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Stevia as a Natural Sweetener, Hypoglycemic, and Antihypertensive

By Michael D. Cirigliano, MD, FACP and Philippe O. Szapary, MD

THE UNITED STATES IS THE LEADING CONSUMER OF SYNTHETIC NON-nutritive sweeteners, accounting for approximately 50% of world demand.[1] Agents such as Nutrasweet™ (aspartame) have attained significant popularity in soft drinks and are currently added to more than 6,000 foods, personal care products, and pharmaceuticals. Many people use them in their efforts to control their weight and blood sugar levels.

Questions of personal cost, safety, and potential risk to long-term, heavy users of chemical sweeteners have recently resurfaced. Possible links to cancer, mutagenesis, multiple sclerosis, Gulf War syndrome, and chronic fatigue syndrome have been noted.[2,3] Although controversial, these concerns have led many to seek alternative natural agents possessing noncaloric sweetening properties.

One such natural alternative is the leaves of the plant stevia (*Stevia rebaudiana*). Although accepted for general use in Japan and Brazil as a natural sweetening agent, its use in the United States is currently limited to that of a dietary supplement only.

History and Worldwide Consumption

A member of the Asteraceae family, stevia is a perennial shrub indigenous to South America that is commercially grown in Central America, Israel, Thailand, and China.[4] Used for centuries in Paraguay, its country of origin, to sweeten beverages and other foods, stevia's popularity continues to rise—both as a sweetener, and for the treatment of hyperglycemia.[4,5] In Paraguay, stevia was used by the Guarani Indians to sweeten various beverages before that country's colonization by the Spaniards in the 16th century. European interest in stevia began around that time.

The use of stevia as a natural sweetener for widespread use has been approved in Japan since 1975. In Japan, it is used as a noncaloric sweetener in a variety of foods including seafood, pickled

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vegetables, desserts, ice cream, soft drinks, and confectionery. It is also sold as a table sweetener, as it is in the United States, to be mixed with tea and coffee.[4] Sales figures for 1997 estimated that 700-1000 tons of stevia were imported to Japan alone; one company reported producing two to three tons of stevioside per month.[6]

Pharmacology

Stevia leaf contains a number of sweet *ent*-kaurene glycosides including stevioside and rebaudioside A. These represent the most significant natural sweeteners contained in the plant.[4]

Stevioside comprises 5% of the dry weight of the leaves[7] and is formed by three glucose molecules and steviol, a diterpenic carboxylic alcohol. Other related compounds found in the plant include rebaudioside A-E, steviolbioside, steviol, and dulcoside A, several of which are also sweet.

Stevioside administered orally is excreted into the feces but most of it is decomposed by bacterial flora in the cecum to steviolbioside, steviol, and glucose. Steviol then becomes conjugated in the liver and is excreted into the intestinal tract through the bile.

Stevioside has been noted to be 300 times as sweet as sucrose. Stevioside itself offers particular advantages over other noncaloric sucrose substitutes in that it is heat-stable, somewhat resistant to acid hydrolysis, and nonfermentable.[8]

Mechanism of Action

Stevia and its major active constituents exhibit a number of pharmacological properties. Although mainly known for its noncaloric sweetening properties, components of stevia have also been shown to have hypoglycemic as well as antihypertensive activity.

Further studies have found that steviol inhibits gluconeogenesis, thereby possibly explaining the hypoglycemic effects seen with its use.[9] It has been shown, however, to have no direct action on pancreatic A and B cells.[10]

Stevia is also noted to possess some hypotensive activity, possibly secondary to a diuretic and/or vasodilatory effect, modulated via prostaglandin activity.[11] Other investigators believe that steviol's diuretic activity may derive from its ability to inhibit sodium reabsorption in the renal tubular cells. Increased water and solute excretion result, with no effect on the glomerular filtration rate.[7] Several other studies have implicated calcium channel blockade as a cause of stevia's hypotensive effects. Stevia may inhibit calcium influx by blocking excitation-coupling in smooth muscle, and therefore may promote vasodilatation.[12]

Animal Studies

Studies have evaluated the hypoglycemic effects of stevia. In one small animal study, an unstandardized preparation containing stevia and the chrysanthemum flower were administered orally to nondiabetic dogs over a three-day period.[13] The animals underwent a five-day pretreatment phase with normal dietary intake and then were administered daily dosages of stevia for three days using an escalating regimen of 3 drops, 1/2 ml, 1 ml, and 3 ml. This was followed by a one-time dose of 6 ml. The animals were maintained on their regular diets throughout the experiment. Laboratory studies including plasma glucose were measured daily with no reductions in blood glucose.

The authors determined that the product utilized had no effect on blood sugar levels but noted that the study was small and uncontrolled.

Clinical Trials

Despite its widespread use by the public and use as a food additive in Japan and Brazil, there is a surprising lack of human clinical trials evaluating the safety and efficacy of stevia.

In an often quoted Brazilian study,[14] the effect of *Stevia*

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Conflict of Interest Disclosure

Physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. La Puma is Director of CHEF Research. Dr. Ofman has the following relationships: Consultant for Zynx Health, Inc., Cedars-Sinai Health System; Research for Astra USA, Johnson & Johnson, Janssen. Dr. Barrette, Dr. Cirigliano, Dr. deLeon, Dr. Kattapong, Dr. Schiedermayer, Dr. Sorrentino, Dr. Szapary, and Dr. Tillem have no relationships with companies related to the field of study covered by this CME program.

Table 1

Stevia cost and formulation comparison

Manufacturer/ Product Name	Formulation	Manufacturer's Recommended Dose	Price
Only Natural, Inc. Stevia Alcohol Free	100% pure stevia extract 4:1 in water base not less than 4 lbs pure Paraguayan leaves used to make 1 liter of extract	2-5 drops, 3-6 times daily	$18.95/2 oz
NuNaturals Pure Liquid™ Clear Stevia™ Extract	Standardized to contain a minimum of 85% steviosides	5-10 drops to favorite food or beverage	$10.99/2 oz
Nature's Herbs Stevia Power	Each capsule contains 57 mg certified potency stevia extract concentrated and standardized for a minimum of preferred 85% steviosides	1-2 capsules with beverage	$8.69/60 capsules
Optimum Nutrition Alcohol-Free Stevia Liquid Extract	*Stevia rebaudiana* (leaf) extract standardized to contain 90% steviosides	1-3 drops to tea, water or beverage	$6.99/2 oz

Source: Online mail-order companies

rebaudiana on glucose tolerance was studied in 22 non-diabetic adult volunteers receiving aqueous extracts of stevia leaves (20 g/d) during a three-day period. Aqueous extracts of *Stevia rebaudiana* were prepared by immersing the leaves in boiling water for 20 minutes. Sixteen subjects were nonrandomly assigned to receive stevia in a dose roughly corresponding to 5 g of extracted leaves, administered orally at six-hour intervals over three days. Each subject had a baseline glucose tolerance test (GTT) and then a follow-up GTT after three days of stevia treatment. A control group of six patients received 13 doses of 250 mg of arabinose (a sugar used as an active placebo). During the experimental period, the volunteers ate their usual diets.

Findings revealed that the plasma glucose levels measured after stevia treatment were significantly lower than the control at each of the times tested ($P < 0.05$-0.01). Of note, no test subjects developed hypoglycemia. In one volunteer, the renal threshold for glycosuria was exceeded during the first 90 minutes. After stevia administration, his glycosuria was completely abolished. In the control group, no differences in serum glucose were noted. The authors concluded that in every period studied, serum glucose levels were diminished after treatment with stevia. However, no generalizable conclusions can be drawn from this study as it was small, of short duration, nonrandomized, and used a nonstandardized preparation. Additionally, no mention was made of blinding subjects or investigators. Other small studies have also noted a decrease in blood sugars after ingestion of stevia.[15]

Adverse Effects and Contraindications

Stevia is not listed in the German Commission E Monographs. It is, however, categorized as a Class 1 agent by the *American Herbal Products Association's Botanical Safety Handbook* indicating that stevia can be safely consumed when used appropriately.[16]

In May of 1991, the FDA issued an import alert identifying stevia as an "unsafe food additive."[17] This ruling was later amended in 1995 to allow entry of stevia into the United States "explicitly labeled as a dietary supplement or for use as a dietary ingredient in a dietary supplement." The FDA reasoning for this initial import alert was the absence of extensive toxicological data on stevia. This lack of long-term human data was felt to be important enough to prohibit widespread U.S. consumption of stevioside. Of note, stevia is not currently allowed as a nonnutritional ingredient in Canada.

Several studies have attempted to evaluate the safety of stevia. One study in animals revealed no adverse effects on growth or reproduction in hamsters given dosages of stevioside as high as 2.5 g/kg body weight per day.[18] In a report published by the Proceedings of the National Academy of Science,[6] stevioside and the crude product used as a sweetening agent revealed no mutagenic activity on a variety of bacterial strains. Carcinogenicity was not detected in hamsters given stevioside orally for six months or in rats fed stevioside for two years.[19,20]

However, several animal studies indicating possible nephrotoxicity in hamsters given steviol intravenously have been noted.[21] Found both in the stevia leaf and as a

metabolite of stevioside, steviol has been found to be highly mutagenic in several in vitro studies.[6]

Despite these early reports, no recent information has appeared indicating that adverse effects have resulted from human use of stevia products. Neither stevia extract nor stevioside has been shown to be toxic or teratogenic in mice, rats, hamsters, and guinea pigs by oral administration at low doses.[22] Unlike saccharin, no evidence has been reported that stevioside and its metabolites are carcinogenic.

Given the noted hypoglycemic and hypotensive properties of stevia, a theoretical concern exists in diabetic and hypertensive patients who might consume stevia. Patients with known sensitivities to plants of the Asteraceae/Compositae family, such as ragweed, should avoid stevia. Insufficient human data exist regarding safety in pregnancy and lactation: There, its use should be avoided.

Formulations and Dosage

Stevioside is classified as a nontoxic compound when given by an oral route (LD_{50} >15 g/kg) according to a toxicity rating chart.[23] Despite this, no universally accepted method of standardization and dosing exists. Stevia is mainly consumed by mouth either in powder or liquid form and is most often used as an additive to foods and beverages. (*See Table 1 for price/formulation comparison*.)

Conclusion

Despite extensive use of stevia in Japan and South America as a food additive and nonnutritive sweetener, a remarkable lack of significant human data regarding safety and efficacy precludes recommending its use in the clinical setting. Despite a lack of significant human toxicity reports in the literature, animal reports of nephrotoxicity and possible mutagenicity with long-term use do exist. Randomized controlled trials investigating its long-term safety in humans are certainly needed before broad recommendations can be made regarding the use of stevia.

Recommendation

Historical and widespread use in low doses as a natural sweetener does not appear to be associated with any morbidity. Patients using these products, however, should be counseled regarding the potential risks and benefits of their use: Pregnant and lactating patients should avoid stevia.

Because of the scant published scientific data supporting the use of stevia in the treatment of hyperglycemia, its widespread use by diabetic patients as an adjunctive hypoglycemic agent cannot be recommended currently.

Although animal studies suggest a possible hypotensive effect from use of stevia, use in humans for control of high blood pressure also cannot be recommended. ❖

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Black Cohosh for the Treatment of Perimenopausal and Menopausal Symptoms

By Joya Tillem, MD

As baby boomer women now approach menopause, the search for an herbal remedy to curb symptoms has become increasingly important. Black cohosh has emerged as a possible solution, and may be the most promising herbal remedy for treating menopausal symptoms. This bitter root has a long history of traditional use by American Indians, has been widely studied in Germany, and is approved by the German Commission E for painful menstruation and symptoms of menopause. Several studies show that black cohosh is efficacious for menopausal symptoms.

Source Identity

A member of the Ranunculaceae (buttercup) family, black cohosh (*Cimicifuga racemosa*) is native to Eastern North America. Typically found in moist or dry woods, this widely cultivated, decorative wildflower is a hardy perennial that grows up to 9 ft and produces beautiful flowers on a tall stalk. The supplement, however, is derived from the black cohosh root and contains triterpene glycosides, which are believed to be the principal pharmacologically active constituents.

Traditional Uses

Known as "squawroot" by American Indians, black cohosh has been used historically for female conditions, rheumatism, and snake bites, and as an insect repellent. Its generic name, cimicifuga, was derived from its traditional use as a bug repellent; the Latin *cimex* means bug and the Latin *fugare* means to put to flight. In the early 20th century, black cohosh was an essential ingredient in Lydia Pinkham's Vegetable Compound, an enormously popular patent remedy used for "female complaints." The root was part of the U.S. Pharmacopoeia from 1820 to 1926.

Pharmacology

All the phytoconstituents of black cohosh are not yet known. The principal triterpene glycosides are xylosides, actein, and cimicifugoside. Anti-inflammatory, hypoglycemic, and hypotensive effects have all been measured in animals. Early on, the phytoestrogen/isoflavone formononetin was isolated,[1] but more recent investigations failed to show its presence.[2] Other compounds isolated include fatty acids, resins, tannins, as well as butyric, salicylic, and oleic acids.

Common Indications

Black cohosh is used for common symptoms associated with menopause, hot flashes, and psychological symptoms including insomnia, depression, anxiety, and forgetfulness.

Laboratory/Animal Studies

In vitro, black cohosh extract hinders the growth of breast cancer cells.[3] In mice, black cohosh has been found to lack estrogenic effects. In one study, black cohosh (600 mg/kg) was administered to 10 immature mice, resulting in no uterine growth. In that same investigation, black cohosh was given to 12 ovariectomized rats. Vaginal smears after three days showed no signs of cornified cells.[4]

Clinical Studies

Black cohosh was studied as early as the 1940s as a natural agent for dysmenorrhea and menopausal symptoms.[5] The majority of the reported investigations were

Table 1

Black cohosh price and formulation comparison

Manufacturer/ Product	Formulation	Manufacturer's Recommended Dose	Price/Quantity
Enzymatic Therapy Inc. Remifemin™ Plus	Each tablet contains standardized *Cimicifuga racemosa* root and rhizome extract corresponding to 20 mg *Cimicifuga racemosa*. Standardized for triterpene glycosides content (calculated as 27-deoxyactein); St. John's wort extract standardized to contain 250 mcg hypericin	1 tablet bid	$27.95/60 tablets
Solgar Co. Sfp Black Cohosh	Each vegicap contains 1 g total carbohydrate, 200 mg black cohosh extract, 200 mg raw black powder, 200 mg soy isoflavone concentrate	1-2 vegicaps/d, taken with meals	$23.90/60 vegicaps
Nature's Herbs Black Cohosh Root	Each capsule contains wild countryside black cohosh root (545 mg each)	1-3 capsules tid	$10.39/100 capsules
Natrol Black Cohosh	Each capsule contains 80 mg of guaranteed potency black cohosh 2.5% extract	1-2 capsules/d with meals	$8.95/60 capsules
The Vitamin Shoppe Black Cohosh Extract	Each capsule contains 40 mg black cohosh root and rhizome extract standardized to contain 2.5% triterpene glycosides	1 capsule/d	$8.50/60 capsules

Source: Online mail-order companies

performed in Germany, with almost all utilizing Remifemin™, a commercial isopropanolic extract of black cohosh.

In 1982, 629 women with menopausal symptoms received 40 drops black cohosh (Remifemin) bid for 6-8 weeks. Outcome measures included hot flashes, sweating, headache, heart palpitations, and psychological disturbances. Eighty percent of participants showed improvement in menopausal symptoms at four weeks. Additionally, 93% of patients reported good tolerance without side effects.[6]

In gynecologic practices, two open-label studies were done looking at menopausal symptoms (n = 36, n = 50).[7,8] Patients either refused hormone treatment (31 of 36) or had a contraindication to hormonal therapy (39 of 50). Both studies used 40 drops black cohosh extract (Remifemin) bid for 12 weeks. Efficacy criteria scales included Menopausal Index (Kupperman), Clinical Global Impressions (CGI), and Profile of Mood States (POMS). Results included a decrease in Kupperman index (< 15), a positive CGI, and a decrease on POMS including an overall elevation in mood, suggesting improvement.

A 12-week, nonblinded, controlled study of 60 patients compared the effectiveness of 40 drops black cohosh extract (Remifemin) bid vs. conjugated estrogens (0.625 mg/d) vs. 2 mg/d diazepam for menopausal symptoms. Outcomes were measured with the Menopausal Index, CGI, Self-Assessment Depression Scale (SDS), and Hamilton Anxiety Scale (HAMA). All three therapies decreased menopausal symptoms, with a significant decrease in the Kupperman index and the SDS index. All therapies equally reduced CGI, but not significantly.[9]

In 1987, a randomized, double-blind study compared a standardized extract of black cohosh (Remifemin) containing 2 mg of 27-deoxyactein per tablet to estrogen. Over 12 weeks, 80 women were given either two tablets Remifemin bid, conjugated estrogens 0.625 mg (plus three placebo tablets daily to equal two tablets bid), or two placebo tablets bid. Outcomes were based on Kupperman and HAMA scores, and maturation of vaginal epithelium. Cimicifuga conferred a benefit in menopausal symptoms which rivaled the benefits of estrogen replacement therapy with a decrease in Kupperman and HAMA scores (< 15). No improvement was noted in the participants taking placebo. The vaginal epithelium of those on black cohosh showed an increase in proliferation, whereas the estrogens showed only a small influence.[10]

A 1991 German prospective, placebo-controlled study of 110 menopausal women receiving 8 mg/d black

cohosh extract (Remifemin) for eight weeks found that levels of luteinizing hormone but not follicle-stimulating hormone were significantly reduced.[11] Although a clear mechanism remains elusive, these results imply that black cohosh confers some estrogen-like effects.

Dosage/Formulation

Most studies were performed with the commercially prepared isopropanolic extract of black cohosh Remifemin. The dose most supported by clinical data is 40 mg of herb daily in a standardized extract to contain 2.5% triterpene glycosides (or 2 mg triterpene glycosides/d). In liquid extracts, the total daily doses should be 40 drops of standardized extract containing 5% triterpene glycosides. Black cohosh is also available as a dried rhizome (recommended dose 40-200 mg/d) or an ethanol tincture (recommended dose 1:10 60%).[12] A water/alcohol extraction method is used in a ratio of 60:40 to yield a decoction. (*See Table 1 for price/formulation comparison.*)

Safety

Although black cohosh has been widely used in Europe, long-term toxicity data are lacking in humans. The German Commission E recommends limiting use to six months.[13] Side effects include occasional gastrointestinal disturbance. Because of lack of existing data, black cohosh is not recommended in pregnancy and lactation.[14]

Conclusion

In the pursuit of a remedy to aid women who want to move through menopause smoothly, hormone replacement therapy (HRT) has many benefits. In addition to helping with menopausal symptoms, HRT also offers likely cardioprotective effects[15,16] and remains the cornerstone of osteoporosis prevention as well.[17,18] Black cohosh is not known to offer these same benefits. However, several well-designed studies indicate that black cohosh is a safe and effective treatment for menopausal symptoms for those women who cannot or will not take HRT.

Recommendation

Studies thus far seem to indicate that black cohosh is safe and effective in decreasing the burden of menopausal symptoms. ❖

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Biofeedback as a Treatment for Migraine

By V. Jane Kattapong, MD, MPH

Look into the depths of your own soul and learn first to know yourself, then you will understand why this illness was bound to come upon you and perhaps you will thenceforth avoid falling ill.

Sigmund Freud, MD
One of the Difficulties of Psychoanalysis

MIGRAINE HEADACHE IS AN EXTREMELY COMMON DISorder, and the prevalence is reportedly increasing.[1] At some point in their lives, up to 15% of the world's population suffers from migraine. Migraine headache continues to be undertreated, resulting in temporary disability, lost work days, and decreased quality of life. In fact, many migraineurs have never been diagnosed and have never received treatment.

Reasons for not seeking treatment include reluctance to rely on pharmaceutical agents, which may have side effects, be costly, or lead to dependence. Employing nonpharmacologic treatment can circumvent these obstacles to obtaining migraine relief and may help migraineurs help themselves.

Migraine Risk Factors

Many risk factors, including diet and environmental factors, play a role in the genesis of migraine episodes in those who are susceptible. Skipping meals, weather changes, and high altitude may trigger migraine. In addition, lifestyle factors that can trigger migraines include changes in sleep pattern or amount of sleep; stress or the stress letdown that occurs after a positively or negatively stressful event; exposure to bright light, fluorescent light, or sunlight; loud noises; strong odors; or overuse of headache medication.

Mechanism of Action

Nonpharmacologic treatments, more so than pharmacologic treatments, may allow migraineurs to be in control of their headaches,[2] since nonpharmacologic treatments are self-directed, in contrast to the external control imposed by pharmacologic agents.

Nonpharmacologic treatments of migraine include biofeedback and relaxation. The mechanism for their effectiveness is not well understood.[3] Of these two techniques, a greater body of literature has accumulated regarding outcomes from biofeedback.[4] One possible mechanism for the effectiveness of biofeedback is a decrease in sympathetic outflow or stabilization of autonomic nervous system activity, and a resulting improvement in migraine activity.[5] However, since a dose-response relationship between the effectiveness of biofeedback and headache relief has not been proven,[6] an alternative hypothesis is that biofeedback brings migraine relief through implicating conditioned relaxation.[7]

What Is Biofeedback?

Biofeedback techniques take advantage of the fact that patients can be made aware of measurable aspects of physiologic function which are potential indicators of migraine susceptibility. Provision of this information enables patients to attempt consciously to alter these physiologic functions.

There are several varieties of biofeedback. Thermal biofeedback, frontalis EMG biofeedback, and cephalic vasomotor feedback are among the varied types of techniques that have been employed to alter physiologic manifestations of migraine. Chapman believes that biofeedback is most likely to be effective in younger patients who are not habituated to analgesics.[8] Thus it seems likely that biofeedback will differentially benefit some subgroups of patients more than others.

Thermal Biofeedback

Thermal biofeedback involves obtaining skin temperature measurements, usually from the finger, and conveying this information to the patient. The goal of thermal biofeedback is to teach the migraineur to raise the peripheral finger and hand temperature.[8] In essence, the technique teaches cognitively controlled handwarming.

Frontalis EMG Biofeedback

EMG biofeedback uses EMG data to provide patients with measurements of the intensity of muscle contraction. These data are then used to induce a decrease in intensity of muscle contraction.

Cephalic Vasomotor Feedback

Cephalic vasomotor feedback utilizes photoplethysmography to present a visual representation of temporal artery blood-volume pulse amplitude. As the signal width varies with vasodilatation and vasoconstriction, patients are asked to cause the signal to become more narrow. Guided imagery, such as description and visualization of traversing a tunnel, and methods of positive reinforcement may be employed to enhance results.[2]

Procedure

Biofeedback training sessions usually are provided by psychologists or other practitioners who have had

counseling training.[9] However, no license is required for health professionals who utilize biofeedback techniques. Sessions may take 30-60 minutes, and typically 4-16 sessions are given.[10] During the course of the sessions, patients are taught techniques that they can perform on their own.

Clinical Trials

Numerous controlled trials have reported a therapeutic effect of thermal biofeedback for migraine sufferers.[11] One uncontrolled comparison study of biofeedback and relaxation found biofeedback to be more effective.[4] In a nonrandomized study of 27 adult migraine patients, the effectiveness of thermal biofeedback, frontalis EMG biofeedback, and relaxation training was compared.[4] A total of 24 training and maintenance sessions were given to each patient, with subsequent follow-up for up to six months. Significant longitudinal improvements in headache frequency were demonstrated in all three groups.[4]

In a randomized, eight-month trial of psychological and pharmacological treatment of pediatric migraine, 43 German schoolchildren received either psychological treatment or pharmacologic treatment with metoprolol, a beta blocker.[2] Those receiving psychological treatment were separated into two groups: those receiving biofeedback from cephalic vasomotor training and those receiving relaxation training.

The children were asked to complete headache diaries including entries regarding quality, duration, frequency, and intensity of headaches. Relaxation training was the most effective treatment ($P = 0.04$) and metoprolol was the least effective, with biofeedback intermediate in effectiveness. However, in a comparison of pre- and post-treatment data, children treated with cephalic vasomotor feedback demonstrated significant improvements in headache frequency, headache duration, and mood.

The usefulness of biofeedback technique as an adjunctive and alternative therapy for pregnant migraineurs is accepted in the medical literature.[10] Relatively few pharmacologic treatments are believed to be safe. With this constraint in place, biofeedback has taken on more importance as a therapeutic option among practitioners of standard medical therapy.

In a controlled study involving 30 pregnant women with a history of migraines, Marcus found that women taught to engage in relaxation and biofeedback experienced an 81% decline in headache intensity and frequency, compared to a 33% decline in controls (although it is unclear if the differences reached statistical significance).[12] The beneficial effects of this non-medical treatment persisted for up to one year following delivery.[13]

Biofeedback Performance Feedback

Utilizing an intriguing paradigm, Allen and Shriver[7] investigated the possibility that outcome in childhood migraine could be improved with enhanced performance feedback. This study used a time-lagged control design in which children who were migraineurs were taught thermal biofeedback techniques, and then subsequently were given feedback that reflected successful employment of these techniques. Only a few patients were studied. Four of six children subjectively experienced a significant reduction in headache, even when no objective improvement occurred in biofeedback response, as measured by improvement in handwarming. These findings suggest that providing patients with encouraging feedback regarding their performance of biofeedback techniques can enhance the headache relief they experience.

Adverse Effects

No adverse effects have been reported.

Conclusion

Most migraineurs will never be entirely free of headaches, so the goal of migraine management is to keep headaches manageable. When this goal is achieved, patients can expect to have minimal, if any, disruption of their lives caused by migraines.

Although the effectiveness of biofeedback and relaxation are probably comparable, limited evidence suggests greater effectiveness for biofeedback. The key appears to be to help migraineurs control their headaches. This empowerment can help migraineurs stay active and productive at home and at work. Specific populations that have been studied and found to have a beneficial response from biofeedback include adults, pediatric patients, and pregnant patients. While it may not be possible to prevent headaches entirely, making use of biofeedback techniques should help enable prevention of disability from migraines.

Recommendation

There is no reason not to recommend that all migraineurs learn biofeedback techniques for migraine reduction. Biofeedback techniques have no reported side effects, and can be employed both on a regular basis and when environmental or psychosocial factors result in susceptibility to a migraine attack. ❖

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CME Questions

7. *Stevia rebaudiana* represents a:
a. nutritive natural sweetener.
b. nonnutritive natural sweetener.
c. natural glucose sweetener.

8. Extensive human clinical data exist regarding the safety and efficacy of *Stevia rebaudiana*.
a. True
b. False

9. *Stevia rebaudiana* is thought to have hypotensive effects secondary to:
a. calcium channel blockade.
b. sodium reabsorption in renal tubular cells resulting in diuresis.
c. modulation of prostaglandin.
d. All of the above.

10. Black cohosh has been widely studied as an agent for:
a. breast cancer.
b. menopausal symptoms.
c. benign prostatic hyperplasia.

11. Black cohosh:
a. has proven cardioprotective effects similar to traditional hormone replacement therapy.
b. appears to be safe and effective in decreasing menopausal symptoms.
c. increases bone density in post-menopausal women.

12. What is a possible mechanism for the effectiveness of biofeedback?
a. Decrease in sympathetic outflow
b. Increase in autonomic nervous system activity
c. Conditioned relaxation
d. a and c
e. All of the above.

13. What are some specific techniques utilized for biofeedback?
a. Thermal biofeedback
b. Frontalis EMG biofeedback
c. Cephalic vasomotor biofeedback
d. All of the above.

14. How great a decline in headache frequency might be experienced by pregnant women who practice biofeedback?
a. 12%
b. 36%
c. 81%
d. 100%

With Comments from John La Puma, MD, FACP

Antioxidants and Age-related Cataracts

Source: Brown L, et al. A prospective study of carotenoid intake and risk of cataract extraction in US men. *Am J Clin Nutr* 1999;70:517-524.

DIETARY ANTIOXIDANTS, INCLUDING carotenoids, are hypothesized to decrease the risk of age-related cataracts by preventing oxidation of proteins or lipids within the lens. We examined the association between carotenoid and vitamin A intakes and cataract extraction in men.

We included U.S. male health professionals (n = 36,644) who were 45-75 years of age in 1986 in this prospective cohort study. Others were subsequently included as they became 45 years of age. A detailed dietary questionnaire was used to assess intake of carotenoids and other nutrients, and was mailed to respondents every two years until and including 1994. Age, smoking, and other potential cataract risk factors were controlled for.

During eight years of follow-up, 840 cases of senile cataract extraction were documented. We observed a modestly lower risk of cataract extraction in men with higher intakes of lutein and zeaxanthin but not of other carotenoids (alpha-carotene, beta-carotene, lycopene, and beta-cryptoxanthin) or vitamin A after controlling for other potential risk factors including age and smoking.

Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract relative to men in the lowest fifth (relative risk: 0.81; 95% confidence interval [CI] 0.65-1.01; P for trend = 0.03). Among specific foods high in carotenoids, broccoli and spinach were most consistently associated with a lower risk of cataract. Lutein and zeaxanthin may decrease the risk of cataracts severe enough to require extraction, although this relation appears modest in magnitude.

COMMENT

More than a million cataract extractions are performed annually. Are foods high in lutein and zeaxanthin able to reduce this number and improve vision? Lutein is found in green leafy vegetables, especially spinach and kale, and in broccoli.

A parallel prospective study (*Am J Clin Nutr* 1999;70:509-516) by the same investigator group examined the dietary recalls of 77,466 nurses from 1980 through 12 years of follow-up. Those with the highest intake of lutein and zeaxanthin had a 22% reduced risk of cataract extraction compared with those in the lowest quintile.

How might antioxidants prevent cataracts? By blocking the oxidative modification of lens protein or by preventing lipid peroxidation within the epithelium of the lens? Why carotenoids? Lutein and zeaxanthin are accumulated by ocular tissues; when extra lutein and zeaxanthin are taken as supplements, macular pigment increases. What about other carotenoids? In these studies, no other carotenoid made a difference, and neither did vitamin A, whether in supplements or in food.

Weaknesses of this data include the weaknesses of all recalled dietary data (even from middle-aged and elderly health professionals).

Although the lack of randomized controlled data of either supplements or food is real, high antioxidant food consumption may be something people can do to reduce their risk of cataracts. As a reminder about where much of the public is on this, Visionade (stocked with lutein, bilberry, and ginkgo, and blended with blueberry and cranberry juices) is now on the shelves of some health food stores.

Recommendations

More spinach made Popeye strong, and only two servings per week appears to reduce relative risk of cataract extraction. Sauté spinach over high heat with a little olive oil, sliced garlic cloves, and coins of fresh ginger for extra flavor. Hold off on lutein supplements. ❖

Supplements for Degenerative Joint Disease

Source: Leffler CT, et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: A randomized, double-blind, placebo-controlled pilot study. *Mil Med* 1999; 164:85-91.

WE CONDUCTED A 16-WEEK RANdomized, double-blind, placebo-controlled crossover trial of a combination of glucosamine HCl (1,500 mg/d), chondroitin sulfate (1,200 mg/d), and manganese ascorbate (228 mg/d) in degenerative joint disease (DJD) of the knee or low back. Thirty-four males (mean age 43.5 +/-1.7 years, average BMI 27.2 kg/m^2) from the U.S. Navy diving and special warfare community with chronic pain and radiographic DJD of the knee or low back were randomized. A summary disease score incorporated results of pain and functional questionnaires, physical examination scores, and running times. Changes were presented as a percentage of the patient's average score. Acetaminophen, but not NSAIDS, was permitted for pain. Outcomes were assessed by averaging data from two clinic visits after weeks 2 and 3 of the baseline period, and after weeks 7 and 8 of both eight-week treatment periods.

Knee osteoarthritis symptoms were relieved as demonstrated by the summary disease score (-16.3%; P = 0.05), patient assessment of treatment effect (P = 0.02), visual analog scale for pain recorded at clinic visits (-26.6%; P = 0.05) and in a diary (-28.6%; P = 0.02), and physical examination

score (-43.3%; P = 0.01). Running times (100-yd dash, and up and down a tower with 80 stairs) did not change.

Symptoms of spinal DJD were not affected. Side effect frequency was similar to that at baseline. There were no hematologic effects. Short-term combination therapy appears safe in this setting.

COMMENT

DJD hurts 21 million Americans, and in 1998 one billion capsules of glucosamine tried to soothe that hurt. The evidence for glucosamine's effectiveness as an analgesic equivalent to ibuprofen for DJD is reasonably strong (*Alternative Medicine Alert*, November 1998, pp. 121-124), and with many fewer side effects. But what of combination therapy in an overweight population with high activity levels?

Dr. Philippi and colleagues endeavored to find out. Twenty-one men with knee DJD (three withdrawals) and 23 with low back DJD (seven withdrawals) were randomized: Of the 10 withdrawals, four did so to take NSAIDS, five had military orders to leave the area, and one did not have time to comply. Those who remained in the study reported using between 15% and 22% less acetaminophen than they had at baseline. No changes in hematologic evaluations or prothrombin times were reported.

The role of manganese in these results is unclear; the 30 mg given here is well above the 2.5-5 mg range deemed safe. Signs of toxicity (tremor, weakness, hypertension) were not reported. Chondroitin's role is also unclear: Although synthesized in the body and found in cartilage, there is little evidence for its role as an effective analgesic.

This is a small study conducted for a short period, though larger analyses have had some of the same methodological problems. The NIH has invested $6.6 million at nine medical centers nationwide over the next several years to find out whether glucosamine and chondroitin help knee DJD.

Recent Belgian reports of a placebo-controlled three-year study of joint space narrowing and DJD knee symptoms suggest that glucosamine may control narrowing and pain. The concept of repairing cartilage with agents that stimulate proteoglycan production is appealing (see *The Arthritis Cure*, still a steady seller), but not proven.

Recommendation

Recommend weight management first to patients with DJD of the knee and back. For those who do not want to rely on NSAIDs, or are wary of their effects, try another popular commercial glucosamine preparation, perhaps without manganese, to alleviate symptoms of knee DJD. Give the trial a full eight weeks. ❖

Acupuncturists Should Know Anatomy

Source: Peuker ET, et al. Traumatic complications of acupuncture. Therapists need to know human anatomy. *Arch Fam Med* 1999;8:553-558.

To review the traumatic injuries that have been associated with acupuncture and to discuss how these adverse effects may be reduced by increased awareness of normal anatomy and anatomical variations, we undertook an extensive literature search accompanied by postmortem anatomical studies. Traumatic lesions after acupuncture have been described in thoracic and abdominal viscera, in the peripheral and central nervous systems, and in blood vessels. Deaths have been recorded from pneumothorax and cardiac tamponade. The frequency of adverse effects of acupuncture is unknown and they may be rare. Nevertheless, acupuncturists' knowledge of normal anatomy and anatomical variations is essential for safe practice. Regulatory bodies and those responsible for training courses should test acupuncturists for this knowledge.

COMMENT

This thorough brief report notes that acupuncture treatment can penetrate the skin up to several centimeters. Acupuncture treatments in the United States now number more than 10 million annually.

The authors provide 68 references to English-, French-, and German-language articles (including those reviewing the Asian experience) on adverse effects. The authors also "froze four fresh human cadavers, and took cross-sections at the level of acupuncture points lying within close proximity to vulnerable organs."

The most often reported injury was pneumothorax: Ninety incidents were found, including two fatal ones. Supraclavicular, infraclavicular, parasternal, and midclavicular points were particularly risky. Postmortem exams revealed that a puncture depth of 10-20 mm "can reach the lungs." Six cases of injury to the heart were found, two of which were fatal. Ten cases of injury to the spinal cord, including four caused by migration of needle fragments were also found. In contrast, lesions of abdominal viscera, the peripheral nerves, and blood vessels were rarely reported.

Case reports, of course, do not yield frequency, and may not yield causation. Underreporting is likely, and variables are many. But acupuncture is not all incense and history.

Recommendation

Acupuncture is not benign, and can have serious adverse effects. Make sure your acupuncturist knows anatomy, and uses it. ❖

In Future Issues:

Cordyceps and Sports Performance

Hypnosis for Pain

Acupuncture for Allergies

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ALTERNATIVE MEDICINE ALERT™

A Clinician's Guide to Alternative Therapies

Clinician Fact Sheet: Review of Herbal Supplements

Echinacea (*Echinacea angustifolia* DC*; Echinacea pallida* Nutt.*; Echinacea purpurea* L. Family: Asteraceae/Compositae)

1998 Retail Sales: $69,702,144[1]

Part Used: Root or aerial (pallida) parts

Intended Indications

Colds, immune system stimulant, influenza, minor external infections, upper respiratory tract infections (URTIs), urogenital infections, topical wound healing, adjunctive for colorectal cancer patients

Formulation and Dosage

- For short-term, acute use
- Fluid extract (1:1): 1-2 ml (1/4-1/2 teaspoonful) tid
- Dried root or solid extract (6:5:1): 300 mg tid
- Tincture (1:5) 45% alcohol (1/4-1/2 teaspoonful) tid
- Apply cream or liquid tid
- Preparations vary widely

Adverse Effects

Transient, tingling sensation on tongue, cross-sensitivity in patients allergic to the daisy family (chamomile, chrysanthemums, feverfew, and ragweed), GI upset, diarrhea

Interactions

- Echinacea should not be administered with immunosuppressant therapies

Contraindications

- Echinacea is not recommended by some authorities for patients with autoimmune diseases, AIDS, or leukemia because of T-cell and macrophage stimulation
- Safety not determined in pregnancy and lactation

Saw Palmetto (*Serenoa repens* Bartr. Family: Arecaceae Palmae)

1998 Retail Sales: $32,102,622[1]

Part Used: Berry extract

Intended Indications

Benign prostatic hyperplasia/hypertrophy

Formulation and Dosage

- 160 mg bid of standardized fat-soluble saw palmetto extract containing 80-95% fatty acids and sterols

Adverse Effects

Generally well tolerated, occasional headache, mild abdominal pain, nausea, diarrhea, dizziness; there is no known effect on PSA

Interactions

- None known

Contraindications

- Saw palmetto should be avoided during pregnancy and lactation
- Saw palmetto should be avoided in patients with breast cancer

Kava Kava (*Piper methysticum* Forest. Family: Piperaceae)

1998 Retail Sales: $16,584,425[1]

Part Used: Rhizome and roots

Intended Indications

Anxiety, insomnia, restlessness, stress

Formulation and Dosage

- As an anxiolytic, 45-70 mg tid
- As a sedative, 180-210 mg, 1 hour before bedtime
- Product standardized to 30-55% kavalactones

Adverse Effects

GI upset, allergic reactions, dizziness, scaly rash, red eyes, puffy face, marked muscle relaxation, and long-term, chronic use may cause kava dermopathy

Interactions

- Kava may have additive effects with other muscle relaxants, sedatives, antianxiety agents, and antidepressants
- Alcohol should not be consumed concomitantly

Contraindications

- Avoid in endogenous depression
- May adversely affect motor reflexes and judgment and should be avoided if required to operate a car or machinery
- Safety not determined in pregnancy and lactation

Grape Seed Extract (*Vitis vinifera* L. and *Vitis Coignetiae*. Family: Vitaceae)

1998 Retail Sales: $12,113,555[1]

Part Used: Seeds, skin, oil from ground seeds

Intended Indications

Anti-enzyme nutritional supplement, atherosclerosis, causes endothelium-dependent vasorelaxation, inhibits LDL-oxidation, inhibits tooth decay, raises serum antioxidant capacity, reduces HDL-cholesterol levels, reduces platelet aggregation

Formulation and Dosage

- Freeze-dried extract contains 75-85% procyanidins, mixed with other flavonoids and organic acids
- Tablets or capsules containing 150 mg extract bid
- Red wine contains about 1 g polyphenols/liter

Adverse Effects

None documented. However caution should be exercised before recommending use in smokers given the harmful effects found among smokers taking beta-carotene; hepatoxicity has been shown in mice

Interactions

- None documented

Contraindications

- Safety not determined in pregnancy and lactation

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Additional Resources

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