questions about energy healing to maintain patient blinding. To account for therapist bias, participants were asked to guess which treatment they received. No significant differences were found between the two groups receiving either intervention. The third group was a waiting-list control group.

Patients were females who had completed breast cancer treatment 1 month to 10 years earlier. Only those with scores > 50 on the RAND SF-36 vigor-fatigue subscale were included. A power analysis established that 65 subjects were needed to detect a small effect size. To account for attrition, the plan was to recruit 80 subjects and randomly assign 30 to each of the intervention groups and 20 to the waiting-list control. In the end, 76 were recruited with 27 receiving biofield therapy, 30 receiving the mock

treatment, and 19 in the control. The interventions were given for 4 weeks, with two 1-hour sessions each week.

The primary outcome measured was cancer-related fatigue using the validated Multidimensional Fatigue Symptom Inventory-short form. Secondary outcomes were cortisol variability, depression, and quality of life (QOL). An exploratory aim was to investigate the influence of prior beliefs about energy healing and spirituality on outcomes.

Significant reductions in fatigue scores were found for the biofield therapy group ($P < 0.0005$) and the mock treatment group ($P < 0.02$) compared to control. However, the two intervention groups did not differ significantly ($P = 0.12$). For the secondary outcomes, significantly greater increased variability occurred in cortisol levels between biofield therapy and control ($P = 0.004$) and between biofield therapy and mock treatment ($P = 0.039$). This finding was relied on by the study authors to suggest that the impact of the biofield therapy was not simply due to factors of human touch and presence. No significant differences were found for depression and QOL scores. However, those subjects who believed they received biofield therapy (whether they did or not) showed significantly greater increases in QOL than those subjects who believed they did not receive biofield therapy ($P = 0.004$). Belief did not impact fatigue or cortisol outcomes.

The authors concluded: "Overall, our results suggest that biofield healing may be a promising intervention for ameliorating cancer-related fatigue, and that it warrants further study. Effects of biofield healing on fatigue may in part be because of nonspecific factors such as touch and rest, but not belief."

■ COMMENTARY

This randomized controlled trial was designed and reported well. Details about power calculations, randomization, patient attrition, and other factors listed in the CONSORT statement were provided. The subjects were blinded, and when asked which intervention they thought they received, each group gave similar answers. All other research personnel were blinded to the nature of the intervention given each subject. The authors are to be commended for conducting a high-quality study. However, a few comments must still be made.

Although standard methods were used in the study design, some justification for examining "energy chelation" therapy was needed. A search of PubMed and the NCCAM databases revealed no other references to this therapy. Given the acknowledgment by the study authors that few high-quality studies have been conducted on any biofield therapy, further investigation of biofield therapies which already have been assessed, like Reiki or Therapeutic Touch, would have been preferable. At the very least, justification for using this obscure therapy was warranted.

The authors used the popularity of CAM in general to justify their study, but NCCAM notes that biofield therapies are not very popular. They cite a study that found that about 0.5% of adults have used biofield therapies.[2] Jain and colleagues claimed that biofield therapies are "often used by breast cancer patients." Yet the study they themselves cite found that 2% of breast cancer patients in Portland, Oregon, used energy healing.[3]

In spite of this, the only significant problem with this study lies with the implications the authors draw from their results. As quoted above, they made generalized comments about biofield therapies for cancer-related fatigue, even though they investigated one specific therapy. In addition, their results support the importance of nonspecific factors, not the energy-related factors. The excellent design of their study allowed the energy and practitioner intention factors to be distinguished from the presence and touch of the practitioner and the patient getting rest. Since the biofield therapy and mock therapy groups did not differ significantly in fatigue scores, the implication is that energy chelation is not the beneficial variable. Rather, allowing patients to relax for an hour in the presence of someone who touches them in specific ways brings significant relief from cancer-related fatigue. The significant difference found in cortisol slope is intriguing, although much remains to be understood about the relevance of this for clinical symptoms.

The lack of significant differences in primary outcomes suggests that specific training in energy manipulation may not be needed. While biofield therapies will continue to be investigated, touch and presence should be examined for their own value, not just factors to be controlled against. Such investigations would be challenging to design. However, in these days of scarce resources, it would be helpful to explore the impact of friends or family members carrying out a touch routine at home. It could be that the health care setting used in this study is a necessary factor. If not, a finding that touching someone at home for an hour twice a week brings significant benefit would help many patients. ■

References

1. Bower JE, et al. Fatigue in long-term breast carcinoma survivors: A longitudinal investigation. *Cancer* 2006;106:751-758.
2. NCCAM. What is complementary and alternative medicine? Available at: http://nccam.nih.gov/health/whatiscam/. Accessed Sept. 8, 2011.
3. Henderson JW, Donatelle RJ. Complementary and alternative medicine use by women after completion of allopathic treatment for breast cancer. *Altern Ther Health Med* 2004;10:52-57.

No Preventive Manual — Lymphedema Related to Breast Cancer

ABSTRACT & COMMENTARY

By Russell H. Greenfield, MD, Editor

Synopsis: *In a prospective study of women with breast cancer who had undergone axillary node dissection, use of manual lymphatic drainage techniques over 5 months provided no additional preventive benefit with respect to development of arm lymphedema over general preventive lifestyle measures and individualized exercise therapy.*

Source: Devoogdt N, et al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: Randomized controlled trial. *BMJ* 2011;343:d5326.

The Belgian authors of this randomized, controlled, single-blind study point out at the onset that early detection and treatment of breast cancer have advanced to such a degree that increased emphasis is now being placed on the prevention and management of long-term side effects and complications of therapy, including lymphedema, for survivors. Toward this end, the researchers set their sights on determining whether a program of manual lymph drainage (MLD) combined with exercise therapy and general preventive guidelines might be more effective against the development of lymphedema related to breast cancer than the exercises + guidance alone.

Over approximately 2 years, 160 consecutive women who had undergone unilateral axillary node dissection in association with treatment for breast cancer were randomized to either active (MLD + exercise + guidance, n = 79) or control (exercise + guidance, n = 81) groups (337 women were asked to participate, 52% declined). Subjects were stratified based on BMI and whether post-surgical axillary radiation therapy was performed (two of the factors most commonly cited as increasing the risk for development of lymphedema, along with the number and levels of axillary nodes dissected). Treatment allocation was concealed, and the groups were comparable at baseline.

All subjects received a brochure and, if desired, tutorials regarding the prevention of lymphedema (guidelines included but were not limited to avoidance of lifting heavy objects and performing repetitive movements, wearing a therapeutic sleeve during air travel, and avoiding weight gain), and individualized exercise training beginning shortly after surgery. The frequency of exercise training sessions was dependent on improvements in limb range of motion, with less frequent sessions the farther a subject was out from surgery.

Starting approximately 5 weeks post-surgical intervention, subjects in the active group also received standardized MLD over 20 weeks, the goal being that each participant would receive a total of 40 MLD treatments, "... with an increase in frequency from once a week to three times a week, and then a decrease to once a week, to create a gradual adaptation of the lymph system and not to end too abruptly." The 1-hour treatments were described thus: "Firstly, lymph nodes of neck and axilla were emptied. Secondly, axilloaxillary anastomoses at the breast and back and lymphatics at the lateral side of the shoulder (Mascagni pathway) were stimulated. Thirdly, the arm and hand were drained from proximal to distal."

All interventions (MLD, exercise, and preventive guidelines) were provided by a group of four therapists, two of whom had more than 10 years' experience with MLD and who performed more than 70% of all the MLD treatments. Arm volume was determined using a volumeter by blinded assessors at 1, 3, 6, and 12 months post-surgery. Lymphedema was defined as an increase of 200 mL or more in the difference in arm volume between the affected and healthy side compared with the difference from presurgical measurements, and an increase of 2 cm or more in the difference in arm circumference between the affected and healthy side at two or more adjacent measurement points compared with the preoperative difference. Health-related quality of life (SF-36) was assessed at 3, 6, and 12 months after surgery.

Four patients in the active group and two in the control group developed arm lymphedema before the start of the 20-week treatment period and were excluded from the final analysis. By the trial's end, 4% of participants had dropped out of the study (4 in the intervention group, 2 controls); 11 members of the active group (15%) had received 23-29 manual lymph drainage sessions, 26 had (36%) received 30-35 sessions, and 36 (49%) underwent > 35 sessions of MLD (reasons for absence were primarily illness related to chemotherapy and radiotherapy).

At 1 year post-op, participants in the active group had a cumulative incidence rate for arm lymphedema of 24% vs 19% in the control group (OR = 1.3, 95% CI 0.6 to 2.9; $P = 0.45$). Time to development of arm lymphedema was also comparable between the two groups (HR = 1.3, 0.6 to 2.5; $P = 0.49$), with similar cumulative incidences at 3 and 6 months post-surgery. Results remained consistent when controlled for risk factors such as BMI and axillary radiation therapy. Quality-of-life measures were similar between the two groups.

The researchers concluded that MLD in addition to lifestyle guidelines and individualized exercise therapy

after axillary lymph node dissection for breast cancer is unlikely to have a significant beneficial effect in reducing the incidence of arm lymphedema in the short term.

■ COMMENTARY

MLD remains an integral part of the treatment of established limb edema after cancer treatment, but the results of the current study suggest that it does not offer a preventive benefit for women having undergone axillary node dissection as part of the treatment for breast cancer. This is more than unfortunate, as arm lymphedema is recognized as a presently incurable problem that negatively impacts quality of life in many ways. In addition, those who have escaped arm edema for the year following axillary dissection are still at risk for developing the disorder (more than 20% of cases develop > 1 year following surgery).

MLD is purported to enhance resorption and transport of lymph through existing collaterals. Studies suggest it to be an effective treatment strategy, though researchers often fail to make mention of additional health benefits the technique may offer simply through the application of compassionate and healing touch.

The authors are to be commended for exploring preventive measures against the development of lymphedema secondary to treatment of breast cancer. It is true that their conclusion regarding lack of clinical benefit of MLD in this setting are weakened by the fact that two of the therapists providing care were not experts in the field, though they had received specialized training prior to the study; however, the majority of MLD was performed by the two experienced therapists, and most all of the women in the intervention group received more than 30 MLD sessions.

In light of recent data suggesting that even women with abnormal sentinel node biopsy results may not need to undergo axillary node dissection,[1] it is likely that fewer women will be at risk for the development of this life-altering disorder (thankfully). This is welcome news, because an effective program of prevention against the development of arm edema has yet to be identified. MLD does not appear to be the answer. ■

References

1. Spiguel L, et al. Sentinel node biopsy alone for node-positive breast cancer: 12-year experience at a single institution. *J Am Coll Surg* 2011;213:122-128.

CME Instructions

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

1. Standardized preparations of butterbur (Petadolex) and Feverfew (MIG-99) can safely be used in pregnant patients with chronic migraine headaches.
a. True
b. False

2. Migraine headaches are associated with which of the following comorbidities?
a. Depression
b. Anxiety
c. Sleep disorders
d. All of the above

3. Magnesium supplementation is not a problem in the presence of renal insufficiency.
a. True
b. False

4. Coenzyme Q10 may antagonize the effects of warfarin anticoagulation.
a. True
b. False

5. Which of the following can trigger migraine headaches in certain individuals?
a. Diminished sleep
b. Skipped meals or fasting
c. Caffeine withdrawal
d. All of the above

In Future Issues:

How Research Is Designed and What Can Go Wrong

Teas and Supplements for Infants