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S-adenosylmethionine (SAMe) for Treatment of Depression

By Barak Gaster, MD

A YOUNG WOMAN SITS IN YOUR EXAM ROOM COMPLAINING OF chronic headaches and sleep disturbances. She is clearly depressed, but when you raise the possibility of an antidepressant she shudders. "A chemical like that in my body? Never." And therein lies the source of the multimillion dollar nutritional supplement industry aimed at people suffering from depression.

The most recent addition to the growing cadre of "natural mood-enhancers" in the United States is SAMe, a common intermediary molecule found throughout the body, whose formal biochemical name is S-adenosylmethionine. The efficacy claims for SAMe in commercial advertising are subtle, as required by law, but they are glowing nonetheless. Unfortunately, although a modest amount of data suggests that the parenteral form of SAMe is probably effective, there are minimal data to support the efficacy of oral SAMe.

History

SAMe was first discovered in 1953 in Italy. Reports that SAMe could treat depression were widely disseminated in Europe in the early 1970s, and in 1977 it became commercially available there for that purpose. SAMe was not available in the United States until the spring of 1999.

Mechanism of Action

SAMe is a ubiquitous methyl-donor molecule located throughout the body. It plays a key role in numerous metabolic pathways that involve the transfer of methyl groups. SAMe is not present in the diet in a significant amount, but is formed in the body by the combination of adenosine triphosphate (ATP) and the amino-acid methionine. (*See Figure 1.*) SAMe then donates its methyl group to any of a wide range of molecules and is subsequently transformed to homocysteine.[1]

As it is for other common conditions for which SAMe is sometimes used (osteoarthritis and liver disease), the mechanism by which SAMe might treat depression is a mystery. Possible hypotheses

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include: increasing the synthesis of neurotransmitters such as serotonin and norepinephrine, increasing the responsiveness of neurotransmitter receptors, and increasing the fluidity of cell membranes through the production of phospholipids.[2] Unfortunately, the evidence for any of these hypotheses is scant.

Pharmacology

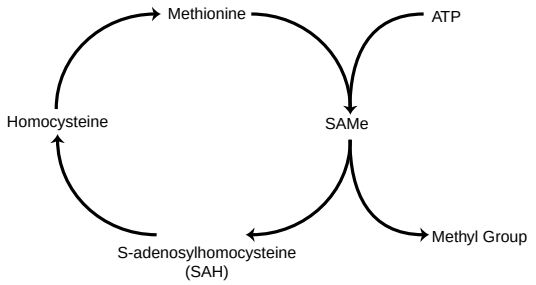
Oral SAMe has a very low bioavailability, estimated to be < 1%, so its usefulness as an oral agent is open to question.[3] In a study by Bell et al, only 71% of the patients treated with oral SAMe had a rise in their serum SAMe concentrations.[4] Parenterally administered SAMe does appear to cross the blood brain barrier.[5] The half-life, metabolism, and excretion of SAMe have not been well defined.

Clinical Studies

Although there have been more than 40 trials evaluating SAMe for depression, almost all have been of parenteral formulations. Only five trials have tested oral forms of SAMe.[4,6-9] Only three of these were randomized controlled trials (RCTs), and all were extremely small. One trial of 15 patients tested SAMe vs. placebo,[6] and two trials, one with 17 patients[4] and one with 23 patients,[7] compared SAMe to a tricyclic antidepressant (TCA).

Figure 1

Biochemical pathway of SAMe metabolism



All three RCTs suffered from serious methodological flaws, including failure to provide baseline data, failure to perform an intention-to-treat analysis, and failure to report the response rates of the study subjects. In the single placebo controlled trial, patients with severe depression who were given oral SAMe experienced more of an improvement in their depression scores than those who received placebo, a result that was statistically significant despite the very small sample size.[6] The two trials comparing SAMe to a TCA showed no significant difference between the two,[4,7] but both studies were too small to draw conclusions from a null result.

Review articles often claim that SAMe has a faster onset of action than TCAs, but the results from the two trials comparing oral SAMe to a TCA do not support this.[4,7] The rapid onset of action reported in early studies of parenterally administered SAMe is probably attributable more to the parenteral dosing route rather than to the SAMe itself, since parenterally administered TCAs also appear to have a faster onset of action than oral TCAs.

The numerous trials that have tested the parenteral dosing of SAMe have generally shown it to be effective.[10] Given SAMe's questionable absorption from the gastrointestinal tract, however, it is not valid to extrapolate this data to the use of oral SAMe.

Adverse Effects

The primary adverse event associated with the use of SAMe has been mania, manifested by pressured speech and the display of grandiose ideas. Four trials have reported this effect in 5-30% of study subjects, none of whom had a history of mania.[2,6,7,11] In all of these subjects except one, patients' thought processes seemed to return to normal when SAMe was discontinued. In one patient, however, mania was still present three months after SAMe was discontinued.[6]

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SAMe otherwise appears to be well tolerated. It does not appear to cause anticholinergic side effects, as do TCAs. Some patients taking oral SAMe report nausea. Because homocysteine levels have been implicated in the development of coronary atherosclerosis,[12] the fact that SAMe is transformed to homocysteine raises an additional safety concern. It is not known whether the administration of SAMe raises homocysteine levels or has an effect on the development of coronary artery disease. A literature search revealed no drug or supplement interactions with SAMe.

Contraindications

SAMe is contraindicated in patients with a history of mania or bipolar disorder.

Formulation and Dosage

Studies testing parenteral forms of SAMe have used a wide variety of doses, ranging from 45-400 mg/d. Parenteral SAMe is not commercially available in the United States. The five trials of oral SAMe all used 1,600 mg/d, divided in two equal doses. Oral SAMe is available in 200 mg tablets. Distributor instructions typically recommend that patients take 400 mg twice per day, but this dose has never been tested in trials. Although it is routinely recommended that SAMe be taken on an empty stomach because of its poor bioavailability, no data are available to suggest that this dosing schedule increases SAMe absorption. SAMe is significantly more expensive than common pharmaceutical agents that are used to treat depression. (*See Table 1.*)

Conclusion

A significant amount of evidence suggests that intramuscular or intravenous SAMe may be effective in treating serious depression. SAMe is very poorly absorbed, however, and there are very little data to support the efficacy of oral SAMe. SAMe may potentially be harmful by inducing mania or by increasing serum levels of homocysteine.

Table 1

Retail cost of pharmacologic therapies for depression

Therapeutic Agent	Usual Dosage	Cost (30-day supply)
St. John's wort	300 mg tid	$15
Desipramine	150 mg qd	$44
Sertraline (Zoloft®)	50 mg qd	$71
Paroxetine (Paxil®)	20 mg qd	$74
Fluoxetine (Prozac®)	20 mg qd	$81
SAMe	800 mg bid	$240

Average cost based on the author's phone survey of national pharmacy chains and online nutritional supplement distributors, October 1999.

Recommendation

Oral SAMe cannot currently be recommended for the treatment of depression given its uncertain absorption, its high cost, and its significant potential for causing mania. ❖

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Reiki as an Adjunctive Therapy for Relaxation and Pain Relief

By Dónal P. O'Mathúna, PhD

THE TERM "REIKI" (PRONOUNCED "RAY-KEY") COMES from two Japanese words, *rei*, meaning universal spirit, and *ki*, meaning life energy.[1] Other therapies based on the existence of a non-physical life energy include Therapeutic Touch (the energy being called prana)[2] and the traditional Chinese medical interpretation of acupuncture (based on chi).[3] Patients will ask about Reiki, and some medical professionals will consider incorporating Reiki into standard care. Clinicians need some knowledge of this therapy.

Common Usage

Reiki is an alternative manual healing therapy growing in popularity among clinicians, especially nurses. Reiki can be used "for treating heart attacks, emphysema, varicose veins, hemorrhoids, prostate problems, hiccups, nosebleeds, accidents, and emotional and mental problems."[4] Most commonly, Reiki is used to promote healing, wholeness, and enlightenment. A survey of Canadian Reiki patients reported using it primarily for emotional difficulties and self-development.[5] Conventional journals have carried articles recommending Reiki to improve patient well-being.[1,6,7] One hospital already does so for all preoperative patients, except those of one dissenting physician.[8] Numerous hospitals and healthcare agencies have conducted Reiki in-services.[9]

Historical Background

Reiki is an ancient Buddhist practice, rediscovered in Japan by Mikao Usui during the mid-1800s. Reiki is still practiced according to the "Usui System." Usui allegedly earned a theology doctorate from the University of Chicago and was principal of Doshisha University in Japan. No records exist of his involvement in any capacity with either university.[10]

Usui entered a Buddhist monastery searching for insight into healing. Reiki was revealed to Usui during a spiritual experience on a Japanese mountaintop after fasting for 21 days.[10] One of his disciples trained Mrs. Hawayo Takata, who introduced Reiki to the Western world around 1940. Only Mrs. Takata was allowed to teach Reiki in the West until 1975. Since then, knowledge and practice of Reiki has grown substantially.[4]

Mechanism of Action

Reiki is based on the belief that all life depends on a universal, nonphysical energy. Health requires a sustained and balanced flow of this energy throughout the body. Disturbances result in physical, emotional, or mental problems.

Reiki allegedly corrects life energy imbalances and blockages and makes people aware of the life energy flowing through them. The following description from one of Mrs. Tanaka's disciples is typical: "Reiki is a natural consciousness-expanding technique that will put you in touch with your real self—with your own eternal being."[4]

Whether Reiki is a healing therapy or a religious practice is uncertain, as the International Center for Reiki Training's description demonstrates: "It is the God-consciousness called Rei that guides the life force called Ki in the practice we call Reiki. Therefore, Reiki can be defined as spiritually guided life force energy."[11]

Procedure

A person relaxes in any position to receive Reiki. Practitioners gently rest their hands in specific ways on approximately 12 standard sites throughout the body, which may vary slightly among practitioners. Reiki practitioners begin with the head and spend a few minutes at each site, with a complete session taking 60 to 90 minutes. Eventually, practitioners may expand the therapy beyond the standard 12 sites.

More advanced practitioners claim to be as effective when physically absent from patients, simply visualizing their hand movements with patients (called distance healing). Practitioners are believed to act as passive channels for the life energy, which comes from its universal source. Practitioners do not direct the energy, which guides itself solely to where it is needed.

Practitioner Training

Practitioner training involves opening trainees' life energy channels (or chakras) in special training sessions called "attunements." Only Reiki Masters (or Level III practitioners) may perform attunements, viewed by many as "sacred ceremonies."[9,10,12] The Master makes special hand movements around the trainee to open the energy channels. Trainees' hands become warm, signaling they are ready to channel life energy as Level I practitioners.

After some experience, Reiki Level II can be attained with another attunement when the practitioner "intuitively" receives special symbols, believed to be healing gifts from personal beings called spirit guides.[10,13] The symbols increase the practitioner's healing powers.

Practitioners draw the symbols on patients' bodies, or visualize them, while silently chanting the symbol's name. Level II must be attained before Reiki distance healing is possible.[4,10] Becoming a Reiki Master requires another attunement during which further symbols are received for use in the Level I initiation rituals.

Clinical Studies

Literature searches for "Reiki" in Medline, CINAHL, Dissertation Abstracts, the Cochrane Library, and the Registry of Nursing Research revealed four clinical trials, with their references leading to three more. Two hypothesized that Reiki would change the blood's oxygen-carrying capability as reflected by hemoglobin and hematocrit levels with mixed results.[14,15]

One examiner reported slower wound healing in patients receiving a combination of Reiki, Therapeutic Touch, LeShan (a distance healing technique said to raise people's conscious awareness of healing processes), and Intercessory Prayer.[16] After 10 days, one of 15 subjects given 4 mm skin biopsy wounds and treated was fully healed, compared to seven fully healed out of 15 untreated subjects.

Two studies tested the widespread claim that Reiki powerfully induces relaxation. The first used distance Reiki to induce relaxation monitored by skin resistance response (SRR) measurements.[13] Three Reiki practitioners treated 15 healthy subjects recruited from relaxation courses at the researchers' institute. Practitioners attempted to either relax or arouse subjects' autonomic activity for 30-second intervals in a randomly determined sequence (25 minutes altogether). SRR changes during relaxation or arousal intervals did not differ significantly. In the other study, nursing students received either hands-on Reiki (n = 22) or mimic-Reiki (n = 20).[17] No significant differences were found for perceptions of anxiety, personal power, or well-being using two questionnaire instruments.

Two clinical studies examined Reiki's pain-relieving effects. Impacted third molars were extracted from 21 patients in a randomized, double-blind, within-subject crossover study.[18] Subjects were randomly assigned to one group for the removal of one lower third molar, and about two weeks later crossed over to the other group for the removal of their second lower third molar. Subjects took 1,000 mg acetaminophen orally at 3, 6, and 9 hours postoperatively. Practitioners were "several miles" away and commenced either Reiki or LeShan treatments at hour 3, alternating hourly for six hours. A visual analogue scale assessing pain intensity and a Likert scale assessing pain relief were administered hourly from hour 3 to 9 (subjects unsupervised at home). The treatment group had significantly lower pain intensity and significantly higher pain relief at hours 4 through 7 ($P < 0.05$) and hours 8 and 9 ($P < 0.01$).

A pilot project used hands-on Reiki with 20 subjects experiencing moderate pain at 55 sites for a variety of reasons.[19] Subjects used various pharmaceutical and alternative pain reducing therapies concurrently. Reiki was administered in a dimly lit room accompanied by burning candles and soft music. Pain scores were significantly lower after therapy compared to immediately before therapy (2.25 reduction on a visual analogue scale; 1.25 reduction on a Likert scale; $P < 0.0001$). A control group was not used.

Adverse Effects

No patient adverse effects have been reported. Proponents claim Reiki cannot cause harm as the energy adjusts itself to provide only the needed effects. An Australian nursing journal printed a letter claiming Reiki training caused a nurse much anxiety and discomfort.[20] A storm of controversy erupted subsequently, with some nurses reporting similar negative effects and others defending Reiki as completely harmless.[21]

Conclusion

The few Reiki studies have diverse designs and often include other therapies. Confounding factors, such as the lighting, candles, and music in reference 19, could account for the improvements found. The authors of one Reiki study concluded: "Despite the growing interest in Reiki, no strong evidence is yet available regarding its effectiveness."[12]

Recommendation

Reiki's growing popularity probably reflects the importance of meaningful, personal interactions between healthcare providers and patients. Controversy regarding Reiki's spiritual roots, and the secrecy associated with many aspects of Reiki, require particular caution before suggesting Reiki to patients. There is meager scientific evidence to support recommending Reiki in pain relief. ❖

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Phytoestrogens for the Prevention and Treatment of Osteoporosis

By Nicole Nisly, MD and Teresa Klepser, PharmD

OSTEOPOROSIS IS A MAJOR PUBLIC HEALTH PROBLEM occurring primarily among postmenopausal women (PMW). A diet rich in legumes, especially soy, has been linked to a lower risk of fractures in Asian women, despite their lower bone density, when compared with Caucasian women.[1] Hormone replacement therapy (HRT) is effective in maintaining bone and reducing susceptibility to osteoporotic fractures associated with menopause, but the negative potential effects of HRT make it unacceptable to many women, and adherence is poor.[2] To identify substances that may provide the benefits of estrogen therapy without some of its negative effects, attention has been given to plant-derived phytoestrogens.

Definition and Classification

Phytoestrogens are nonsteroidal plant compounds structurally resembling estradiol (E2), that are shown to have both estrogenic and anti-estrogenic activities in both humans and animals.[3] Phytoestrogens are found in many fruits, vegetables, and grains, but leguminous seeds are especially rich in these compounds.[4]

There are three main classes of phytoestrogens: flavonoids, coumestans, and resorcyclic acid lactones. Isoflavones have the most potent hormonal-like activity and an extensive range of biological activities in the body. More than 1,000 isoflavonoids are known, and they are exclusively found in leguminous seeds (such as soybeans, chickpeas, lentils, and beans). The most important isoflavones are genistein, daidzein, glycetin, formonetin, and biochanin (the last two are 4-methyl ether derivatives of genistein and daidzein, respectively).

Soybean is a rich source of isoflavones, especially daidzein and genistein.[4] In some individuals, daidzein may be converted into equol,[5] a potent mammalian isoflavone metabolite. Clover sprouts also contain the isoflavone formonetin, which is metabolized in the gut via daidzein into equol. Despite its weak estrogenic activity (equol is about 1,000 times less potent than estradiol), its urinary excretion in humans eating a soy-rich diet can greatly exceed the concentration of urinary endogenous estrogens, enhancing the plausibility of human health effects.[5]

Ipriflavone (7-isopropoxyisoflavone) is a synthetic isoflavone derivative used in several countries in

Europe, in particular Italy, and in Japan, for prevention and treatment of osteoporosis. In the United States, ipriflavone (IP) is available as a dietary supplement.

Metabolism

In nature, isoflavones are sugar-bound (glycoside) and are not biologically active. To transform these inactive compounds into their free active form (aglycone), they must be metabolized in the bowel.[6]

The extent of this metabolism appears to be highly variable, and is influenced by diet and microflora, including the use of antibiotics.[7] Like endogenous estrogens, isoflavones undergo enterohepatic circulation and are secreted in the bile. Estrogens are strongly protein bound, so that less than 5% circulate free. Isoflavones are less avidly bound; equol has about tenfold less affinity for serum protein than estradiol, theoretically increasing equol's effectiveness.

Mechanism of Action

Like estrogen, isoflavone molecules are complex with estrogen receptors (ER), particularly ER beta,[8] which predominates in bone, heart, and bladder. In normal reproductive women, these phytoestrogens behave as anti-estrogens, but in hypo-estrogenic PMW, isoflavones behave as weak estrogens. Isoflavones have also been found to interface with transforming growth factor beta[9] and to inhibit tyrosine kinase,[10] which may explain some of their non-estrogenic activity on bone. Similarly to estrogen, isoflavones decrease post-menopausal bone loss and in high doses may increase bone density.

Ipriflavone structurally resembles soybean's isoflavones.[11] One of its metabolites is daidzein. It does not possess estrogenic activity,[12] affecting bone remodeling by inhibiting bone resorption and possibly stimulating bone formation.[13]

Selected Animal Studies

Preclinical studies suggest cytostatic activity against human mammary cancer cell lines and the ability to suppress carcinogen-induced mammary cancer in murine models. Case-control studies show reduced risk for premenopausal and post-menopausal breast cancers.[14] Clinical studies are lacking to confirm these beneficial effects.

Human Studies

Potter et al studied the effects of soy protein with moderate and greater isoflavone content on bone mineral density in 66 PMW with hypercholesterolemia, during a six-month, parallel group, double-blind trial.[15] The incidence of osteoporosis on the study subjects was not reported. The women were randomly assigned to three sources of protein: milk protein, medium isoflavone content soy (55.6 mg/d), or high isoflavone isolated soy protein (90 mg/d). Dual energy x-ray absorptiometry bone density studies were performed of lumbar spine, proximal femur, and total body at the beginning of the study and six months later. The hypothesis was that the three groups would maintain similar bone density levels. The high isoflavone group experienced a 2% increase in bone density of the vertebral bone ($P < 0.05$), with similar trends noted for other skeletal areas (not statistically

Table 1

Estimated protein and isoflavone concentration in soy foods

	Serving Size	Protein g/100 g	Genistein mg/100g	Daidzein mg/100 g	Total Isoflavone* mg/serving
Soy Food					
Mature soybeans (uncooked)	1/2 cup	37.0	73.76	46.64	175.6
Roasted soybeans	1/2 cup	35.2	65.88	52.04	167.0
Soy flour	1/4 cup	37.8	96.83	71.19	43.8
Textured soy protein	1/4 cup	18.0	78.90	59.62	27.8
Green soybeans (uncooked)	1/2 cup	16.6	72.51	67.79	70.1
Soy milk	1 cup	4.4	6.06	4.45	20.0
Tempeh (uncooked)	4 oz	17.0	24.85	17.59	60.5
Tofu (uncooked)	4 oz	15.8	13.60	9.02	38.3
Soy isolate (dry)	1 oz	92.0	59.62	33.59	56.5
Soy concentrate (dry)	1 oz	63.6	5.33	6.83	12.4
Soy cheese	1 oz	7.0	20.08	11.24	31.3

Adapted from: Anderson JW. American Dietetic Association 80th Annual Meeting and USDA — Iowa State University Database on Isoflavone Content of Foods. 1999.

*The above isoflavone content is a mean estimate. It varies widely among soybean varieties and manufacturers.

significant). No other significant differences were noted among the three groups. This is the only well-designed human study available in the literature on soy and bone density.

Experiments in animals on the effect of IP on the treatment of bone diseases related to bone mass loss started in 1974, when this isoflavone analog was selected among several similar compounds because of its observed activity on bone and lack of estrogenic activity. Human studies began in 1981.[11] As of 1997, 2,769 patients have been treated with IP in 60 clinical trials: Many are randomized control trials (RCTs).[16] Two small studies have shown fewer vertebral fractures after two years of treatment with IP than without it.[16]

Gennari and colleagues[17] conducted two multicenter randomized, placebo-controlled, two-year studies in Italy, evaluating the efficacy and tolerability of IP in PMW with low bone mass. Four hundred fifty-three PMW aged 50-65 years with vertebral (study A) or radial (study B) bone mineral density decrease (one SD below age matched peers) were randomly selected to receive IP 200 mg tid or matching placebo. All patients received 1 g of oral calcium daily (amount of elemental calcium not specified). At the end of the two-year treatment, patients receiving IP plus calcium maintained their bone density on both spine (trabecular bone) and distal radius (cortical bone) whereas significant bone loss occurred in the control group. A slight trend toward reduction of bone turnover rate was noted in the IP treated group. IP seemed to prevent axial and peripheral bone loss in PMW and was well tolerated.

Adverse Effects

Side effects of IP may include gastrointestinal complaints and allergic reactions. A meta-analysis of the 60 trials conducted on IP revealed an incidence of ADR of 14.5% vs. 16.1% ADR on the placebo group.[16] GI complaints accounted for 77.9% of the reported ADR on the IP group (placebo 81.8%) and allergic reactions accounting for 9.1% (7.4 % on the placebo group). The effects of overdosage in humans are unknown. Animals exposed to high levels (80 mg/kg) of isoflavones show evidence of hyper-estrogenization, including both temporary and permanent infertility.[18]

Based on company information on the isoflavone concentrate Promensil™, acute and chronic toxicity tests in animals (3,000 mg/kg in single dose and daily for 28 days) did not reveal any abnormalities. Six clinical trials, including two RCTs, were performed by this company in humans. No significant side effects were observed with doses varying from 40-160 mg/d. The pooled number of participants in these studies was 110 PMW.[19]

Several human studies on IP revealed an excellent side effect profile.[16] The recommended dose should be adjusted for renal failure, as follows: creatine clearance of 40-80 ml/min, 400 mg/d; less than 40 ml/min, 200 mg/d.[16]

Contraindications and Precautions

There are concerns in the literature with the use of high doses of isoflavones by patients with hormone-sensitive cancers and in pregnancy. In animal studies, genistein in high doses (14-70 mg/kg) was associated with decreased anogenital distance at birth,[20] delayed onset of puberty, and decreased birth weight. Genistein should be avoided in pregnancy and lactation. Until use in cancer patients is more carefully evaluated, concentrated supplements should be taken with caution.

Drug Interactions

When used in conjunction with estrogens, isoflavone concentrates may potentially cause competitive inhibition. Until data are available, concomitant use of isoflavone concentrates with estrogenic preparations should be discouraged and practitioners should monitor PMW for decreased HRT effectiveness. Competitive inhibition has not been demonstrated with IP, which acts synergistically with estrogen,[21] preserving bone density. Individuals treated with proton pump inhibitors or H2 antagonists may not attain maximal benefits with isoflavone use because of decreased absorption of aglycone isoflavones. Similarly, antibiotics may reduce isoflavone metabolism by changing bowel flora. Potential elevation of serum theophylline levels may occur with IP through inhibition of cytochrome P450 enzymes.[16] IP has increased anticoagulant activity and prolonged prothrombin time, when administered with coumadin.[16]

Use in Lactation and Pregnancy

Use of isoflavone dietary supplements in pregnancy and lactation is not recommended. Isoflavones are secreted in breast milk. Infants fed soy-based formulas will receive equivalent or higher doses of isoflavones than those fed breast milk. IP has not been evaluated in this population.

Dosage and Formulation

Isoflavone consumption in Eastern countries is in the order of 20-150 mg/d (average 40 mg/d),[22,23] as compared with 2-5 mg/d in Western countries. In adults consuming 50 mg/d total isoflavones (such as found in the traditional Japanese diet) a plasma isoflavone concentration of

Commonly used soy foods and preparations

Tempeh: This firm, cultured soybean cake, native to Indonesia, is incubated with bacteria that act as a binding agent. It is rich in protein and B_{12} and is often sautéed or roasted.

Tofu: Originated in China, this product is made from curdled soy milk that is pressed to compact the curd and separate the whey. High in protein and calcium, this adaptable, cholesterol-free food can be baked, stir-fried, blended, and grilled.

Textured Soy Protein: This highly refined soy protein is very high in protein (90-95%) and low in carbohydrate. Mildly flavored, it is often used as a ground meat substitute in the United States.

Green Soybeans: Whole, unrefined green soybeans have a soft texture and mildly sweet flavor. Higher in protein, fiber, iron, and calcium than sweet corn, green beans, and peas, they are served steamed, simmered, boiled, or even grilled.

Soy Nut Butter: This blend of roasted soybeans, soy oil and sweeteners is high in protein, densely nutty, and contains less fat than peanut butter.

Miso: This seasoned, fermented soybean paste is made from soybean and a grain such as rice, plus salt and a mold culture. It is aged for one to three years, comes in different colors and strengths, and is used as a base for soup or stock, and to give depth and richness to dips, stews, and casseroles.

Soy Milk: Soaked, finely ground soy beans are strained to produce a fluid (milk). Soy milk is available in reduced fat and chocolate versions.

Soy Cheese: Made from soy milk, soy cheese is often flavored; cheese made with sodium caseinate melts.

Source: http://soyfoods.com/soyfoodsdescriptions/descriptions.html

50-800 ng/ml may be achieved, far exceeding normal plasma estradiol concentrations (40-80 pg/ml).[7]

Persons with risk factors for osteoporosis should consume about 14 servings of soy protein per week.[24] This would provide an average of approximately 16-20 g of soy protein/d with 32-40 mg of isoflavones/d. Persons with osteoporosis should consume 21 servings of soy protein per week, which would yield about 24-30 g of soy protein and 48-60 mg of isoflavones daily.

The average dose recommendation of isoflavone dietary supplements is 40 mg/d of aglycone isoflavones. Doses of 40-160 mg/d have been used in humans with a favorable side effect profile.[19] The usual dose of IP is 200 mg tid. (*See Table 1 for protein and isoflavone concentration in soy foods.*)

Conclusion

Isoflavone consumption may reduce the risk for osteoporosis and have therapeutic value for persons with it.[15] However, before firm conclusions can be drawn, long-term human studies need to be conducted on the effects of isoflavones on bone density and fracture risk. The use of standardized isoflavone concentrates[19] needs to be further studied, but small human studies conducted in Australia by one of the manufacturers reveal an excellent safety profile and promising data. IP is widely used in Europe and Japan for osteoporosis prevention and treatment, with good evidence of safety and efficacy.[16]

Recommendation

IP should be considered for patients at risk for or diagnosed with osteoporosis, who cannot tolerate or decline the use of HRT, raloxifene, or alendronate and who are unable to increase their dietary consumption of isoflavones. The use of standardized isoflavone preparations within the dosing guidelines and following the precautions summarized above may be considered for women at risk for or diagnosed with osteoporosis, who cannot or will not use HRT, raloxifene, or alendronate, and who are unable to increase their dietary isoflavone consumption to the levels found to be beneficial. ❖

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CME Questions

29. Which of the following best describes SAMe?
a. Naturally occurring hormone
b. Substance derived from plants
c. Synthetically altered vitamin
d. Common biochemical pathway molecule

30. Which of the following is *not* a valid concern regarding the use of SAMe?
a. It has very poor bioavailability.
b. It may induce symptoms of manic thought disorder.
c. It may cause cardiac arrhythmias.
d. It may increase serum homocysteine levels.

31. The most commonly accepted hypothesis for Reiki's mechanism of action is that it influences:
a. the immune system.
b. the flow of blood.
c. the flow of life energy.
d. the hormonal system.

32. Reiki is an alternative therapy that developed out of:
a. Buddhism.
b. Islam.
c. Christianity.
d. Judaism.

33. The more than 1,000 isoflavonoids are found exclusively in all of the following *except*:
a. soybeans.
b. chickpeas.
c. peanuts.
d. lentils.
e. beans.

With Comments from John La Puma, MD, FACP

Oral NADH for Chronic Fatigue Syndrome

Source: Forsyth LM, et al. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. *Ann Allergy Asthma Immunol* 1999; 82:185-191.

CHRONIC FATIGUE SYNDROME (CFS) IS a disorder of unknown etiology, consisting of prolonged, debilitating fatigue, and a multitude of symptoms including neurocognitive dysfunction, flu-like symptoms, myalgia, weakness, arthralgia, low-grade fever, sore throat, headaches, sleep disturbances, and swelling and tenderness of the lymph nodes. No effective treatment for CFS is known.

The purpose of the study was to evaluate the efficacy of the reduced form of nicotinamide adenine dinucleotide (NADH) in a stabilized oral absorbable form. We conducted a randomized, double blind, placebo-controlled crossover study in patients with CFS. NADH is known to trigger energy production through ATP generation, which may form the basis of its potential effects.

Twenty-six eligible patients (17 female, mean age 39.6 years, mean duration of fatigue 7.2 years) who fulfilled the Center for Disease Control and Prevention (CDC) criteria for CFS completed the study. Medical history, physical examination, laboratory studies, and questionnaire were obtained at baseline, 4, 8, and 12 weeks. Subjects were randomly assigned to receive either 10 mg of NADH or placebo for a four-week period. Following a four-week washout period, subjects were crossed over to the alternate regimen for a final four-week period. An arbitrary symptom scoring system was externally validated with the use of a 50-item questionnaire.

No severe adverse effects were observed related to the study drug. Within this cohort of 26 patients, eight of 26 (31%) responded favorably to NADH in contrast to two of 26 patients (8%) to placebo. A 10% improvement in symptom score was considered a favorable response. Based upon these encouraging results we have decided to conduct an open-label study in a larger cohort of patients.

Collectively, the results of this pilot study indicate that NADH may be a valuable adjunctive therapy in the management of CFS.

COMMENT

CFS is a wearing, energy-zapping disease. Patients with it are very difficult to treat, and must accommodate to the chronicity of their illness; physicians who treat them search for new treatments regularly.

Immune abnormalities have been variably reported, as has metabolic dysfunction, including hypothesized depletion of cellular ATP. Also known as Coenzyme I, NADH catalyzes ATP production in mitochondria, and according to the authors, may catalyze a change in CFS symptoms. It does not have an accepted clinical use of which I am aware.

Sponsored in part by Birkmayer Laboratories, makers of the NADH preparation used in the study, and conducted by Georgetown and Birkmayer investigators, the study has a familiar investigator, Dr. Jorg Birkmayer of Austria, who has performed a number of other open-labeled studies of proprietary preparations of NADH in patients with Alzheimer's, Parkinson's, and depression. Thirty-five patients were initially enrolled; two dropped out because of nonadherence, and nine were excluded because they were receiving psychotropic medications. Three of 35 were found to be seropositive for hepatitis C virus, apparently previously undetected.

Limitations of the study include the drop-out rate, the short treatment period, the open design, and the absence of a control group.

Recommendation

NADH is an enzymatic cofactor which is a potential treatment in search of a disease. CFS would be a good one. It should be tested in a randomized, controlled trial. Its likelihood of harm appears to be small. ❖

Do Coffee and Tea Affect MI Risk?

Source: Sesso HD, et al. Coffee and tea intake and the risk of myocardial infarction. *Am J Epidemiol* 1999;149:162-167.

WE INVESTIGATED THE ASSOCIATION of caffeinated coffee, decaffeinated coffee, and tea with myocardial infarction (MI) in a study of 340 cases and age-, sex-, and community-matched controls. The odds ratio (OR) for drinking four or more cups of caffeinated coffee vs. drinking one or less cups per week was 0.84 (95% confidence interval [CI] 0.49-1.42) after adjustment for coronary risk factors (1 cup = 237 ml). The OR for drinking more than one cup per day of decaffeinated coffee vs. nondrinkers was 1.25 (95% CI 0.76-2.04). For tea, the OR for drinking one or more cups per day vs. nondrinkers was 0.56 (95% CI 0.35-0.90). In these data, only tea was associated with a lower risk of MI.

COMMENT

These Harvard-associated investigators analyzed data from the Boston Health Study, collected from healthy Caucasian men and women aged less than 76 years in the early 1980s. The investigators selected a control matched on age, sex, and area of residence, yielding 340 case-control pairs. A self-reported food frequency questionnaire gave them the data from which they draw the conclusions above.

Investigators found that 70.2% of MI cases and 71.5% of controls drank at least one cup of caffeinated coffee daily.

The short drink: Coffee had no effect on risk of MI, even when adjustment for coronary risk factors, including lipid levels, was included.

These data are in the middle about coffee and MI. On the one hand, cohort studies have yielded mixed results. On the other hand, most case-control studies have associated caffeine with MI, leading some to speculate about coffee's effect being acute, like that of saturated fat: It is where the onion ring last lands that the oxidation of atherosclerotic plaque takes place. Maybe the same is true for the caffeine of coffee.

The difficulty in teasing out individual risk factors and their precise association with infarction is daunting. No wonder the public is confused about nutrition. In these data, people who drank caffeinated coffee were more likely to be type A, male, and to smoke more. The decaf drinkers, though, actually had higher rates of hypertension and diabetes, perhaps indicating that someone had already advised them that their morning fuel should come unleaded.

The real interest here is in tea: The methods didn't identify black, green, or oolong, but the flavonoids in black tea have been touted to inhibit cholesterol oxidation, and green tea has been reported to reduce the incidence of prostate cancer in men, among other benefits.

Problems with this study include a great deal of missing data, from coffee type to brewing method to tea type, to the confounder of smoking, noted above.

Recommendation

Patients who want to know about caffeinated coffee and MI should be told it probably has no direct effect. Tea is probably a healthier choice than decaf. Be especially vigilant for the man whose breakfast is coffee (or tea) and whose midnight snack was alcohol: Beverage choice probably is a marker for lifestyle factors separate and apart from its phytocomponents. ❖

Patients Preferences about Prayer Inquiry

Source: Ehman JW, et al. Do patients want physicians to inquire about their spiritual or religious beliefs if they become gravely ill? *Arch Intern Med* 1999;159:1803-1806.

TO EXAMINE PATIENT ACCEPTANCE OF asking "Do you have spiritual or religious beliefs that would influence your medical decisions if you become gravely ill?" in the medical history, we conducted a self-administered questionnaire study of 177 ambulatory adult outpatients visiting a pulmonary faculty office practice at a university teaching hospital in 1997. Respondents were 63% white and female, 75% Christian, and had a mean age 52 +/- 16 years.

Ninety percent of respondents believed that prayer may sometimes influence recovery from an illness, and 51% of respondents described themselves as religious. Almost half of respondents (45%) reported that religious beliefs would influence their medical decisions if they became gravely ill; 94% of these individuals agreed or strongly agreed that physicians should ask them whether they have such beliefs, and 45% of the respondents who denied having such beliefs also agreed that physicians should ask about them. Altogether, two thirds of all respondents indicated that they would welcome the study question in a medical history; 16% reported that they would not. Only 15% of the study group recalled having been asked whether spiritual or religious beliefs would influence their medical decisions. Another 15% identified themselves as currently gravely ill.

We conclude that many adult outpatients would welcome a carefully worded inquiry about their spiritual or religious beliefs in the event that they become gravely ill.

COMMENT

As the authors point out, this provocative study from University of Pennsylvania investigators contradicts in part the findings of three earlier studies published in the family medicine literature. Previous investigators asked about the discussion of religious issues in the medical office. The current investigators framed the question in terms of medical decision making and personal values.

The limitations of this study are many—selection bias, lack of follow-up, setting specificity—but its chief benefit is its effort to make explicit the spiritual issues underlying decision making. Clearly, spiritual and religious issues matter deeply to patients: When to use what we learn about spiritual and religious beliefs, and whether and how to put into practice efforts to pray with patients are "how-to" questions that can be carefully asked.

Recommendation

Presenting the question quoted above in a careful, nonjudgmental manner to patients who are chronically ill can do no harm, and will probably help. Integrate it into the Social History part of an initial assessment. ❖

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