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INSIDE

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Russell H. Greenfield, MD (executive editor), Mary L. Hardy, MD (fact sheet editor), and Paula L. Cousins (managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Kava: *Piper methysticum*

By Roberta Lee, MD

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KAVA IS A MEMBER OF THE PEPPER FAMILY (PIPERACEA) THAT HAS been central to Pacific Island cultures as far back as 2,000 years.[1] J.G. Forester, a botanist accompanying Captain Cook on his voyages through the Pacific, is credited as being the first scientist to describe kava. After sampling it, he described kava as tasting mildly peppery and thus assigned the kava plant its Latin name *Piper methysticum*, which is loosely translated to mean intoxicating pepper.

The exact geographic origin of this plant remains unclear and two hypotheses exist: The first suggests that kava is a plant derived from the Southeast Asia and New Guinea area.[2] The second hypothesis suggests that Vanuatu[1] served as the original central region from which kava spread to the Melanesian and Pacific Island areas. In 1886, Lewin, a German pharmacologist studying psychoactive plants, characterized kava as a hypnotic based on its pharmacologic effects.[3]

Ethnobotanical and anthropological texts have documented many different and elaborate ceremonies for kava's use among the numerous Pacific Islands where it has been cultivated. Perhaps the most intriguing ethnobotanical facts surrounding its use is the means by which it has been served in the Pacific. Two methods have been described: The first method, which was widely practiced in Tonga and Samoa, is identified as the "Tongan method" and involves young men or women masticating the root before soaking it in water, followed by decanting (gentle pouring without disturbing the sediment) and serving to others—this method is no longer in active use due to public health issues.[4] The second method, often referred to as the "Fiji method," involves mechanical pounding and pulverizing of the root with subsequent dilution with water.[4] The second method is widely in use on many islands today.

VOLUME 10 • NUMBER 5 • MAY 2007 • PAGES 49-60

Traditional medical uses for this plant were extensive and included treatment of: inflammation of the urogenital system, gonorrhea, menstrual problems, migraine headaches, chills, vaginal prolapse, rheumatism, dermatological conditions, and nervousness.[1] In the last 150 years, numerous scientific publications on the chemical and pharmacologic activity of kava have given us greater clarity and insight into this plant's pharmacologic value.

During the last 20 years kava gained enormous popularity as an herbal treatment for anxiety, nervousness, insomnia, stress, benzodiazepine withdrawal, and menopausal anxiety. In 1998, kava ranked fifth in the North American botanical sales market.[5] However, its use and sales rapidly declined beginning in the fall of 2001 after increasing reports of hepatotoxicity surfaced in association with its use. By the end of 2001, public health authorities in Germany initiated a new evaluation of the benefit-risk ratio of kava. This led to a withdrawal of the drug authorization for kava products by the German health authorities. Many other public health authorities in Europe including Switzerland and other countries around the world followed Germany's example.[6] Today, strict warnings exist in countries where sales of kava are permitted, dampening the public and professional use of this botanical product.

Description

P. methysticum is a slow-growing perennial. When cultivated, the plant is harvested when it reaches 2-3 years of age or 2-2.5 meters in height. Kava is cultivated for its rootstock or stump. The stump is a thick tuberous and knotty mass with a fringe of lateral roots. Kavalactones, the active constituents that are responsible for the psychoactive characteristics of this plant, are concentrated in the lateral roots. Propagation has occurred primarily by human cultivation.

The roots are dried or freshly pounded to make a ceremonial beverage, or dried and pulverized to make standardized liquid or solid extracts, alcohol-based tinctures, teas, and salves. Preparations vary in kavalactone content depending on the source of kava. There exist 118 cultivar morphotypes (varieties of plants) which are called *P. methysticum*, and each morphotype has subtle variations in the percentages of kavalactones present in the rootstock.

The method of kavalactone extraction also determines the kavalactone content, as these constituents are known to be lipophilic. In 2001, lesser-quality products were noted to include the use of the stem peelings as well as the rootstock, diluting the concentration of active constituents and possibly contributing unwanted toxic compounds.[7] Standardized preparations are generally extracted to not less than 30% kavalactones in powdered dried extracts or not less than 50% kavalactones in semi-solid (paste) extracts.[8]

Pharmacology

As noted, kava's psychoactive activity is attributed to a group of compounds known as kavalactones (also known as kavapyrones). These compounds consist of 13 carbon atoms, six of which form a benzene ring attached by a double bond to an unsaturated lactone. There are 18 kavalactones identified in the rhizome, but six major kavalactones are credited for the majority of pharmacologic activity: methysticin, dihydromethysticin, kavain, 5,6-dehydrokavain, 5-6,dehydromethysticin, and yangonin. These constituents are highly concentrated in the roots (15%) and decrease to 5% in the basal stems. A small amount of alkaloids were identified in the rootstock in earlier studies but have not been found to be part of the resinous rootstock responsible for kava's psychoactive properties.[9]

Although kavalactones such as kavain and methysticin can be synthesized, early studies evaluating the psychoactive effects using these singular compounds reveal that they are less effective physiologically than the natural raw extracts. Thus, it seems that the kavalactones as a group have synergistic pharmacologic activity.[10] Other constituents identified in the rhizome include chalcones (flavokavains A, B, and C), a phytosterol, amino acids, and minerals including potassium, calcium, magnesium, sodium, aluminum, and iron.[8]

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

SENIOR VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

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.

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Kava's reported neuropharmacologic effects include analgesia, anesthesia, sedation, and hyporeflexia.[2] In animal trials, kava has shown anticonvulsive, antispasmodic, and central muscular relaxant effects. Antimycotic properties have also been reported.[11] Recently, in vitro studies reported antithrombotic and COX-2 inhibitory activity as well.[12]

The mechanism of action on the central nervous system (CNS) is not entirely clear. Kava acts on several areas in the CNS. Differing results have been reported across in vitro and in vivo studies, and it remains uncertain whether kava binds at GABA receptors.[8,13-17] A possible nor-adrenaline uptake effect was also reported for three kavalactones.[18] Activation of mesolimbic dopaminergic neurons resulting in relaxation and slight euphoria has also been reported in an animal trial.[19] Additional CNS actions have been reported including interaction with glutamate receptors,[20] reduction in monoamine receptors and reduced transmitter release.[21]

In some studies, kava has been shown to relax skeletal muscle through direct action on the muscle fiber without inducing central nervous depression.[22] Kavain applied topically or injected subcutaneously was found to induce local anesthesia, but higher doses caused paralysis of the peripheral nerves.[23]

Kava at therapeutic doses does not appear to have sedative effects, a potential advantage of this botanical alternative. However, no large trials have examined this aspect of kava. Previous trials have been small and criticized for flaws in methodology.[24]

Pharmacokinetics

After oral administration, intestinal absorption is extremely rapid (10 minutes) for kavain and dihydrokavain.[1] In contrast, methysticin and its dihydroderivatives are more slowly absorbed (45 minutes).[25] When 40 mg/kg of dihydrokavain was given orally, half of it was found in the urine within 48 hours in the form of hydroxylated derivatives.[26] Quantitative uptake of four kavalactones in mice brains indicate that kavain and dihydrokavain attain maximal brain concentration within five minutes, whereas desmethoxy-yangonin and yangonin entered the brain more slowly.[27] It is generally agreed that kavain and dihydrokavain are the two kavalactones that pass the blood-brain barrier most easily. Peak levels occur (for kavain) at 1.8 hours with an elimination half-life of approximately 9 hours and distribution half-life of 50 minutes.[28] In test animals, the LD_{50} (lethal dose required to kill 50% of subjects) of kavalactones is believed to be approximately 300-400 mg/kg.[29]

Review of the Evidence

Anxiety

Kava has been evaluated in 14 randomized clinical trials for anxiety with the duration of treatment ranging from four to 25 weeks. A meta-analysis of randomized trials initially published in 2000 and updated in the Cochrane Database 2002[30] and 2003[31] concluded that kava had moderate efficacy in the treatment of anxiety. In the meta-analysis, although 14 clinical trials were identified, seven trials were excluded due to a variety of factors including duplicate reporting, concurrent benzodiazepine use, or use of an isolated kavalactone. The remaining seven clinical trials were evaluated and three were selected for analysis involving a total of 198 patients. Pooled data from the three studies that used a common outcome measure, the Hamilton Anxiety Rating Scale (HAM-A), found a significant reduction in mean anxiety score in the kava group as compared to placebo, with a mean difference of 9.69 points (95% confidence interval).[30] In the 2003 updated meta-analysis, 11 trials representing a total of 645 participants were eligible for inclusion.[31] Six studies using the HAM- A rating scale as a common outcome measure showed that kava was effective for the treatment of anxiety and "relatively safe for short term treatment (1-24 weeks)."[31]

Menopausal/Perimenopausal Anxiety

Three randomized, placebo-controlled clinical trials examined kava for perimenopausal and menopausal anxiety using kava in a dose of 100 mg/d with hormone replacement therapy,[32] or kava at 100 mg/d or 200 mg/d and combined with calcium.[33,34] All three trials used the HAM-A or State Trait Anxiety Inventory as an outcome instrument to assess anxiety. In each trial, reduction of anxiety was more pronounced in the kava treatment arms than in the placebo arms.

Equivalence Trials

Several clinical trials comparing kava to benzodiazepines have been performed.[35-37] In each of the trials no significant difference was found on anxiety measures. However, the trials lacked placebo arms and the sample sizes of the earlier trials were possibly too small to measure equivalence. In the largest randomized, controlled multicenter trial, 129 outpatients were given either 400 mg of LI 150 (kava), 10 mg of buspirone, or 100 mg of opipramol daily for eight weeks. Subjects were evaluated for anxiety (using HAM-A), sleep quality, quality of life, and well-being. Approximately 70% were classified as responders with a reduction of 50% on the HAM-A scale, with 60% achieving full remission.[37] The authors deemed kava a well-tolerated

treatment that was as effective as the pharmaceutical agents employed.

In a small (n = 40) randomized placebo-controlled trial, patients with anxiety on benzodiazepines were given increasing amounts of kava (WS 1490) up to 300 mg a day as the benzodiazepines were tapered. The dose adjustments were followed by three weeks of monotherapy with kava or placebo. Patients were monitored for benzodiazepine withdrawal, subjective well-being, and anxiety. Results confirmed the anxiolytic efficacy of kava.[38]

Unresolved Safety Issues

In recommended doses over short periods of time kava has been regarded as safe. However, since 2001, potential hepatotoxicity of kava has become a concern as more than 30 cases of liver damage in association with its use have been reported in Europe. In several cases, liver transplants were required due to the extent of hepatic damage. An independent assessment of the adverse effects in these cases was undertaken by a noted expert in the field of hepatotoxicology, Donald Waller, PhD, from the University of Illinois at Chicago. He concluded that "there are only a few of these cases in which kava might be directly associated with liver damage. Each of the cases appears to have been hypersensitivity or idiosyncratic based responses."[39]

As of this writing, the FDA has issued a warning to consumers, and a number of countries have removed kava from public access.[6] It remains unclear what dose or what duration of use is correlated with hepatic damage. Equally unclear are the mechanisms responsible for the hepatic damage. Potential causes include the method of extraction of kava causing an increased proportion of one or more kavalactone constituents that predispose some individuals to liver damage, or contamination by alkaloids.

One hypothesis involves the presence of pyridine alkaloids in the form of the alkaloid pipermethystine known to be cytotoxic and present in the stem of kava. Dragull et al suggested that stems rather than lateral roots, the usual source of kava, may have been added as a "contaminant" to supplements but unrecognized by dietary supplement companies as such until patients emerged with liver abnormalities.[7]

Another hypothesis accounting for the presence of kava hepatotoxicity proposes that there is a group of patients with a polymorphism that creates a cytochrome P450 2D6 deficiency that makes them poor metabolizers of kavalactone metabolites.[40] In Europe, there exists a 10% prevalence of the cytochrome P450 2D6 deficiency; however, this phenomenon has not been detected in Pacific Islanders who have used kava ceremonially for hundreds of years. Thus, those with this deficiency taking supplements are hypothesized to develop elevated liver enzymes because they are unable to detoxify intermediary metabolites damaging to the liver.[12] In the Pacific Islands, kava is served as a water-extracted preparation, whereas extraction associated with kava supplements employs acetone and alcohol as solvents. Experts believe that the use of acetone and alcohol as an extractant may draw out different kava constituents and/or proportions of kavalactones, making those at risk for hepatotoxicity more vulnerable.[41,42]

It is estimated that approximately 250 million daily doses of ethanolic kava extract have been ingested in the previous decade with only two causal, firmly related cases of hepatotoxicity. These cases used kava at doses far beyond the recommended levels. Based on these two cases, the Adverse Events Reports (AERs) rate was 0.008 AERs for kava in a million daily doses. Benzodiazepines in contrast have a much higher AERs rate per million daily doses: 0.90 AERs for bromazepam, 1.23 for oxazepam, and 2.12 for diazepam. The authors concluded that changing patients from using kava to a benzodiazepine could potentially increase the risk of adverse effects.[43]

Guidelines for Use[44]

Kava should be used primarily for anxiety, and may be considered potentially therapeutic for people with sleep disorders related to anxiety. The American Botanical Council suggested in December 2001 that kava not be taken longer than one month without professional supervision.[8] Thus, botanical preparation should be avoided in patients with: known liver disease, chronic use of alcohol, Parkinson's disease, or use in patients who are taking benzodiazepines or other sedative medications. Patients who are pregnant or lactating should not be given this botanical product.

Typical daily dosage for adults using a standardized preparation of 30% kavalactones is a dosage equivalent of 60-120 mg of kavalactones or total dose of 70-210 mg of kava. Most controlled clinical trials are based on three 100 mg doses of a dried extract standardized to 70 mg of kavalactones or 210 mg of kavalactones/d. The onset of response appears to be 2-4 weeks, comparable to prescription anxiolytic medications.[8]

There is great concern regarding hepatotoxicity, as discussed earlier. In contrast to therapeutic use, heavy chronic use of kava has been associated with renal dysfunction, hematologic abnormalities, pulmonary hypertension, dermopathy, and choreathetosis. These conditions have been cited in case reports and the causal

relationship with kava is unclear due to multiple confounding variables and/or incomplete reporting.

Side Effects

A dermatological condition known as kava dermopathy, may appear during prolonged and heavy use. This condition is reversible upon discontinuation.[45]

Several cases of extrapyramidal side effects[46] and the exacerbation of Parkinsonian symptoms[47] have been reported after use for 1-4 days. Sedation has been reported anecdotally, although small human studies suggest that kava does not cause neurological-psychological impairment. Apathy has been noted with long-term use.[8]

Pulmonary hypertension was proposed as a mechanism for shortness of breath in one study where heavy Aboriginal users complained of breathing difficulty (69%) vs. non users (25%).[8] Antiplatelet activity was reported with kavain, a single kavalactone. Blood dyscrasias have been reported with heavy intake in Aboriginal kava users.[48]

Hepatotoxicity has been a concern and was discussed earlier. Gastrointestinal upset has been reported as an infrequent adverse effect in some studies.[8]

Drug Interactions

Animal studies have reported increases in sedative effects. Kava has been shown in case reports to prolong the sedative action of anesthesia. Kava has been found to potentiate some CNS depressants and to antagonize the effect of dopamine and elicit extrapyramidal effects. Constituents of kava have been shown to have weak MAO inhibitory activity in vitro.

Kavain, an isolated kavalactone, has been reported to have antiplatelet activity.

Preliminary studies indicate that kava may inhibit multiple cytochrome P450 substrates (1A2, 2C9, 2C19, 2D6, 3A4).

Conclusion

Until the last decade, kava has been used safely by Pacific Islanders as a ceremonial and social beverage, serving as a plant of great significance both culturally and medicinally. In the West, we have found kava to be a useful alternative in the management of anxiety, insomnia, and muscle tension. Furthermore, it should be acknowledged that detailed analysis of reports of kava use and hepatotoxicity has found the complication to be infrequent despite widespread use either as a dietary supplement or traditionally prepared beverage. Nonetheless, reports of hepatotoxicity involving kava supplements warrant caution in recommending its use.

Recommendation

Those using kava as an alternative treatment for mild anxiety or perimenopause-related anxiety should do so with caution. The dose should be not more than a dose equivalent to 60-120 mg/d of kavalactones. It should not be taken on a daily basis for more than a month without medical advice and monitoring of hepatic function. Patients should be advised of the potential for synergistic sedative activity if combined with agents such as benzodiazepines. Patients should also be warned that use of kava can adversely affect motor coordination when driving or operating heavy machinery. ❖

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Nonpharmacologic Management of Migraines

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PART 1 OF A SERIES ON MIGRAINES

DEFINED AS A RECURRENT, DISABLING PRIMARY headache disorder, migraine is a chronic illness that requires a two-pronged management strategy: 1) treatment of the acute attack, and 2) mitigation of recurrences by balancing risk factors with physiologic resources for decreasing severity, duration, and frequency of the attacks. Although effective drug therapies exist for the treatment of migraines, patients may have contraindications to their use, such as poor tolerance, pregnancy, or side effects. If medication is overused, it can actually exacerbate headaches.[1,2]

Primary care physicians can guide patients toward nonpharmacologic treatment strategies that can be used alone or in conjunction with pharmacotherapy. A personal headache diary provides clues to the patients' headache history, which allow patients and their doctors to understand environmental, dietary, and lifestyle precipitants and seek appropriate interventions.[3] Table 1 summarizes the International Headache Society's (IHS) diagnostic criteria for migraine.[4] Application of these classification criteria for headache improves the accuracy of the headache diagnosis and reserves neuroimaging procedures for patients presenting with headache plus one or more of the "nine notable" features outlined in Table 2. These worrisome features are indicative of secondary headache disorders and can be seen in patients with and without previous migraine histories.

Table 1

International Headache Society criteria for migraine

At least five attacks that fulfill the following:
- Headache duration of 4-72 hours
- Headache with two of the following characteristics:
  - –Unilateral location
  - –Pulsating quality
  - –Moderate-to-severe intensity
  - –Aggravation with physical exertion
- Headache plus one of the following:
  - –Nausea and/or vomiting
  - –Photophobia and phonophobia
- No evidence of organic disorder causing chronic headache

Source: Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004;24(Suppl 1):1-160.

Public Health Implications

Migraine headaches are a common condition with a prevalence rate of 12-14% in the United States. Women experience them 3.3 times more than men. Lipton reported that 90% of migraineurs report functional impairment with their headaches, 53% of them exhibit impairment severe enough to require bed rest, and 51% report a 50% reduction in school or work productivity due to headache. The impact on household, family, and social activities is even greater.[5]

Pathophysiology of Migraines

The essential biologic element of the migraine condition is neuronal hyperexcitability, a condition that is often inherited but may also arise spontaneously or from central nervous system trauma. Common triggers for migraine attacks *(see Table 3)* destabilize the sensitive nervous system and result in headaches. Common migraine comorbidities such as generalized anxiety and panic disorder, depression and bipolar disease, insomnia, irritable bowel syndrome, epilepsy, and stroke confirm the presence of nervous system irritability.[6]

The pain of migraine headaches arises from trigeminovascular system activation, primarily mediated through serotoninergic (5HT) mechanisms. Disrupted activity at the vascular 5HT1b and neuronal 5HT1d receptors is postulated to result in vasodilation, nerve terminal activation, neurochemical release, and pain. A form of sterile neurogenic inflammation and blood-

Table 2

The "nine notable" clinical indications for prompt diagnostic headache evaluation

1. First, worst headache
2. Abrupt onset ("thunderclap")
3. Progressive, changing pattern of headache
4. Abnormal physical examination
5. New onset headaches in children younger than age 5 and adults older than age 50
6. New onset headaches in immunosuppressed, cancer, trauma, or pregnant patients
7. Exacerbation of headache with valsalva, exertion, sexual activity
8. Headache patient with neurologic symptoms and/or rash
9. Syncope or seizure with headache

Adapted from: headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004; 24(Suppl 1):1-160.

Table 3

Common migraine triggers for migraineurs

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

Adapted from: Millichamp JG, et al. The diet factor in pediatric and adolescent migraine. Pediatr Neurol 2003;28:9-15.

brain barrier breakdown occurs. Once intracranial branches of the first order trigeminal nerve (V1 or ophthalmic division) are stimulated, the nervous system is activated by second order trigeminal neurons in the brainstem and third order neurons in the thalamus and higher cortical centers. This activation sequence results in central neuronal sensitization along pain pathways of the upper cervical spine and activation of other brainstem nuclei. These processes account for migraine associated referred neck pain (reported in 75% of migraine patients), as well as autonomic symptoms of lacrimation, rhinorrhea, and nasal congestion (reported by 50% of migraineurs).[7] Although these autonomic features are more typically seen in cluster type headaches, the key differentiating feature by IHS criteria is headache duration. While migraines typically last more than four hours, cluster headaches almost universally last less than four hours and occur more commonly in males.[4]

Management Considerations

Lifestyle Modifications

Diet. Dietary evaluation in the management of migraine is complicated since multiple triggers and variables can modify the pain threshold for an individual. For certain patients, primarily children and adolescents, food and food additives can be a significant precipitant of headaches. Such triggers are outlined in Table 3.[8] Egger et al, in an old double-blind controlled trial of 88 children with severe, frequent migraines, showed that 93% fully recovered with institution of oligoantigenic diets.[9]

Caffeine. Caffeine withdrawal headaches have been reported after cessation of caffeine dosages as low as 100 mg/d (the equivalent of one cup of coffee or two cups of tea).[10] These headaches begin within 24-48 hours after discontinuing caffeine and last for 1-6 days.[11]

Low-fat Diet. Bic et al conducted a prospective cohort trial of 54 migraine patients and found that lowering dietary fat intake from 66 g/d to 28 g/d resulted in a significant decrease in headache frequency, intensity, duration, and medication use ($P < 0.001$ for all measures).[12]

Exercise. Regular exercise is known to increase plasma beta endorphin levels. Koseoglu et al studied 36 patients with migraine who engaged in regular aerobic exercise three times weekly for 30 minutes over six weeks. Their pre-exercise beta endorphin levels were inversely proportional to the degree of improvement in their post-exercise headache parameters ($P < 0.0001$). Additionally, persons who exercise regularly increase their cardiovascular and cerebrovascular health, and experience improved psychological states with decreases in depression, anxiety, and stress.[13,14]

Sleep Patterns. Sleep patterns in migraine patients can be causal or contributory to their headaches. Overnight headaches or headaches upon awakening reflect a sleep disturbance in 55% of patients. It is important to rule out sleep apnea with a sleep study because treatment results in improvement of both

headaches and general medical health.[15] The Somogyi effect (marked fasting hyperglycemia following antecedent, usually asymptomatic nocturnal hypoglycemia) may also account for chronic morning headaches in patients with diabetes.[16]

Nutritional Supplements

Botanical Preventive Therapy

Feverfew (*Tanacetum parthenium* L.). The pharmacologic role of feverfew in migraine physiology is not completely understood, although it is known that feverfew extract causes serotonin release from platelets. Additionally, feverfew extracts and parthenolide, the principal ingredient in feverfew, inhibit prostaglandin synthesis.[17]

Pittler and Ernst, in an updated Cochrane Review, evaluated five randomized controlled trials involving 343 patients treated with feverfew extract for migraine headache prophylaxis. Results from these trials did not establish feverfew to be significantly more efficacious than placebo. They also noted difficulties with trial designs and contradictory results when ethanolic extracts of feverfew were used in trials vs. herbal powders in capsule form.[18]

Implementation of a supercritical CO_2 extraction method produced a stable, standardized parthenolide extract called MIG-99. Using this extract, Pfaffenrath et al conducted a double-blind, placebo-controlled, randomized dose-response comparison of four parallel groups: three dosages of MIG-99 extract vs. placebo. The active treatment patients received either 2.08 mg MIG-99 (approximately 17 mg parthenolide), 6.25 mg MIG-99 (0.5 mg parthenolide), 18.75 mg MIG-99 (1.5 mg parthenolide), or placebo. Each dose was taken three times daily. Patients kept a headache diary during a four-week baseline period followed by the 12-week active treatment phase with MIG-99 or placebo. Overall, the researchers found no significant improvement in migraine headaches compared to placebo. However, in a small subgroup of patients with at least four headache attacks during the 28-day baseline period, MIG-99 extract at 6.25 mg three times per day significantly reduced migraine frequency after two months.[19]

Deiner et al, as a follow-up to this 2002 study, performed a second multicenter phase III prospective randomized controlled trial in which 170 patients were randomized to either the active arm and received MIG-99, 6.25 mg three times daily, or placebo. They reported that 30% of the feverfew group and 17% of the placebo group experienced a 50% or greater reduction in headaches/month ($P = 0.047$).[20]

Vitamins and Minerals

Riboflavin (Vitamin B_2). Shoenen et al, in a randomized, controlled trial of 55 patients treated with either riboflavin 400 mg/d or placebo, demonstrated that after three months of supplementation with riboflavin, there was a statistically significant reduction of headache attack frequency ($P = 0.005$) and headache days ($P = 0.012$).[21]

Magnesium. Peikert et al, in a three-month randomized, double-blind, placebo-controlled trial of 81 adults with migraine, showed that 600 mg of magnesium (trimagnesium dicitrate) reduced the headache frequency by 41.6% compared to a reduction of 15.8% for the placebo group.[22] The drawback was an 18.6% incidence of diarrhea among those in the magnesium treatment arm.

Facchinetti et al, in a small study of 20 women with menstrual related migraine headaches, found that if patients were given 360 mg/d magnesium during the luteal phase of the menstrual cycle, the number of days with migraine were significantly reduced ($P < 0.03$). They also noted an inverse correlation between the Pain Total Index questionnaire and magnesium levels in the polymorphonuclear leukocytes (PMNs), which supports the theory that a lower migraine threshold could be related to magnesium deficiency.[23]

Dietary Supplements

Coenzyme Q10. Coenzyme Q10 (CoQ10) may produce beneficial effects for migraine prevention in two unique ways: it may affect mitochondrial function and energy production at the molecular level and it functions as an antioxidant. It is the only lipid-soluble antioxidant synthesized in living cells. Up to 80% of human CoQ10 is intrinsically synthesized and is widely distributed in all cellular membranes, which has resulted in its alternative name, ubiquinone. Dietary CoQ10 intake is primarily from meat and poultry, although Weber et al have observed that diet alone cannot replenish a deficient state.[24]

Tang demonstrated that migraineurs have altered expression of mitochondrial-related genes both during acute headaches and between attacks. Therefore, if the mitochondrial response is limited or inhibited due to deficiency of CoQ10 substrate, more severe or frequent migraine headaches may be expected.[25] Hershey et al showed that supplementation of CoQ10-deficient pediatric and adolescent migraine patients and subsequent normalization of total CoQ10 levels significantly decreased headache frequency, and improved quality of life and Pediatric Migraine Disability Questionnaire (Ped MIDAS) scores.[26]

Recent large-scale standardized references levels have been established and allow for the determination of CoQ10 deficiency. Of note, since elevated cholesterol levels artificially increase levels of CoQ10, a correction is needed to detect deficiency states.

Hershey et al have recommended supplementation of migraine patients found to have total CoQ10 levels below 700 µg/mL or CoQ10:cholesterol ratios below 0.350 µg/mL. Depending upon clinical circumstances, headache patients who have such deficiencies should be treated and their clinical responses monitored.[27,28] ❖

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Clinical Briefs

With Comments from Russell H. Greenfield, MD

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Tai Gee! Immune Augmentation and Tai Chi

Source: Irwin MR, et al. Augmenting immune responses to varicella zoster virus in older adults: A randomized, controlled trial of Tai Chi. *J Am Geriatr Soc* 2007;55: 511-517.

Goal: To compare the effects of tai chi (TC) to that of health education (HE), an active control intervention, on resting and vaccine-stimulated levels of cell-mediated immunity (CMI) to varicella zoster virus (VZV), and on health functioning in older adults.

Study design: Prospective, randomized, controlled trial performed in two urban California communities.

Subjects: Healthy adults aged 59-86 years (n = 112, mean age 70 years).

Methods: Participants were recruited through community advertisements and randomized to receive either TC (n = 59) or HE (n = 53) in groups of 7-10. Both TC and HE sessions were provided each week for a total of 120 minutes. A specific set of exercises was used in TC, and individual skill attainment monitored by TC instructors. HE involved 16 didactic sessions addressing various health-related themes and offered by a physician or psychologist, with group discussion following. After 16 weeks of the specified intervention all subjects received a single dose of VARIVAX (live attenuated varicella vaccine). The primary endpoint of interest was a quantitative measure of VZV-CMI as assessed on five occasions (baseline, weeks 8, 12, and 16 before vaccination, and at week 25, or nine weeks post-vaccination) using peripheral blood mononuclear cells. Secondary outcomes included scores on measures of quality of life (SF-36) and the Beck Depression Inventory (BDI), both of which were administered at the same five time frames. Other potentially important factors were also evaluated, including daily TC practice time and average weekly metabolic equivalents.

Results: Subjects in the TC group showed higher levels of VZV-CMI than the HE group at every measurement period after intervention initiation, with a rate of increase in VZV-CMI almost twice that of the HE group. Notably, the increase in VZV-CMI with TC alone was comparable to that obtained with HE plus vaccination. In addition, the effects of TC and varicella vaccine combined were additive (TC + vaccine produced levels of VZV-CMI significantly higher than that produced by the vaccine alone). Specific scores on the SF-36 were also better in the TC group (physical functioning, bodily pain, vitality, and mental health). Symptoms of depression were improved by both interventions, and subjects in both groups reported with equal confidence that the interventions they had experienced would help improve the health of older adults.

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

20. The most convincing reports of an association between kava use and liver damage appear to be cases of hypersensitivity or idiosyncratic based responses.
a. True
b. False

21. Kava should be avoided in patients with:
a. known liver disease.
b. chronic use of alcohol.
c. Parkinson's disease.
d. use of benzodiazepines or other sedative medications.
e. All of the above

22. Common migraine comorbidities include:
a. anxiety and panic disorder and insomnia.
b. depression and bipolar disease.
c. irritable bowel syndrome.
d. epilepsy and stroke.
e. All of the above

Answers: 20. a, 21. e, 22. e.

Conclusion: In healthy older adults, TC enhances resting levels of VZV-specific CMI and the VZV-CMI associated with varicella vaccination.

Study strengths: Use of intention-to-treat analysis; high rate of attendance at sessions and completion rate for interventions.

Study weaknesses: Use of varicella vaccine rather than ZOSTAVAX; questionable generalizability (only healthy people were studied); lack of long-term follow-up to test durability of effects.

Of note: TC incorporates meditation, relaxation, and aerobic activity, each of which has separately been reported to enhance CMI responses; people with a prior history of shingles were excluded from the study; subjects in the current trial had experienced varicella earlier in life and were thus already immune; subjects were compensated for participation in and completion of the study; two of the authors hail from the Cousins Center for Psychoneuroimmunology at the University of California-Los Angeles; one small, controlled pilot study employing a standardized form of TC showed increased levels of VZV-CMI; prior research showed that administration of a high-potency VZV vaccine (ZOSTAVAX) reduces the incidence of herpes zoster by 51% and the incidence of post-herpetic neuralgia (PHN) by > 60% in people aged 60 years and older, but the numbers belie that risk of herpes zoster was not completely eliminated; the ZOSTAVAX vaccine used in the Shingles Prevention Study was not used in this trial (VARIVAX, the vaccine used in this study, contains < 7% of the amount of VZV found in ZOSTAVAX); subjects in the HE group had higher baseline scores on SF-36 role physical and bodily pain assessments, but this had no impact on VZV assessments; overall metabolic equivalents for the TC group were unchanged in the face of increasing levels of TC practice, implying that participants substituted TC for other fitness activities; neither the number of weekly minutes of practice nor the number of TC sessions attended per week was related to magnitude of increase in VZV-CMI; subjects in the TC group achieved a level of post-vaccination VZV-CMI similar to that reported in studies of healthy young adults; over the course of the trial, people in the TC group showed an increase in the number of minutes of at-home TC practice per week, and maintained a high level of practice after the intervention period; the technician performing the VZV-CMI assays was blinded to subjects' group allocation.

We knew that: Older adults often respond poorly to immunization; shingles (herpes zoster) results from reactivation of latent VZV, manifests in the form of a painful vesicular rash, and occurs most often in people over age 60 years; levels of pain and disability experienced by people with shingles and PHN create a diminished quality of life comparable to that experienced by people with heart failure, diabetes, or major depression; immunosuppressed patients should not receive live-attenuated vaccines; the level of VZV-specific CMI appears to be very important with respect to risk of developing herpes zoster; levels of antibody to VZV remain relatively constant in old age and thus do not correlate with risk for development of herpes zoster, but VZV-specific memory T-cells decline progressively with advancing age; TC is known to decrease sympathetic nervous system activity.

Comments: Not very long ago the very idea that a behavioral intervention like TC could have a beneficial impact on immune system functioning would be deemed preposterous. Consider the remarkable implications of these data—in healthy people who "normally" develop a less responsive immune system with advancing age, a technique readily accessible to the elderly (TC) can better immune system function, as well as help improve a number of measures of quality of life. In addition, one should not lose sight of the fact that immune system improvements were also identified in those subjects who simply participated in HE. In this instance, it appears that the specific activity plays a role in the degree of immune augmentation elicited, but being part of a group, being social, again appears to have its role in good health, too. As the authors of the trial point out, if these findings were to be extrapolated to other clinical circumstances the ramifications are significant: Could TC have a positive impact on response to other immunizations, such as against the flu or pneumococcal pneumonia? We're left to wait for additional data in this regard, but there is now ample reason for optimism.

What to do with this article: Make a hard copy to hand out to your peers. ❖

Supplement to *Alternative Medicine Alert*
May 2007

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Relaxation Techniques

LEFT UNCHECKED, STRESS CAN HAVE SIGNIFICANT EFFECTS ON YOUR OVERALL HEALTH AND well-being. Stress can impair your immune system, making you more susceptible to infections, and can increase your risk of cardiovascular disease. Pre-existing health concerns, like asthma or gastrointestinal problems, can be exacerbated by stress.

Stress can be divided into two different types: acute (for example, you're late for work) or chronic (coping with the death of a loved one, divorce, or a difficult job). Both types are associated with considerable impairment *(see Table 1)*. In addition, stress may manifest as a physical, perceptual, emotional, or behavioral reaction *(see Table 2)*.

Taking control of your response to stress

The first step in taking control of your stress levels involves identifying your stressors and your body's response to them. When you can recognize that you are stressed, you can use one of several relaxation techniques to reduce your stress levels *(see Table 3)*.

Controlled breathing exercises also can be used to modify your response to stress.

First exercise: Be aware of your breath. As often as possible, bring your attention to your breath. Are you holding your breath? Are you breathing deeply? Try to imagine that your breathing cycle starts with exhaling not inhaling. Put cues around your environment to remind

Table 1

Effects of stress

On your body	On your thoughts and feelings	On your behavior
• Headache	• Anxiety	• Overeating
• Chest pain	• Restlessness	• Undereating
• Pounding heart	• Worrying	• Angry outbursts
• High blood pressure	• Irritability	• Drug abuse
• Shortness of breath	• Depression	• Excessive drinking
• Muscle aches	• Sadness	• Increased smoking
• Back pain	• Anger	• Social withdrawal
• Clenched jaws	• Mood swings	• Crying spells
• Teeth grinding	• Job dissatisfaction	• Relationship conflicts
• Stomach upset	• Feeling insecure	• Decreased productivity
• Constipation	• Confusion	• Blaming others
• Diarrhea	• Burn out	
• Increased sweating	• Nervousness	
• Tiredness	• Resentment	
• Sleep problems	• Guilt	
• Weight gain or loss	• Inability to concentrate	
• Sex problems	• Seeing only the negative	
• Skin breakouts		

Source: MayoClinic.com. Accessed April 18, 2007.

Table 2

Recognize your body's signals of stress

Physical
- Frequent headaches, migraines, numbness in extremities, unusual amount of blinking or yawning, rapid heartbeat, rapid breathing, nervous tics, teeth clenching, nausea, vomiting, sighing

Perceptual
- Losing perspective, repeated forgetfulness, misperceptions, inattentiveness, distractibility

Emotional
- Losing temper, irritability (either everything or nothing bothers you), depression, crying

Behavioral
- Nervous habits, sudden changes in diet, accident prone, increased use of alcohol, caffeine, tobacco, or sugar

Source: Christensen A. *The American Yoga Association's Beginner's Manual.* New York: Simon & Schuster; 1987.

Table 3

Stress relief strategies

- Take a deep breath
- Stretch during the day, especially if you sit at a desk or talk on the phone
- Take a time out and divert your attention for 5 minutes: walk around the block, look out the window
- Listen to a 10-minute relaxation tape
- Listen to soothing music
- Appreciate something beautiful
- Do something physical
- Pick a small task and finish it
- Take a moment to pray for someone less fortunate than you
- Watch fish swim in an aquarium
- Scan your body for tension and consciously release it
- Have a cup of caffeine-free, calming tea
- Leave 15 minutes early for your next appointment and take your time getting there
- Call a friend and hear some good news
- Repeat a prayer and put things in perspective

Source: Venice Family Clinic, Venice, CA.

you to breathe. Notes or colored dots work well, just be sure to change them every three days or so, otherwise you will stop noticing them.

Second exercise: Diaphragmatic breathing. Get into a comfortable position. If you are sitting, place both feet on the floor and use a chair with good back support. If you lie down, place a pillow under your head and behind your knees. Try not to fall asleep unless you are using this exercise to relax before bed.

Place your hands on your abdomen. As you breathe in, push your abdomen out. Once you've reached full expansion, release your breath and let your abdomen relax naturally. Exhale through your mouth with a gentle sigh. Let your next exhalation follow naturally from the last breath.

Clear your mind and only focus on your breathing. If your attention wanders, try counting or saying inhale/exhale to yourself in your mind.

Third exercise: Meditation breathing. Follow the instructions for diaphragmatic breathing.

Focus your attention on the flow of your breath. Feel it enter your nostrils, roll into your body, and release from your lungs with expiration. Use all your senses to track your breath and do not use your mind for thinking. Try to focus your attention on the action in the moment. This type of practice is called mindfulness.

Use the in and out flow of your breath to focus your attention and send a message to yourself. You might say a word that is important to you, for example, calm, peace, or love. You could imagine breathing in peace with your inspiration and releasing tension with your exhalation.

Fourth exercise: Releasing breath. Get into a comfortable position and scan your body for tension. Take a deep breath in and with exhalation, release tension from that part of your body.

To increase the effect of this breathing technique, combine it with progressive muscle relaxation. This technique assumes that a muscle will relax more completely if it has been tensed first.

Once you are breathing comfortably, begin at the top, tensing your face or shoulders or making your hands into fists with your inspiration. Hold your tension and your breath for several seconds and then release your breath through your mouth, allowing the muscle you just tensed to go loose and limp. Continue one area at a time until you have gone through your whole body.

[If you find yourself feeling dizzy or a little numb on your hands and feet while practice these exercises, just breathe less deeply for a few minutes.]

Resources

The National Institute of Mental Health: www.nimh.nih.gov, (301) 443-4513.

The National Center for Complementary and Alternative Medicine: www.nccam.nih.gov, (301) 644-6226.

Center for Mind-Body Medicine: www.cmbm.org, (202) 966-7338.