ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Complementary Therapies

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

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

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

Valerian for Insomnia: The "Natural" Valium

By David Kiefer, MD

Dr. Kiefer is a Clinical Instructor, Family Medicine, University of Washington in Seattle; Clinical Assistant Professor of Medicine, University of Arizona, Tucson, and Adjunct Faculty at Bastyr University in Seattle; Dr. Kiefer reports no financial relationships relevant to this field of study.

FOR MANY PEOPLE WHO HAVE TROUBLE SLEEPING, VALERIAN IS one of the herbal medicines first thought of as a sleep aid. Perhaps they started by trying an infusion of chamomile (*Matricaria recutita*), with some effect, but the insomnia lingered, and word of mouth or internet research led invariably to products containing valerian.

Valerian has an aroma that has been likened to smelly sport socks steeping for a week on the back porch, so do you counsel your patients to stick with the infusion, switch to capsules, try a tincture, use a conventional medical pharmaceutical aid, or move on to the other sleep aids you have learned about in past issues of *Alternative Medicine Alert*? The details behind valerian's sedative effects, and clinical trials for insomnia, as detailed below, will help you make this important decision.

History and Traditional Use

Since the time of ancient Greece, valerian has been used for a variety of psychiatric and medical conditions, including insomnia, epilepsy, stress, anxiety, depression, and for "nervous headache" and "shell shock."[1,2] In Ayurvedic medicine, valerian is used for hysteria and neurosis. The German Commission E mentions valerian root as a bath additive for mild sedation, and valerian oil as a treatment used for cholera during World War II.[1] Various valerian species are used as spasmolytics for the gastrointestinal tract, as well as for hypertension, angina, asthma, menstrual cramps, biliary colic, and palpitations.[2]

Botany and Pharmacology

In Western herbal medicine, the Latin scientific name for valerian,

or European valerian, is *Valeriana officinalis*, one of about 250 species of Valeriana.[2] Herbal medicine sources also mention Mexican valerian (*V. edulis*) and Indian valerian (*V. wallichii, V. jatamansi*).[1,3,4] These plants may grow to 3 feet in height, and are a part of the family Valerianaceae.

The active ingredients thought to account for the medicinal activity of *V. officinalis* are valepotriates (iridoid compounds), essential oil (monoterpenes, sesquiterpenes, esters of valerianic and isovaleric acid), and valerenic acid (cyclopentane sesquiterpenes).[1] Different proportions of these compounds are extracted, each having different stabilities based on the type of solution. For example, different percentages of alcohol used in extractions of valerian root affect the amount of valerenic acid and valepotriates in the final product; the clinical significance of this is still unknown, as the exact physiological effects of the individual phytochemicals continues to be elucidated.[3] Also, whereas ethanolic extracts contain both valepotriates and valerenic acids, according to one analysis, there is a limited presence of valepotriates in aqueous extracts.[2]

The strong smelly sock odor? It comes from isovaleric acid produced when the unstable valepotriate compounds decompose.[1]

Mechanism of Action

Animal studies on valerian root extract have shown a prolongation of barbiturate-induced sleeping time, anticonvulsant effects, decreased neuronal activity, and displacement of GABA from rat brain cortex tissue, but no interaction with benzodiazepine or opiate receptors.[4] In rats, a 70% ethanolic valerian extract was shown to decrease sleep latency without affecting sleep quality (as represented by delta wave sleep), total time of wakefulness, non-REM sleep, or REM sleep.[5]

Both a valerian extract standardized to 0.3% valerenic acid and purified valerenic acid have been shown to inhibit neurons via GABA-A receptors in an in vitro rat brainstem preparation, possibly either by direct GABA receptor action or increasing the availability of GABA.[6,7]

Valerenic acid appears to inhibit GABA breakdown, leading to sedation and decreased CNS activity, whereas the valepotriates may bind to dopamine receptors, thereby decreasing central dopamine excitation.[4]

Also, valerenic acid and the valepotriates act as spasmolytics, the latter by transformation into the active metabolite homobaldrinal and mediated by calcium metabolism.[2,4] In animal models, both ethanolic and aqueous extracts decrease coronary and bronchial spasm, as well as decrease blood pressure.[2]

With respect to how valerian acts, some human trials have begun to illustrate what valerian does not do, at least in a single dose. Fourteen people older than age 65 were randomized to receive single oral doses of temazepam (15-30 mg), diphenhydramine (50-75 mg), or Jamieson brand valerian capsules (400-800 mg) in a double-blind study protocol.[8] No significant differences with placebo were noted with either dose of valerian on subjective or objective sleep measures, mood, psychomotor performance, or side effects. The valerenic acid concentration in these capsules was 0.683%, slightly less than the industry standard of 0.8%.

Another small trial in 10 young healthy volunteers studied 3 different doses of a valerian extract (600, 1,200, 1,800 mg), diazepam, and placebo, and documented no effects in the valerian groups on subjective symptoms, as per five standardized questionnaires exploring mood and psychomotor/cognitive performance.[9]

Clinical trials

There have been numerous clinical trials examining the use of valerian, both alone and in combination with other herbs, to treat insomnia; some of these are summarized in two systematic reviews and one meta-analysis, comprising a total of 62 clinical trials. One showed a relative risk of 1.8 for improved sleep, though there were concerns over methodological flaws and publication bias for the 16 trials examined,[10] and another revealed inconclusive and contradictory findings for its nine trials.[11]

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: Leslie Hamlin.
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.

AHC Media LLC

Subscriber Information

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

Subscription Prices

United States
$299 per year (Student/Resident rate: $165).
Add $9.95 for shipping & handling.
Multiple Copies
Discounts are available for group subscriptions. For pricing information, call Tria Kreutzer at (404) 262-5482.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

Accreditation

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

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

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

For CME credit, add $50.

Questions & Comments

Please call **Leslie Hamlin,** Managing Editor, at (404) 262-5416 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

The most recent review included 37 studies of valerian for insomnia and noted the type of valerian extraction (water-based or alcohol-based), other herbs added to the product, and the sleep measure utilized as an outcome.[3] There were 29 clinical trials (20 using valerian alone, three with valerian and lemon balm, six with valerian and hops, and one with valerian, hops, and lemon balm — and eight open-label trials. A variety of doses, formulations, and subject populations using aqueous extracts were reported in this review. Overall, the clinical trials using ethanol-based extractions failed to show improvement in subjective (sleep efficiency, sleep latency, awakenings) or objective (polysomnographic) sleep outcomes compared to placebo, but valerian improved subjective sleep ratings similarly to benzodiazepines in several of the studies. In some cases, no significant differences were reported between valerian and placebo, while in others an improvement in sleep quality and latency was noted in both elderly individuals with sleep problems and people without sleep problems.

In another small, double-blind trial, 16 patients with insomnia were randomized to either placebo or a single 600 mg dose and 14 subsequent doses of a dry valerian extract in tablet form (Sedonium®).[12] The single dose of valerian caused no change in objective or subjective sleep parameters. After 14 days, however, the valerian group had a significant increase in slow-wave sleep, with a shift to earlier in the sleep period, as well as a decrease in subjective sleep-onset latency. Other parameters were the same between placebo and valerian groups. Twenty-one adverse events were reported, 18 of which were in the placebo group; the three adverse events in the valerian group included a migraine headache, a gastrointestinal condition, and an accident with the polysomnogram machine.

Valerian has been studied in combination with other sedative plants, such as hops (*Humulus lupulus*), passionflower (*Passiflora sp.*), and lemon balm (*Melissa officinalis*). For example, 184 people with mild insomnia were randomized to two tablets of a valerian and hops extract (187 mg of valerian and 42 mg of hops per tablet), diphenhydramine (two tablets, 25 mg each), or two placebo tablets; sleep diaries, polysomnography, a seven-item insomnia index scale, and a self-rated general well-being index were used to analyze the different groups over four weeks.[13] All groups had a decrease in sleep latency and improved insomnia indices, but only diphenhydramine had an improvement in sleep efficiency (P = 0.039), as well as a statistically significant improvement in the insomnia index (P = 0.003). There was no significant difference in adverse effects between the three groups, and no serious adverse events were reported.

Researchers conducting another trial randomized 30 patients with non-organic sleep disorders to receive either a valerian extract (Ze 911, 500 mg of valerian), a valerian-hops combination product (Ze 91019,), or placebo nightly for four weeks.[14] The researchers used P = 0.10 as the cut-off for statistical significance; with this criteria, the valerian-hops combination was statistically better than placebo in reducing sleep latency, the length of slow-wave sleep, and clinical global impression. The rest of the parameters studied, such as sleep time, wake percentage, and other sleep stages, were not statistically significant. No adverse events were reported in any of the groups.

One researcher reviewing valerian studies noted some unique aspects of the use of valerian as a sedative: the lack of documented interactions with alcohol, an absence of "hangover" effects with the use of valerian, and the fact that in many cases it took about two weeks for the sedative effect of valerian to appear.[4]

An extract of *V. wallichii* root (Valmane®) was used in 19 patients who were withdrawing from chronic benzodiazepine use and having trouble sleeping.[15] Compared to the placebo group, the valerian group had subjectively better sleep and less wake time after sleep onset, though valerian did not decrease sleep latency.

Dosages and Formulation

Valerian is available as a tea, tincture, or tablet, but most research has been done on capsules of a root extract. One commercial preparation used in clinical trials is LI 156 (Sedonium), a 70% ethanol extraction of *V. officinalis* usually dosed 300-600 mg before bedtime. One aqueous preparation of valerian used in clinical trials is Valdispert®, dosed 405 mg three times daily.

Adverse Effects, Contraindications, and Drug Interactions

In clinical trials, valerian is generally well tolerated, with an incidence of side effects similar to placebo groups.[3] There have been reports of headache, dizziness, morning "grogginess," and gastrointestinal side effects, such as nausea, diarrhea, stomach discomfort, and a bitter taste in the mouth;[3,16] these were reported more in the trials using aqueous extracts. A randomized, three-armed trial of valerian (extract LI 156, 600 mg), flunitrazepam (1 mg), and placebo failed to find a "hangover" effect from valerian, or adverse effects on median reaction time, alertness, and two-handed coordination.[16]

In one case report, a 58-year-old man with a history of coronary artery disease, hypertension, and congestive heart failure (CHF) taking valerian five times daily experienced acute worsening of his CHF and development of

delirium upon admission to the hospital, presumably secondary to valerian withdrawal.[17]

Other cautions mentioned are possible additive effects with other sedatives, such as benzodiazepines, barbiturates, anesthetic agents, and other central nervous system depressants.[18]

Four people taking herbal tablets for stress relief who suffered liver damage were described in a report; three of the four had jaundice, and hepatic injury began shortly after taking the tablets, suggesting a hypersensitivity reaction.[19] The exact identity of the ingredients in the tablets were not definitively identified, but may have included skullcap (*Scutellaria sp.*) and valerian.

Valerian may have an effect on the cytochrome P450 system. An in vitro study of 14 commercially available valerian products demonstrated inhibition of CYP3A4, the same enzyme system that metabolizes such pharmaceuticals as lovastatin, triazolam, ketoconazole, and numerous chemotherapy agents.[20]

Conclusion

The most commonly used species of valerian, *Valeriana officinalis*, contains several physiologically active phytochemicals, including valepotriates, essential oils, and valerenic acid. In vitro and animal research point to an effect of valerian on the GABA system in the central nervous system.

Numerous clinical trials have been conducted on valerian for insomnia, but sample sizes are typically small and the results are mixed. It appears that no significant effects occur with single doses, but over several weeks of regular use there may be a decrease in sleep latency and an improvement in subjective sleep quality. Most trials have studied 300-600 mg before bed; standardized formulas are commercially available.

Mild side effects are occasionally reported, such as dizziness, gastrointestinal complaints, and headache. Liver damage has been raised as a concern, but it is difficult to distinguish between the reported serious hepatotoxicity in a combination preparation utilizing several other herbal medicines from the potential for hepatotoxicity with valerian alone, for which there currently appears little evidence. There may also be inhibition of the cytochrome P450 system.

Recommendation

Valerian has some convincing in vitro, animal, and human research for its sedative effects, but more research is clearly warranted. If a trial of valerian is to be employed, it should be used regularly for several weeks for the best effect, but it is not a long-term solution for insomnia in and of itself. An adequate dose seems to be 300-600 mg nightly. Caution is advised in people taking medicines metabolized through the CYP3A4 system, and perhaps for those with pre-existing hepatic pathology. ❖

References

1. Mills S, Bone K. Principles and practice of phytotherapy: Modern herbal medicine. Churchill Livingstone, Edinburgh, 2000.
2. Circosta C, et al. Biological and analytical characterization of two extracts from *Valeriana officinalis*. *J Ethnopharmacol.* 2007;112:361-367.
3. Taibi DM, et al. A systematic review of valerian as a sleep aid: Safe but not effective. *Sleep Med Rev*. 2007; 11:209-230.
4. Houghton PJ. The scientific basis for the reputed activity of valerian. *J Pharm Pharmacol*. 1999;51: 505-512.
5. Tokunaga S, et al. Effect of valerian extract preparation (BIM) on the sleep-wake cycle in rats. *Biol Pharm Bull*. 2007;30:363-366.
6. Yuan CS, et al. The gamma-aminobutyric acidergic effects of valerian and valerenic acid on rat brainstem neuronal activity. *Anesth Analg*. 2004;98:353-358.
7. Khom S, et al. Valerenic acid potentiates and inhibits GABA(A) receptors: Molecular mechanism and subunit specificity. *Neuropharmacology*. 2007;53:178-187.
8. Glass JR, et al. Acute pharmacological effects of temazepam, diphenhydramine, and valerian in healthy elderly subjects. *J Clin Psychopharmacol*. 2003;23:260-268.
9. Gutierrez S, et al. Assessing subjective and psychomotor effects of the herbal medication valerian in healthy volunteers. *Pharmacol Biochem Behav*. 2004;78:57-64.
10. Bent S, et al. Valerian for sleep: A systematic review and meta-analysis. *Am J Med*. 2006;119:1005-1012.
11. Stevinson C, Ernst E. Valerian for insomnia: A systematic review of randomized clinical trials. *Sleep Med.* 2000:1:91-99.
12. Donath F, et al. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. *Pharmacopsychiatry*. 2000;33:47-53.
13. Koetter U, et al. A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. *Phytother Res*. 2007;21:847-851.
14. Morin CM, et al. Valerian-hops combination and diphenhydramine for treating insomnia: A randomized placebo-controlled clinical trial. *Sleep*. 2005;28:1465-1471.
15. Poyares DR, et al. Can valerian improve the sleep of

insomniacs after benzodiazepine withdrawal? *Prog Neuropsychpharmacol Biol Psychiatry*. 2002;26:539-545.
16. Kuhlman J, et al. The influence of valerian treatment of "reaction time, alertness and concentration" in volunteers. *Pharmacopsychiatry* 1999;32:235-241.
17. Garges HP, et al. Cardiac complications and delirium associated with valerian root withdrawal. *JAMA*. 1998;280:1566-1567.
18. Hadley S, Petry JJ. Valerian. *Am Fam Physician*. 2003;67:1755-1758.
19. MacGregor FB, et al. Hepatotoxicity of herbal remedies. *BMJ*. 1989;299:1156-1157.
20. Lefebvre T, et al. In vitro activity of commercial valerian root extracts against human cytochrome P450 3A4. *J Pharm Pharm Sci*. 2004;7:265-273.

The Role of Diet and Nutrition in ADHD: Supplements

By Richard G. Petty, MD

Dr. Petty is Scientific Director, Promedica Research Center, Loganville, GA; Adjunct Professor, Georgia State University, Atlanta, GA. Dr. Petty is a consultant for AstraZeneca Pharmaceuticals and Janssen Pharmaceuticals and serves on the speaker's bureau for AstraZeneca Pharmaceuticals, Janssen Pharmaceuticals, Abbott Pharmaceuticals, and Avanir Pharmaceuticals.

In the first part of this series, the evidence concerning the possible association between food and attention-deficit hyperactivity disorder (ADHD) was presented. This second part will examine the evidence for the safety and efficacy of nutritional supplements in the management of ADHD.

Introduction

There are three essential principles of brain function that are important in understanding the role of nutritional supplements in psychological or psychiatric illnesses.

First, the brain is exquisitely sensitive to environmental change. In recent years, there has been a change in understanding the genetics of behavior. Genes expressed in the brain do not so much determine mood, behavior, or cognition; instead, they help influence how we respond to the environment.[1] This sensitivity to the environment extends to essential nutrients, not only during critical periods of brain development but throughout life.

Second, most clinicians are familiar with the impact of food on our mood, level of arousal, and behavior. What is less well-known is that there is growing evidence that nutrition, particularly in the early years of life, may have a lifelong impact on mood and cognition.[2] *(A detailed and well-referenced report entitled* Feeding Minds *was published by the British Mental Health Foundation in January 2006, and was subsequently presented to the British Government. It is available as a free download at http://www.mentalhealth.org.uk/campaigns/food-and-mental-health/)*. For example, not only are breastfed children less likely to get ADHD later in life, but there is also a correlation between the duration of breastfeeding and the risk of developing ADHD. The effect remains, even when controlled for maternal education or intelligence.[3]

Third, there is growing evidence that the composition of neuronal cell membranes may play an important role in neurotransmission and neuromodulation. Most neuronal proteins are embedded in phospholipid membranes, and their structure and function are highly dependent on the local phospholipid environment. Virtually all forms of neuronal signal transduction are dependent on the release of chemical mediators from membrane phospholipids.

This has led many to question the catecholamine hypotheses of mental illness and replace them with a phospholipid theory, in which changes in receptor function are secondary to changes in cell membranes.[4] This theory also provides a possible link between such disparate observations as the virtually linear relationship between fish consumption and rates of depression, the cognitive decline that accompanies hypertriglyceridemia, and high rates of diabetes mellitus in schizophrenia and bipolar disorder. There already exists some support for the hypothesis: rats with low levels of omega-3 (n-3) polyunsaturated fatty acids in their frontal cortices become hyperactive,[5] and children with ADHD have consistently been found to have lower levels of membrane phospholipid precursors in their erythrocyte membranes and in the prefrontal cortex.[6] We shall return to those observations in a moment.

Before reviewing the evidence on dietary supplements, it is important for practitioners to be reminded that the FDA regulates supplements under a different set of regulations than conventional foods and drug products. (See http://www.cfsan.fda.gov/~dms/supplmnt.html). Therefore, purity and contents may vary considerably, and that variation may have been a factor in the disparities between different trials.

Amino Acid Supplementation

The idea of using amino acid supplementation is based on reports of low levels of tyrosine, phenylalanine, and tryptophan in ADHD.[7]

Several open and controlled studies in both adults and children have reported a small short-term benefit from tryptophan (precursor of serotonin), tyrosine (precursor of catecholamines), or phenylalanine (precursor of catecholamines) and S-adenosyl-methionine supplementation.[8,9] However, no lasting benefit beyond 2-3 months has been demonstrated; both children and adults develop tolerance, and although amino acid supplementation is still recommended in some books written for the general public, the approach does not seem to be helpful.

Vitamins

Three strategies for vitamin supplementation are:

• Recommended Daily Allowance (RDA) multivitamin preparations;

• High doses of vitamins and minerals in combination; and

• Megadoses of specific vitamins.

The first is not controversial, although there is always a discussion about whether the RDA is correct. People with ADHD are often "picky" eaters; attentional problems often lead them to stay on much the same diet from day-to-day, and mild nutritional deficiencies of both vitamins and some metals are not uncommon. There is no published evidence that addressing these mild deficiencies has any impact on ADHD. However, in terms of general health, it is advisable to recommend a more balanced diet and perhaps a multivitamin and mineral supplement (*see below*). Recent data on the value of vitamin and mineral supplements in antisocial behavior suggest that further research on vitamin and mineral supplementation would be warranted in ADHD.[10]

The second strategy — combinations of high doses of vitamins and minerals — has not been found effective in treating hyperactivity in double-blind, placebo-controlled trials of up to six months.[11] There have not been any more recent studies of using this approach to help attentional problems.

The third strategy — the use of single vitamins in huge doses to modulate neuronal metabolism — remains largely unexplored despite some encouraging early reports over 20 years ago.[12] Very high doses of vitamins can pose problems as well. This approach should not be recommended until further controlled studies evaluate the risks and benefits of such a strategy.

Minerals

Iron

Iron is a coenzyme involved in the synthesis of catecholamines, hence the interest in iron deficiency as a possible cause of a number of neurological and neurocognitive problems. Iron deficiency may be due to poor diet, celiac disease, excessive milk ingestion, infection, gastrointestinal losses or lead toxicity. Even in affluent societies, many menstruating or recently pregnant women are chronically iron deficient. In a study of 57 children with ADHD and 27 healthy volunteers, there was a significant inverse correlation between ferritin levels and scores on a standard ADHD rating scale.[13] There is evidence that iron supplementation may help some children,[14] but this is another area that is in great need of further research.

Zinc

Zinc is a cofactor for at least 100 enzymes, many involved in neural metabolism. It is also necessary for fatty acid absorption and for the production of melatonin. Zinc is so important for the normal functioning of the brain that it is plausible that deficiency would adversely affect behavior, and that restoring optimal levels may provide some benefit.

In a study of 44 children diagnosed with ADHD, serum zinc levels had a significant inverse correlation with attention, even controlling for gender, age, income, and diagnostic subtype.[15] In a large, randomized, placebo-controlled trial, children given zinc sulfate (150 mg/d) had significantly more improvement in impulsive behavior and socialization; the best response was observed in those children who had low zinc levels to begin with.[16] We do not yet know if using mega-doses of zinc will confer any benefit.

Magnesium

Magnesium deficiency can cause a wide spectrum of neurological and psychiatric disturbance and can result from a wide variety of causes, including increased requirement during childhood.

In one study, children with ADHD had low levels of erythrocyte magnesium. An open-label study supplementing them with 100 mg daily of magnesium and vitamin B_6 for 3-24 weeks led to reduced symptoms of hyper-excitability (physical aggression, instability, attention to school work, muscle tension, and spasms) after 1-6 months of treatment.[17]

Essential Fatty Acid Supplementation

Children with lower plasma levels of omega-3 fatty acids have been shown to have significantly more

behavioral problems and temper tantrums, as well as problems with learning, sleep, and physical health than do those with high levels.[18] In a four-month randomized, controlled trial of 63 children with ADHD, docosahexaenoic acid 345 mg/d was not effective on any symptoms or behaviors.[19]

A key point in trials of fatty acids is the origin and proportions of each moiety. A recent review echoes the view that the data on fish oils for ADHD in both adults and children are encouraging, though not conclusive.[20] It may be that fish oils will be particularly useful for the large numbers of people with ADHD and co-morbid depression. Large doses of fish oil may inhibit platelet aggregation and increase the risk of bleeding; its use should be discontinued at least 48 hours before having surgery. Many people do not like the taste of fish oil, though in capsules that is not normally a problem.

Gamma-Linolenic Acid

Evening primrose oil is rich in gamma-linolenic acid, and although occasionally recommended as a treatment for ADHD, small randomized, controlled trials have thus far failed to show a benefit.[21]

Melatonin

Sleep disturbances are very common with ADHD. In addition, melatonin is involved in modulating dopamine function in several regions of the brain, so it has been a natural candidate for the treatment of ADHD. In a recent study involving 105 medication-free children, melatonin helped with sleep problems in children with ADHD, but had no effect on problem behavior, cognitive performance, or quality of life.[22] If used, the recommended dosage is 3-6 mg/d given one hour before retiring.

Conclusion

The brain is exquisitely sensitive to nutritional imbalances. This may be especially true of children and adults with ADHD who may naturally tend toward repetitive and familiar diets that may not meet their nutritional needs. As a starting point, clinicians should ensure that all patients maintain an adequate, balanced diet.

Recommendations

• Have all patients maintain a one-week diet diary to ensure the adequacy of their diet;

• Be sure that children with ADHD have a diet providing, or consume supplements to ensure, adequate dietary intake of essential vitamins, iron, zinc, and magnesium, but advise patients and their families that there is no good evidence for exceeding the RDA;

• Amino acid supplementation is at best a short-term strategy, and there is no good evidence to support it for longer-term treatment;

• The most promising nutritional supplement for ADHD is omega-3 fatty acids. Although the evidence is not conclusive, there is sufficient confirmation of benefit to recommend a trial of 1-2 g (depending on the child's age and size) of pure omega-3 fatty acids/d. The recommendation for the precise combination of omega-3 and omega-6 fatty acids will change as new research is completed. Ensure that the supplement chosen does not contain mercury, PCBs or dioxins; and

• Melatonin may be helpful for children with ADHD who have trouble sleeping. ❖

References

1. Kendler KS. Reflections on the relationship between psychiatric genetics and psychiatric nosology. *Am J Psychiatry*. 2006;163:1138-1146.
2. Fanjiang G, Kleinman RE. Nutrition and performance in children. *Curr Opin Clin Nutr Metab Care*. 2007; 10:342-347.
3. Julvez J, et al. Attention behaviour and hyperactivity at age 4 and duration of breastfeeding. *Acta Paediatr*. 2007;96:842-847.
4. Peet M, Stokes C. Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs*. 2005;65:1051-1059.
5. Vancassel S, et al. Hyperactivity in the rat is associated with spontaneous low level of n-3 polyunsaturated fatty acids in the frontal cortex. *Behav Brain Res*. 2007;180:119-126.
6. Stanley JA, et al. Regionally specific alterations in membrane phospholipids in children with ADHD: An in vivo 31P spectroscopy study. *Psychiatry Res*. 2006; 148:217-221.
7. Bornstein RA, et al. Plasma amino acids in attention deficit disorder. *Psychiatry Res*. 1990;33:301-306.
8. Nemzer ED, et al. Amino acid supplementation as therapy for attention deficit disorder. *J Am Acad Child Psychiatry*. 1986;25:509-513.
9. Shekim WO, et al. S-adenosyl-L-methionine (SAM) in adults with ADHD, RS: Preliminary results from an open trial. *Psychopharmacol Bull*. 1990;26:249-253.
10. Benton D. The impact of diet on anti-social, violent and criminal behaviour. *Neurosci Biobehav Rev*. 2007;31:752-774.
11. Kershner J, Hawke W. Megavitamins and learning disorders: A controlled double-blind experiment. *J Nutr*. 1979;109(5):819-826.

12. Brenner A. The effects of megadoses of selected B complex vitamins on children with hyperkinesis: Controlled studies with long-term follow-up. *J Learn Disabil*. 1982;15:258-264.
13. Konofal E, et al. Iron deficiency in children with attention-deficit/hyperactivity disorder. *Arch Pediatr Adolesc Med*. 2004;158:1113-1115.
14. Sever Y, et al. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. *Neuropsychobiology*. 1997;35:178-180.
15. Arnold LE, et al. Serum zinc correlates with parent- and teacher- rated inattention in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol*. 2005;15:628-636.
16. Bilici M, et al. Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:181-190.
17. Mousain-Bosc M, et al. Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. I. Attention deficit hyperactivity disorders. *Magnes Res*. 2006;19: 46-52.
18. Richardson AJ, Montgomery P. The Oxford-Durham study: A randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder. *Pediatrics*. 2005;115: 1360-1366.
19. Voigt RG, et al. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J Pediatr*. 2001;139:189-196.
20. Antalis CJ, et al. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fatty Acids*. 2006;75:299-308.
21. Aman MG, et al. The effects of essential fatty acid supplementation by Efamol in hyperactive children. *J Abnorm Child Psychol*. 1987;15:75-90.
22. Van der Heijden KB, et al. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry*. 2007;46:233-241.

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.

After completing the program, physicians will be able to:

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

40. All of the following are phytochemicals thought to account for the medicinal activity of *Valeriana officinalis* EXCEPT:

a. valepotriates.
b. polyphenolic tannins.
c. valerenic acid.
d. essential oils.

41. Which of the following is TRUE regarding the use of *Valeriana officinalis* for insomnia in humans?

a. One-time, single doses have significant clinical effects.
b. Clinical trials are invariably positive (ie, valerian improves sleep parameters, both objective and subjective), though the overall effect is minor.
c. It should be dosed no more than 50-75 milligrams before bed.
d. Mild side effects are occasionally reported, such as dizziness, gastrointestinal complaints, and headache.

42. *TRUE or FALSE?* Children with ADHD have been found to have lower levels of membrane phospholipid precursors in their erythrocyte membranes, as well as the prefrontal cortex.

Answers: 40. (b); 41. (d); 42. (True)

With Comments from Russell H. Greenfield, MD

Dr. Greenfield is Clinical Assistant Professor, School of Medicine, University of North Carolina, Chapel Hill, NC; and Visiting Assistant Professor, University of Arizona, College of Medicine, Tucson, AZ.

Selenium Too Sweet? Supplementation and Type 2 DM

Source: Stranges S, et al: Effects of long-term selenium supplementation on the incidence of type 2 diabetes. *Ann Intern Med.* 2007;147:217-223.

Goal: To assess the effect of long-term selenium supplementation on the incidence of new onset type 2 diabetes mellitus (DM).

Study Design: Secondary analysis of a randomized, double-blind, placebo-controlled trial (part of the Nutritional Prevention of Cancer, or NPC, trial) during its blinded phase.

Subjects: People with a history of nonmelanoma skin cancer in the year prior to randomization, but without DM at baseline, seen in dermatology clinics in locales where selenium consumption is low (average daily dietary intake = 90 µ; analysis on n = 1,202 with a valid selenium value obtained within 4 days of date of randomization, n = 600 receiving selenium).

Methods: Subjects were randomized to receive either a placebo tablet containing yeast or 200 micrograms selenium from high-selenium baker's yeast tablets. Baseline evaluation included collection of demographic information, anthropometric data and behavioral characteristics. Biannual evaluations were subsequently held during which changes in clinical status were documented and blood samples were obtained. Individual medical records were reviewed periodically. An initial report of DM came from 3 possible sources: self-report during the clinical interview, reported use of drugs for DM, and medical records. For analytical purposes, plasma selenium levels were divided at tertiles and at the median level.

Results: Over an average follow-up of 7.7 years, a total of 97 new cases of Type 2 DM were diagnosed, with a higher cumulative incidence in the selenium group (n = 58, hazard ratio = 1.55). The risk for type 2 DM was consistently higher across all subgroups for those taking selenium, except in the highest tertile of body mass index, where no difference between groups was identified. A significantly increased risk for Type 2 DM was found for those subjects whose baseline selenium levels were higher than the median value (hazard ratio = 2.50). An exposure-response gradient was found across all tertiles of baseline plasma selenium level, with a significantly increased risk for Type 2 DM in the top tertile (hazard ratio = 2.70). When results were stratified according to behavioral and anthropometric covariates, lack of benefit with selenium supplementation persisted.

Conclusion: Long-term selenium supplementation at a dose of 200 µ/d does not prevent Type 2 DM, but may instead adversely affect glucose metabolism, and increase risk for the disease.

Study strengths: Sample size; no participants lost to follow-up; selenium content of each batch of pills was determined in laboratories; review of diagnostic documentation.

Study weaknesses: Diabetes was a secondary outcome of the original trial, and conclusions were based on exploratory analyses; self-reported diagnosis of DM; lack of generalizability (most participants were older Caucasian men — non-whites were excluded); as the authors note, lack of detailed information on unmeasured risk factors (eg, family history).

Of note: The goal of the NPC trial was primarily to determine whether selenium supplementation offered benefits with respect to cancer prevention; insulin resistance, impaired glucose tolerance, and Type 2 DM are all linked to oxidative stress, and observational data suggest that dietary or plasma antioxidants protect against development of Type 2 DM; however, the few clinical trials of antioxidant supplementation to help prevent Type 2 DM or its complications have produced negative results; the data assessed in this paper are at least 16 years old; for inclusion, participants had to have a life expectancy of least five years and no history of internal cancer over the prior five years; nonwhite persons were excluded because the trial focused on the effects of selenium on nonmelanoma skin cancer, theoretically controlling for the effects of skin pigmentation on cancer recurrence risk; the incidence of DM in this trial mirrors that found in other studies of mainly white subjects; some data suggest that selenium may help prevent non-skin cancers, but recent research does not support a significant role for selenium with respect to cardioprotection.

We knew that: The majority of multivitamin and mineral supplement products contain 30-200 µ of selenium; findings from animal models suggest that low-dose selenium supplementation improves glucose metabolism, while the effects of high-dose selenium supplementation remain unclear; both in vivo and in vitro studies suggest that selenium mediates many insulin-like actions, thereby enhancing insulin sensitivity; some data suggest that people with DM are relatively deficient in selenium, and that selenium may

help prevent vascular complications in people with DM; the SU.VI. MAX study showed no benefit on fasting blood glucose levels from antioxidant supplementation that included selenium (100 μ) over 7.5 years of follow-up, however longitudinal analysis of the relationship between baseline plasma selenium antioxidants and fasting blood glucose revealed a statistically significant association.

Comments: Selenium's importance in human health continues to be explored and debated. It plays a role in maintaining immunity and proper thyroid function, and there have been high hopes for selenium supplementation as a cancer chemopreventive agent, and as an aid in other endocrinologic realms, most notably DM. As regards the latter, animal data provided reason for optimism, but other research contradicts positive experiments. The current study brings up concerns of selenium actually increasing the risk of DM.

Unless a person suffers from significant gastrointestinal disease or requires total parenteral nutrition, most people in the United States have adequate, though perhaps not optimal, selenium levels. Trials such as the Selenium and Vitamin E Cancer Prevention Trial (SELECT) will help clarify matters regarding selenium supplementation, but results are not expected until 2013.

The conclusions of this study raise real concerns, but methodological limitations severely limit generalizability. It is far too early in this story to start lobbying for the removal of selenium supplements from store shelves, and benefits may yet be identified. Until more is known, no action need be taken, but consideration could be given to lessening supplemental selenium for those at high risk of developing DM.

What to do with this article: Keep a copy on your computer. ❖

My Knee is Stuck! Acupuncture and OA

Source: Manheimer E, et al: Meta-analysis: acupuncture for osteoarthritis of the knee. *Ann Intern Med*. 2007;146:868-877.

Goal: To conduct a systematic review and meta-analysis assessing the efficacy of acupuncture in the management of knee osteoarthritis (OA).

Study design: Meta-analysis.

Study selection: Randomized, controlled trials (RCTs) longer than six weeks' duration that compared needle acupuncture with a sham, usual care, or waiting list control group for patients with knee OA of at least five years duration.

Methods: Data were culled from MEDLINE, EMBASE, and Cochrane databases without language restriction. In addition, unpublished data were obtained from eight authors. Outcomes were limited to pain and function (with an emphasis on WOMAC measures), and only those trials that employed insertion of needles into traditional meridian points were considered (additional insertion into tender points as well as electrical stimulation were deemed acceptable, but trigger-point therapy was not). In addition, trials that only compared two forms of acupuncture were not included in the analysis. RCTs were placed into categories according to control groups, which were sham, usual care, and waiting list. Acupuncturists assessing the data were blinded to results of the study as well as publication. Treatment adequacy was evaluated independently by the acupuncturists, who appraised four different aspects of acupuncture therapy: choice of acupuncture points, number of sessions, needling technique, and experience of the acupuncturist. Pooled effects of acupuncture were assessed to ascertain whether they met thresholds for minimal clinically important differences, defined as the smallest differences in scores that patients would perceive as beneficial.

Results: A total of 11 RCTs were included in the analysis, reflecting data on over 2,800 patients. No studies reported diagnosis according to the principles of traditional Chinese medicine, and all but one required radiographic confirmation of OA. Two RCTs used a flexible formula for point selection, eight used a set formula. The one remaining trial was pragmatic in nature, where both point selection and needling technique were left to practitioner discretion. Superficial needling alone was employed in one trial, while nine used deep needle stimulation. Electrical stimulation of the needles was used in four of the trials. Acupuncture was deemed adequate in all but the one pragmatic trial, where assessment was not possible due to individualization of therapy. Of the seven trials that employed a sham control, two used sham techniques that may have had physiologic effects. Four of the seven sham controlled trials were appraised to be of high internal validity, and together comprised the main source of evidence for the review (three of four also included a nonacupuncture group). With respect to efficacy, acupuncture provided clinically insignificant improvements in pain in the short-term and at six months when compared with a sham control. Acupuncture offered clinically relevant short-term improvements compared with patients who were in waiting list or usual care groups, improvements that were largely sustained at six months for the trials with usual care groups. As regards safety, only three RCTs described adverse events (AEs), and minor AEs occurred with equal frequency between acupuncture and control groups (no serious AEs were reported). Pooled effects of acupuncture were clinically relevant when compared with the waiting list and usual care controls, but not when compared with sham control.

Conclusion: Sham-controlled trials show clinically irrelevant short-term benefits of acupuncture for treating knee OA. Waiting list-control trials suggest clinically relevant benefits, some of which may be due to placebo or expectation effects.

Study strengths: Exclusion of trials of short duration; internal validity of studies assessed; use of minimal clinically important difference measures; examination of pooled effects of acupuncture; separate control group comparisons.

Study weaknesses: Problems inherent with meta-analyses (heterogeneity, etc.); challenge posed by potentially active sham interventions.

Of note: Exercise and weight loss are established beneficial non-pharmacologic interventions for OA, though some patients may have difficulty exercising due to their condition; the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index pain and function measures are the most thoroughly validated instruments for assessing patients with knee OA; there is as yet no consensus regarding how best to assess treatment adequacy in RCTs of acupuncture; there are an estimated 400 active acupuncture points on the body, making physiologically inactive sham acupuncture challenging at the least.

We knew that: Data from large-scale RCTs suggest acupuncture to be an effective treatment for older people with knee OA, but meaningful conclusions remain elusive because the effects seem to differ depending on type of control group employed; OA is the leading cause of disability among older adults (with the knee being the most commonly affected joint); NSAIDs are only slightly better than placebo at providing short-term pain relief for people with OA, and are often associated with significant side effects (gastrointestinal bleeding is especially prevalent among elderly patients on NSAIDs); acetaminophen is even less effective in relieving OA pain than NSAIDs; acupuncture is safe in trained hands, with a low risk for serious side effects; a sham acupuncture control should be inert yet credible; PET scan research suggests that sham acupuncture may stimulate areas of the brain associated with natural opiate production.

Comments: This research team arguably comprises the North American leaders in the study of acupuncture, and while the article is not an easy read, its findings are fascinating. Many trials have floated the hypothesis that acupuncture therapy can reduce the pain of large joint OA, but results have been contradictory. Much of the contradiction may be traced to the type of control employed and, as the authors state, the impact of the meaning response or placebo effect, if not straightforward patient preference or pre-randomization expectation. Acupuncture appears to create a biological effect as evidenced by slight but measurable improvements in OA pain when compared with sham controls; however, some of the benefit of acupuncture for OA may stem from the placebo effect or emotional responses.

In considering positive research on acupuncture or CAM therapies in general, there are typically three camps: those who believe the intervention to be active and useful, those who believe the therapy to reflect "nothing more" than the placebo effect, and those withholding judgment until convincing evidence appears. What is intriguing is that the authors put forth that acupuncture is active and that patient expectation or the placebo effect are also at work. Indeed, as experts have promoted for any conventional medical intervention, to prudently engage the placebo effect may enhance therapeutic efficacy in association with biologic activity.

The authors note that acupuncture for the treatment of knee OA may be appropriate for short-term pain relief, but that it is too early to recommend that it be included as a routine part of treatment. This conclusion makes sense. The more notable aspect of the paper, however, is that it gently encourages us to consider additional possibilities regarding how any of our recommended therapies might work, even conventional ones proven biologically effective.

What to do with this article: Make copies to hand out to your peers. ❖

Worth in Papworth? Breath work and asthma

Source: Holloway EA, West R. Integrated breathing and relaxation training (the Papworth Method) for adults with asthma in primary care: A randomized controlled trial. *Thorax*. 2007. [Epub ahead of print].

Goal: To evaluate the effectiveness of the Papworth Method (PM, a multicomponent integrated breathing and relaxation technique) on people with asthma and dysfunctional breathing.

Study design: Randomized, controlled clinical trial.

Subjects: Adults (16-70 years) with mild-to-moderate asthma and no serious comorbidity who were recruited from a single primary care practice in semi-rural Great Britain (n = 85, 36 men).

Methods: All adults cared for by the medical group and with a prior diagnosis of asthma were contacted regarding participation in the trial. Interested patients who met study criteria continued to receive usual medical care, including routine asthma education, and were randomized to either a control group (n = 46) or to an intervention group who were to receive five Papworth treatment sessions from a respiratory therapist (n = 39). Assessments lasting approximately one hour each were made at baseline, and then six (approximately post-treatment) and 12 months later. The primary outcome measure was score on the St. George's Respiratory Symptoms Questionnaire (SGRQ); secondary outcomes included tallies of the Hospital Anxiety and Depression Scale (HADS), the Nijmegen dysfunctional breathing questionnaire, and objective measures of respiratory function (including spirometry). Relaxed breathing rate and end-tidal carbon dioxide were also measured.

Results: Post-treatment data were available for 78/85 subjects, and 12-month data for 72/85 subjects. Mean score on the SGRQ symptom subscale at six-months was 21.8 compared to 32.8 in the control group, with like findings at 12 months (24.9 for the active group, 33.5 for the control group). Total SGRQ scores, HADS and Nijmegen scores were all significantly lower in the intervention group. There were no significant between-group differences noted with respect to objective measures of respiratory function save for relaxed breathing rate. No adverse effects were reported.

Conclusion: The PM improves dysfunctional breathing, respiratory symptoms, anxiety, and quality of life when compared with usual care for adults with asthma.

Study strengths: Provides data on feasibility; multiple outcome measures.

Study weaknesses: Lack of generalizability (all subjects from a single, non-urban medical practice); small sample size; inadequate data imputation for those lost to follow-up; lack of information on changes in pharmacological treatment during the course of the trial as well as frequency of exacerbations; same person administered intervention and made assessments; added personal attention given to members of intervention group.

Of note: Dysfunctional breathing includes problems like hyperventilation and hyperinflation that are often seen in people with asthma; a Cochrane review on breathing methods for asthma concluded there was a trend towards clinical improvement when such methods were employed, but only seven small and disparate trials met inclusion criteria; usual care in this study did not include information on breathing exercises; the SGRQ is used to assess respiratory symptoms and associated quality of life issues, and provides a total score, as well as subscale information on experience of symptoms, their impact, and impairment in levels of activity; the Nijmegen questionnaire elicits information relating to hypocapnic symptoms like breathlessness associated with hyperventilation; logistical reasons were the most common cause for lack of participant follow-up; of the 612 adults with asthma in the practice, only 359 responded to a mailed survey regarding their condition and were then invited to a "physiotherapy-oriented" asthma assessment, of whom 142 responded, 85 of which comprised the study group; the PM technique was recommended for use at the first sign of asthma symptoms, as well as during the course of otherwise normal days.

We knew that: An estimated 300 million people worldwide have asthma; the cyclic wheezing and breathlessness seen with asthma is often complicated by anxiety; PM is best taught to patients during periods of remission; PM emphasizes five components — diaphragmatic and "nose-breathing," stress management, specific and general relaxation training, integration of breathing and relaxation techniques into daily living activities, and home exercises; a change of 3-3.5 points in SGRQ domains is considered clinically relevant.

Comments: As noted, a small number of trials have explored the possibility that mind / body therapies and specific breathing techniques might help ameliorate respiratory symptoms during asthma exacerbations. The underlying hypothesis is attractive — people understandably become anxious during an asthma exacerbation, often hyperventilate and then develop symptoms compatible with hypocapnia. If there were a way to help individuals calm themselves, perhaps even gain an added sense of control over the way asthma manifests, then emotional if not physical improvements might be experienced during acute episodes. The findings of this study support that hypothesis, but while the results are interesting, major study flaws make them far from definitive.

Breath work and stress management training might well be of benefit to most of our patients, if not ourselves. Provided asthma patients understand well when medical attention is required, training in select breathing and relaxation techniques would seem harmless and potentially helpful, but more out of commonsense than the results of existing research to date.

What to do with this article: Remember that you read the abstract. ❖

In Future Issues:

Melatonin and Hypertension

Supplement to *Alternative Medicine Alert*
October 2007

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

Patient Handout: The Science of Soy

A STROLL THROUGH NEARLY ANY AMERICAN GROCERY STORE OR PHARMACY YIELDS AMPLE proof of the soybean's increasing role in the U.S. diet. Food packaging offers statements about products' soy content and the purported associated health benefits. Products such as tofu, soy milk, soy-based infant formula, and meatless "texturized vegetable protein" burgers are widely available. Shelves of dietary supplements and nutraceuticals are stocked with isoflavones, naturally occurring estrogen-like compounds found in soy. The general impression is one of certainty that both soy and soy isoflavones deliver many health benefits, including prevention of cardiovascular disease, cancer, and osteoporosis, as well as treatment of menopausal symptoms. The science is less absolute, however, and still evolving.

Soy provides a complete source of dietary protein, meaning that, unlike most plant proteins, it contains all the essential amino acids. According to the American Soybean Association, 3.14 billion bushels (85.5 million metric tons) of soybeans were harvested in the United States in 2004. Approximately half of the harvest was exported, and most of the remainder was crushed to produce oil and protein meal for domestic use. An April 2006 report from the USDA Economic Research Service indicates that only a small amount of whole soybeans are used to produce soy foods, and just 2% of soy protein meal is used for human consumption; the rest is used for animal feed.

The Soyfoods Association of North America reports that U.S. sales of soy foods reached $3.9 billion in 2003, continuing an 11-year trend of 15% average annual increases. According to the United Soybean Board's 2004-2005 Consumer Attitudes About Nutrition report, 25% of Americans consume soy foods or beverages at least once per week, and 74% view soy products as healthy.

Nevertheless, Americans as a whole still consume very little soy protein. Based on 2003 data from the UN Food and Agriculture Organization, per-capita soy protein consumption is less than 1 g per day in most European and North American countries, although certain subpopulations such as vegetarians, Asian immigrants, and infants fed soy-based formula consume more. The Japanese, on the other hand, consume an average 8.7 g of soy protein per day; Koreans, 6.2-9.6 g; Indonesians, 7.4 g; and the Chinese, 3.4 g.

Traditional soy foods include tofu, which is produced by puréeing cooked soybeans and precipitating the solids, and miso and tempeh, which are made by fermenting soybeans with grains. "Second generation" soy products involve chemical extractions and other processing, and include soy protein isolate and soy flour. These products become primary ingredients in items such as meatless burgers, dietary protein supplements, and infant formula, and are also used as nonnutritive additives to improve the characteristics of processed foods.

Health Effects of Soy

Soybeans and soy foods contain a variety of bioactive components, including saponins, protease inhibitors, phytic acid, and isoflavones. Isoflavones belong to a class of compounds generally known as phytoestrogens, plant compounds that have estrogen-like structures.

The dominant isoflavone in soy is genistein, with daidzein and glycitein composing the

remainder. Within soy, isoflavones are almost entirely bound to sugars, producing the respective compounds genistin, daidzin, and glycitin. Soy isoflavones have been linked with numerous health effects, but the strength of the relationships and whether the effects are beneficial are strongly debated.

Soy isoflavones are frequently referred to as weak estrogens, and depending upon the specific circumstance, they can act as agonists, partial agonists, or antagonists to endogenous estrogens (such as estradiol) and xenoestrogens (including phytoestrogens) at estrogen receptors. They are not especially potent, however, and activity varies by tissue concentration, cell type, hormone receptor type, and stage of differentiation. In addition to their estrogen receptor activity, isoflavones may also interfere with steroid metabolism by inhibiting aromatase, hydroxysteroid dehydrogenase, and steroid α-reductase, and by altering the ratio of estradiol metabolites. Soy isoflavones may also act as antioxidants; inhibitors of proteases, tyrosine kinases, and topoisomerases; inducers of Phase I and/or Phase II enzymes such as cytochrome P450s, glutathione S-transferase, quinone reductase, and inhibitors of angiogenesis.

Isoflavone Variables and Risks

Soy research is complicated because there's considerable variation in isoflavone exposure among people classified as soy consumers. Agronomic factors (such as the soybean cultivar and the environmental conditions under which the crop grew) affect a food's isoflavone profile, as does the way a soy food is processed. For example, soy protein concentrate produced by alcohol extraction may have only 12.5 mg total isoflavones per 100 g, in contrast to the nearly 199.0 mg total isoflavones per 100 g of full-fat roasted soy flour. Additionally, the fact that most of the isoflavones in food occur bound to sugar affects how they are digested.

Once genistin enters the digestive tract, it releases its sugar and becomes "free" genistein. Some of this free genistein is absorbed. However, most is reconjugated into glucuronides or sulfates, the primary circulating forms of genistein, which are thought to have either low or no biological activity. Only a very small amount of free genistein escapes conjugation by the liver and circulates in that form.

Finessing Investigations

On balance, it does not seem that soy and its constituent isoflavones have met original expectations. Clinical results with regard to soy's ability to reduce the risk of cardiovascular disease have been inconsistent; a review in the February 2006 issue of *Circulation* indicated there was little to no effect. The only apparent impact of soy and soy isoflavones on cardiovascular disease risks seems to be a slight reduction in low-density lipoproteins in individuals who had very high levels of cholesterol. An August 2005 report from the DHHS Agency for Healthcare Research and Quality, *Effects of Soy on Health Outcomes*, also concluded that there was little evidence to support a beneficial role of soy and soy isoflavones in bone health, cancer, reproductive health, neurocognitive function, and other health parameters.

Nevertheless, there remain tantalizing clues that soy may benefit human health. For example, in vitro studies with human breast cancer cells suggest that genistein may induce detoxification enzymes and inhibit growth of both estrogen receptor-positive and estrogen receptor-negative cancers. Additionally, in vitro studies demonstrate that genistein inhibits prostate cancer cell growth, and epidemiologic studies continue to find an inverse relationship between consumption of isoflavone-rich foods and prostate cancer. Rodent models and in vitro systems have suggested beneficial effects on bone density; similar results have not been observed in humans, although clinical trials have shown a promising effect on biomarkers of bone turnover.

Although there has been comparatively little research on the effects of soy and isoflavones on cognition and other brain activity, Thomas Clarkson, a professor of comparative medicine at the Wake Forest University School of Medicine, says this area may also hold some promise. "Our group has done some work [in monkeys] showing that [soy] modifies serotonin metabolism in a direction that should be useful in the prevention of depression," he says.

What most researchers do agree on is that we are only just beginning to truly understand the nature of soy, and that much more research is needed before it is possible to make firm health recommendations. "If you look at nutritional research in general," says Jay Kaplan, head of comparative medicine at Wake Forest University School of Medicine, "there are kinds of proteins that are described as being 'bioactive.' Most people had assumed that if soy is bioactive, it's because of the isoflavones. We're no longer certain of that at all."

Source: Barrett R. The science of soy: What do we really know? *EHP Student Edition*. 2006;A352-A358. [Accessed September 10, 2007 at www.ehponline.org].