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S-adenosyl-L-methionine (SAMe) and Depression

By C. W. Fetrow, PharmD

SINCE ITS INTRODUCTION IN 1999, SALES OF S-ADENOSYL-L-METHIONINE (SAMe) have placed it among the 25 top-selling dietary supplements in the United States. What makes this particular dietary supplement so popular? Perhaps the myriad of claims surrounding its use have helped. SAMe is marketed as an antidepressant; an antiarthritic; an agent for liver disorders, cholestasis, and migraines; and even as a therapy for fibromyalgia.

Pharmacology/Mechanism of Action

SAMe is naturally synthesized in the body during the metabolism of methionine and functions as a primary methyl group (-CH3) donor for a broad range of compounds (proteins, phospholipids, fatty acids, DNA, RNA, porphyrins, choline, carnitine, and creatine). The theoretic rationale for general therapeutic application of SAMe is that exogenous administration may bring about restoration of "youthful" levels of this metabolite and thereby induce beneficial changes in individuals whose problems, at least in part, may be attributed to a relative deficiency. Interestingly, activity of methionine adenosyltransferase (the enzyme that forms SAMe) is diminished in patients with major depression and schizophrenia, but elevated in mania.[1] SAMe crosses the blood-brain barrier and increases concentrations of homovanillic acid and 5-hydroxyindoleacetic acid.[2] It has been suggested that SAMe may blunt noradrenergic responsiveness while increasing concentrations of dopamine and serotonin in the CNS.[2,3] Whether this plays a part in the role of SAMe's effects in depression has yet to be determined.

Clinical Trials

Some of the most convincing evidence regarding use of oral SAMe in depression comes from three randomized, double-blind, controlled trials (RDBCTs) of SAMYR™ (BioResearch Inc., Milan, Italy). Kagan and colleagues studied 18 adult male inpatients who met DSM-III criteria for major depression.[4] Patients were randomly assigned to receive SAMe or placebo for a total of 21 days. SAMe was initially administered as an oral 200 mg tablet once daily, then titrated by day 7 to 800 mg PO bid and continued at

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this dose for the remainder of the trial. Subjects were evaluated by Hamilton Rating Scale for Depression (HAMD) and Carroll Rating Scale for Depression (CRSD) scores at various times throughout the trial. No significant differences in age or severity of illness existed between the two treatment groups. Fifteen patients completed the trial and three patients dropped out—one for worsening depression (placebo), one for non-compliance (placebo), and one for documented hypothyroidism (placebo). In the SAMe group, six of nine patients experienced a reduction in HAMD score by more than 50%; one of six experienced this effect in the placebo group. Mean reductions in scores for the SAMe group reached statistical significance ($P < 0.05$) by day 7 and remained significant throughout the 21-day study period. CRSD scores decreased significantly by day 21 ($P < 0.05$). The greatest limitation of this trial is the small study population. Minor limitations include short duration and no information in regard to concomitant medications. *Level II, major limitations (See enclosed insert, "Applying Evidence-Based Medicine to Dietary Supplements," for a complete explanation of the evaluation standards and scales used in rating clinical studies.)*

In 1992, De Vanna and Rigamonti published results from a six-week RDBCT of oral SAMe and imipramine in major depression.[5] Thirty patients (9 men, 21 women) with HAMD scores of 18 or higher were randomized to either imipramine (140 mg daily) or SAMe (1,600 mg daily). No differences in demographics were detected between the groups. Patients were evaluated frequently by HAMD, Hamilton Rating Scale for Anxiety (HAMA), Montgomery-Asberg's Depression Rating Scale (MADRS), and Zung's Self-Rating Scale for Depression (ZSRS). No concomitant medications were allowed with the exception of limited use of triazolam 0.25 mg for insomnia. Twenty-three patients completed the study. At day 10, statistically significant differences in scores compared to baseline were noted for the MADRS, HAMD, and HAMA ($P < 0.001$) in the SAMe treatment group, while only HAMD scores were significantly different from baseline for the imipramine group. By day 20, both MADRS and HAMD yielded similar results for the two treatment groups. At six weeks, all scales suggested efficacy for both treatment groups. The investigators concluded that SAMe was effective and well tolerated for major depression. Major limitation includes a lack of statistical power for non-significant findings and a lack of detailed information with respect to certain aspects of the trial (i.e., laboratory studies). *Level II, major limitations*

In another RDBCT, Salmaggi et al enrolled 80 women between 45 and 59 years who suffered from depression related to onset of natural or surgical menopause.[6] Patients on estrogen replacement therapy were excluded. Patients were randomly assigned to either SAMe (1,600 mg/d PO) or placebo and assessed at regular intervals for 30 days by the HAMD, Rome Depression Inventory (RDI), Clinical Global Impression Improvement Scale (CGIIS), and Minnesota Multiphasic Personality Inventory (MMPI). No significant demographic differences were detected between groups. Ten patients in each group dropped out due to "reduced compliance." From day 10 forward, statistically greater improvements were seen in HAMD scores for SAMe treatment as compared to placebo and baseline. This also held true for RDI scores. At trial endpoint, scores for the MMPI and CGIIS demonstrated statistical significance in favor of SAMe. The investigators concluded that oral SAMe was an effective treatment for depressive symptoms in postmenopausal women with major depressive disorder or dysthymia. This trial is limited primarily by short duration. *Level II, minor limitations*

Several detailed reviews[7-9] and at least two meta-analyses[10,11] have examined the available evidence for SAMe in the therapy of depression. The most recent meta-analysis included almost 800 patients in trials that used oral (> 1,600 mg/d) or parenteral (> 200 mg/d) SAMe for short-term (< 12 weeks) treatment of depression vs. placebo or tricyclic antidepressants.[11] Overall, SAMe was superior to placebo in treating depressive disorders and nearly as effective as standard tricyclic antidepressants. The reviews appear to echo these conclusions.[7-9] However, it is important to realize that these

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reviews and meta-analyses included trials of oral and parenteral formulations and many suffered severely from a lack of sound study design.

SAMe Supplementation and Serum Levels

Despite the availability of a sensitive assay for SAMe, no true therapeutic range for SAMe serum levels has been defined. Although SAMe serum levels change with both SAMe and tricyclic treatment,[2] attempts to correlate SAMe serum levels with successful responses in depressed subjects have not been successful.[2,7]

Adverse Events

In general, SAMe appears to be well tolerated. The majority of side effects are mild to moderate in nature and of brief duration, with an overall incidence of 20%.[12] Although few patients have withdrawn from trials because of SAMe side effects, this agent is not devoid of significant adverse events.

The majority of reported adverse effects are gastrointestinal (heartburn, nausea, vomiting, diarrhea), and can be quite severe,[13] but also include insomnia, dizziness, and headache.[14,15] Anaphylaxis has been documented with parenteral SAMe administration.[14] The subject also experienced dizziness and cognitive impairment that slowly resolved over two months.

Psychoactivation or a "switch" reaction to mania/hypomania has been documented in several trials.[4,15,16] The frequency with which this occurs is concerning given the small number of subjects studied.

Contraindications

Information on use of SAMe in pregnancy and lactation is unavailable. Also, there is no information on actual or potential contraindications other than hypersensitivity to SAMe or any components in the formulation involved.

Patients with a history of bipolar (manic) disorder may be at risk of a manic episode with use of SAMe.

Hyperhomocysteinemia (elevated plasma homocysteine) is a relatively rare disorder, but is associated with a dramatically increased risk of thrombosis and premature cardiovascular disease.[17] Since SAMe participates in the trans-sulfuration pathway of methionine, it poses a theoretical, but potentially dangerous risk in those individuals susceptible to elevated homocysteine levels (defective or absent cystathionine beta-synthase and/or deficiencies of vitamins B_6 or B_{12}). The actual risk remains to be determined.

Interactions

There are no reports of drug or food interactions with SAMe. It is prudent that patients taking SAMe avoid other antidepressants or mood-altering agents.

Formulation/Dosage

GNC and Nature Made distribute the only stable salt form of SAMe available in the United States. Twenty-tablet bottles retail at approximately $18-20. Oral doses in depression trials were 1,600 mg/d—approximately $225 for a 30-day supply.

Conclusion

SAMe is an intriguing compound, and useful antidepressant activity has been demonstrated in small RDBCTs. However, enthusiasm for this entity must be tempered by the lack of information surrounding SAMe's adverse effect profile. More data are needed before SAMe can be evaluated appropriately in the face of the more commonly utilized modern antidepressants and their more clearly defined risk/benefit ratios.

Recommendation

Current evidence does not strongly support a recommendation for use. Future studies must include larger numbers of patients and a dose-response component to identify a minimally effective and maximally tolerated dose, and specifically characterize the incidence of mania/hypomania. Also of concern is the theoretical risk of elevating homocysteine levels in patients prone to hyperhomocysteinemia.

Patients inquiring about the use of SAMe for depression should be counseled about weak efficacy evidence, safety issues, the difference in doses used in trials and those recommended in product labeling, and its high cost. Patients should also be instructed to discuss the use of this dietary supplement with their primary health care (or mental health care) provider. *Grade B* ❖

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Echinacea purpurea and Treatment of the Common Cold

By Ginger Ertel and Cydney E. McQueen, PharmD

FORTY PERCENT OF TIME LOST FROM WORK EACH YEAR can be attributed to the common cold.[1] More than 600 million cases are reported annually, with the average person experiencing 2.4 colds per year. Currently, no FDA-approved antiviral treatment exists for the common cold and treatment is symptomatic only: decongestants, expectorants, antitussives, antipyretics, and analgesics. Patients are eager to try other options including echinacea, which is promoted as boosting the body's immune system to help fight bacterial and viral infections. In the United States alone, 1998 retail sales of echinacea totaled nearly $70 million.[2]

Clinical trials have used various preparations of three different *Echinacea* species: *E. purpurea*, *E. angustifolia*, and *E. pallida*. The German Commission E has approved only preparations of *E. pallida* root for "influenza-like infections," and *E. purpurea* herb as "supportive therapy for colds and chronic infections of the respiratory tract and lower urinary tract." The majority of trials, both for treatment and for prevention of colds and/or upper respiratory tract infections (URTIs), have used *E. purpurea*.

Because of possible differences in activities of the three species, this analysis will concentrate on the evidence for use of *E. purpurea* in acute treatment of the common cold.

History

Echinacea, or purple coneflower, is native to the United States and was used by American Indians as early as the 1600s for snakebites, for aches, as an antiseptic and analgesic, and for prophylaxis and treatment of the common cold. Echinacea was introduced into the *U.S. Materia Medica* in 1887. Widespread use of echinacea declined in the early 1930s with the development of antibiotics; however, it remained in the National Formulary until 1950.[3,4] Most scientific studies on echinacea have been conducted in the last 50 years by European investigators, primarily in Germany.

Pharmacology

Echinacea has many constituents: caffeic acid derivatives (cichoric acid), flavonoids, polysaccharides, alkylamides, and polyacetylenes.[4,5] Components vary between species and have various pharmacological effects. For example, polysaccharides stimulate macrophage activity: phagocytosis, enhanced T-cell binding and replication, and release of immune response modulating cytokines such as interferon, IL-1, IL-6, and TNF-α.[6] Cichoric acid increases phagocytosis both in vitro and in vivo. Despite some knowledge of component activity, the pharmacology of whole plant extracts is not well characterized due to lack of testing of whole extracts and great variability in composition of extracts. For example, those containing alcohol, or prepared with an alcohol extraction process, contain no polysaccharides or only negligible amounts. Cichoric acid will not be present in most prepared extracts, but may be present

in dried products. Increased phagocytosis in vivo has been demonstrated with some echinacea products, but the clinical relevance of many of these tests remains controversial.[7]

Mechanism of Action

Alteration in phagocytosis and cytokine levels have been extrapolated to explain the purported clinical effects of echinacea, but the actual mechanism of action, as with most herbal products, has not been definitively established.

Clinical Trials

Three randomized, double-blind, controlled trials (RDBCTs) of *E. purpurea* for treatment of the common cold or related viral URTIs have been published in the past 10 years.[1,8,9] All trials were conducted outside the United States. The trial by Braunig et al compared two doses of standardized *E. purpurea* radix (root) liquid extract (1:5, 55% EtOH) to placebo.[8] One hundred eighty patients 18-60 years old who had cold or flu-like symptoms for less than three days were randomized into one of three treatment groups: placebo, 450 mg/d of *E. purpurea* (2 droppersful), or 900 mg/d *E. purpurea* (4 droppersful), for a total of 10 days. Primary outcomes were decreases in duration of illness and patient-rated symptom scores. Patients were assessed on days 1, 3-4, and 8-10 for duration of illness, symptom scores, and clinical observations of physical symptoms. Patients in the 900 mg group showed a statistically significant ($P < 0.05$) reduction in symptom scores compared to placebo. Outcomes in the 450 mg dose group were similar to placebo. All treatment groups showed a statistically significant ($P < 0.0001$) decrease in symptom scores during the trial period.

The study has several limitations: Power was not calculated a priori, no demographic information was provided, and no information is included on patient compliance or the time of year the study took place. Study duration coincided with the time a cold may last with no treatment, so that results from day 3-4 assessments would be of more import than day 8-10 results. Also, some patients may have had bacterial infections rather than colds, as indicated by differing granulocyte and lymphocyte levels. *Level II, major limitations*

Hoheisel et al conducted a parallel group trial between December 1996 and March 1997 to determine the therapeutic effect of Echinagard™, a standardized extract from the squeezed sap of the fresh herb.[9] One hundred twenty patients were enrolled and randomized, and treatment was started at the first signs of a cold or URTI. Participants worked in a large furniture factory, had at least three respiratory tract infections in the past six months, and then presented with signs of an acute URTI. Those with signs of an URTI the week prior to the study were excluded. Patients were instructed to take 20 drops of medication every two hours on day 1, then three times a day for a total of 10 days. Placebo and active treatment were identical. Outcome measures included daily patient-ranked and recorded subjective symptoms and a questionnaire administered by the physician at the end of the trial. At the onset of symptoms, 60% of patients receiving Echinagard did not develop fully expressed cold symptoms, as compared to 40% of patients taking placebo ($P = 0.044$). This subgroup of patients was further analyzed; Echinagard patients had a 50% greater reduction in symptoms and duration of illness than the placebo group ($P = 0.0001$).

A priori power calculations indicated the need for 48 patients per group; this was exceeded for the initial period of assessing the number of patients who presented with symptoms and then developed definite illness, but was not met for the secondary analysis for time to improvement—a major limitation. Intensity of symptoms was stated not to vary between groups, but no supportive data were provided. There was no discussion of patient compliance issues or concomitant medication use, which might easily have affected symptom ratings. *Level I for the development of full illness portion; Level II for time to improvement portion; major limitations for both*

In the largest trial, Brinkborn et al attempted to determine efficacy and safety of different doses and preparations of *E. purpurea* in 246 patients with common cold.[1] Patients with chronic diseases, serious non-related illnesses, or on medications that might affect the disease state were excluded. The trial was conducted between November 1996 and May 1997 with an active treatment duration of seven days. Patients were randomized to one of four treatment groups: placebo, Echinaforce™ (6.7 mg *E. purpurea* crude extract, 95% herb, 5% root), Echinaforce™ concentrate (48.27 mg *E. purpurea* crude extract, 95% herb, 5% root), and *E. purpurea* extract (29.60 mg crude extract of root). Patients were instructed to take two tablets of the assigned medication three times a day immediately after onset of cold symptoms and until they felt healthy again, but for no longer than seven days. They were to see the investigator on the first or second day after beginning treatment and again on the day they felt healthy or the seventh day. Patients recorded symptoms in a daily diary. The primary endpoint was a relative reduction in the complaint index as defined by 12 symptoms according to the doctor's record. Secondary endpoints included a relative reduction of the

complaint index according to the patient's diary, assessments of efficacy and tolerance by both investigator and patient, and frequency and severity of adverse events. Reductions in the complaint index per the doctor from day 1-2 to day 5-7 were 64.3%, 62.7%, 44.8%, and 29.3% for the Echinaforce concentrate, Echinaforce, *E. purpurea* extract, and placebo groups, respectively. Reductions in the complaint index per the patients' records were 55.9%, 50.6%, 35.2%, and 37.0%, respectively. Differences for the Echinaforce concentrate and Echinaforce groups were statistically significant in both per protocol and intent-to-treat analyses.

There was no discussion regarding interrater reliability of the investigators who scored the patients' symptoms during the first and final visits. *Level I, minor limitations*

Adverse Events

Mild gastrointestinal side effects are occasionally associated with *E. purpurea*, but side effects were similar to placebo in most of the clinical trials. Overall, echinacea is well tolerated.

Contraindications

A contraindication is often stated for patients taking immunosuppressive agents or with HIV/AIDS, collagen vascular disease, leukemia, multiple sclerosis, or other autoimmune-type diseases.[3,13,14] This theoretical contraindication is presumably based upon the polysaccharide component's action in increasing T-cell activity. This warning may not be warranted due to the lack of polysaccharides in the majority of commercially available products.[8]

Allergic reactions (rash, dyspnea, urticaria, and anaphylaxis)[10] have been rarely reported and there is controversy as to whether allergy to other members of the daisy (*Asteraceae*) plant family should be considered a contraindication.[11] Toxicity studies in rats and mice were unable to induce acute or chronic (4 weeks) toxic responses at doses of 15 and 30 g/kg, respectively.[12] Nonetheless, patients with severe allergy to the daisy plant family (chamomile, chrysanthemum, feverfew, and ragweed), should avoid echinacea products.

Pregnancy and Lactation

Echinacea should be avoided in women who are pregnant or breast feeding due to lack of information regarding safety in this population.[13,15]

Interactions

There are no known drug interactions.[15]

Formulations/Dosage

Formulations of *E. purpurea* include fresh and dried herbs, tinctures, extracts, standardized extracts, capsules, and tablets. The Braunig and Brinkeborn trials are the only ones to attempt to obtain dose-response information. Recommended doses based on clinical data are 900 mg/d of Echinagard and Echinacin™ brand extracts, 48.27 mg/d Echinaforce concentrate, or 6-9 ml/d *E. purpurea* pressed juice.[14] Historically recommended doses include: tincture, 0.75-2.5 ml (15-30 drops) two to five times daily or 60 drops tid;[16] capsules containing powdered whole herb, 900 mg to 1 g tid; and tea (2 teaspoons [4 g] of coarsely powdered herb simmered in 1 cup of boiling water for 10 minutes) three to five times daily.[15]

Evidence on use in the pediatric or geriatric populations is not adequate to reliably recommend dosing for treatment of the common cold. Clinical trials in children have not evaluated use of echinacea for this purpose.[17,18] They have, however, demonstrated safety.

Evidence on long-term safety and efficacy of *E. purpurea* is lacking. The idea that long-term use of echinacea will result in suppression rather than stimulation of the immune system is probably false, and there is some minimal evidence that benefit may continue.[11]

Conclusion

The three clinical trials analyzed above have provided evidence that when started at the onset of symptoms of the common cold, *E. purpurea* can reduce the symptoms and decrease the length of illness. It has been shown to be safe and well tolerated with minimal adverse reactions.

Recommendation

Based on the available evidence, the absence of severe adverse effects, and the limited conventional treatment options, *E. purpurea* extract can be responsibly offered as a complementary treatment for the common cold. However, not all *E. purpurea* preparations can be recommended with confidence due to differences in formulation and lack of information from formal dose-response trials.

Those patients who wish to treat cold symptoms with *E. purpurea* should start treatment at the first signs and symptoms of infections. Patients who worsen or have severe symptoms remaining after an 8- to 10-day treatment period should be seen by their primary health care provider.

Larger clinical trials are needed to determine which types of products have the greatest clinical benefit. Until then, it would seem prudent to limit recommendations to

those products that have shown efficacy in the clinical trials. *Grade B* ❖

Ms. Ertel is a doctoral candidate at the University of Missouri-Kansas City School of Pharmacy.

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Literature Briefs

Analysis by Cydney E. McQueen, PharmD

Tocotrienol Effects on Serum Lipids and Platelet Aggregation

Source: Mensink RP, et al. A vitamin E concentrate rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid concentrations. *Am J Clin Nutr* 1999;69:213-219.

Objective: To examine effects of tocotrienols on serum lipoproteins and platelet function in men with mildly elevated serum total cholesterol or lipoprotein(a) [Lp(a)] concentrations.

Design and Setting: A randomized, double-blind, controlled trial (RDBCT) conducted at the Human Biology Department of Maastricht University in Maastricht, Netherlands.

Subjects: Forty males with total cholesterol levels between 251 and 309 mg/dL, no history of cardiovascular disease, and on no medications known to interfere with lipids or platelet function.

Treatment: Capsules containing 40 mg tocotrienols with 240 mg palm olein (40% palmitic acid, 4% stearic acid, 43% oleic acid, 11% linoleic acid) and 20 mg (22 IU) dL-α-tocopherol vs. placebo capsules of 280 mg palm olein and 20 mg dL-α-tocopherol.

Dose/Duration: 160 mg/day tocotrienols or placebo for six weeks.

Outcome Measures: Changes in total cholesterol, LDL, HDL, triacylglycerol, and Lp(a) concentrations, and in vitro platelet function measures of aggregation velocity, maximum aggregation, TxB2 production, and ATP release, as well as urinary thromboxane metabolites.

Results: No significant differences between groups were found for changes in total cholesterol, LDL, HDL, triacylglycerol, or Lp(a) concentrations (P values = 0.9, 0.33, 0.5, 0.16, and 0.81, respectively). After adjusting statistically for baseline differences in platelet aggregation velocity and maximum aggregation, no significant difference between groups was found for these or for TxB2 formation. ATP release rate and

maximum ATP release were significantly decreased in the treatment group (P = 0.042 and 0.024, respectively). Urinary thromboxane metabolites increased and decreased slightly in treatment and placebo groups respectively, but changes were not significantly different between groups.

Strengths/Limitations: Differences between groups after randomization were found for baseline platelet aggregation velocity and maximum aggregation as well as caloric (but not nutrient) intake. It is unclear whether an a priori power calculation was actually performed. The dose of tocotrienols was low compared to other studies demonstrating positive results. Although the authors concluded that tocotrienol supplementation is not beneficial to "subjects at risk of cardiovascular disease," no information was provided about the study population in regard to any CVD risk factors other than the range of total serum cholesterol.

Level of Evidence: Level II, several major limitations.

Comments: Although the "placebo" and treatment capsules both contained other components (linoleic acid, palmitic acid) known to affect lipids and thromboxane synthesis, differences observed should be attributable to the tocotrienol. Sample size needed to meet power was unclear; because no differences were found between groups for most outcomes, there is a possibility of a Type II statistical error—not detecting a difference when one exists. Despite the negative results, due to dose and power limitations, a larger study is needed to confirm lack of benefit before a firm conclusion can be reached. This is especially important in light of the observed increase in ATP release rate and maximum release, which entertains possibilities of benefit at higher doses.

Clinical Impact: Because tocotrienol-enriched vitamin E is more expensive and does not appear to provide additional beneficial effects, it is recommended that patients wishing to supplement use plain vitamin E until more data are available. ❖

Garcinia cambogia for Weight Loss

Source: Heymsfield SB, et al. *Garcinia cambogia* (hydroxycitric acid) as a potential antiobesity agent: A randomized controlled trial. *JAMA* 1998;280:1596-1600.

Objective: To examine effectiveness of *Garcinia cambogia* (50% hydroxycitric acid, a citrate cleavage enzyme inhibitor) extract for weight loss and fat mass reduction.

Design and Setting: A RDBCT conducted at the Obesity Research Center at St. Luke's-Roosevelt Hospital, Columbia University, New York, NY.

Subjects: One hundred thirty-five subjects (M=19, F=116) with a body mass index of 27-38 kg/m^2, who had not dieted with weight loss in the past six months.

Treatment: A high-fiber, 1,200 Kcal/d diet plus either *G. cambogia* extract or placebo.

Dose/Duration: 3,000 mg/d *G. cambogia* extract in three divided doses 30 minutes before meals for 12 weeks.

Outcome Measures: Body weight change and change in fat mass measured by pencil-beam dual-energy x-ray absorptiometry (DXA) scanner.

Results: There was no significant difference in mean weight loss between treatment and placebo groups (4.1 kg vs. 3.2 kg, respectively, P = 0.14). Mean percentage of fat mass loss for each group (2.16% in the placebo group vs. 1.44% in the treatment group, P = 0.21) also did not differ significantly when tested with analysis of covariance for age, sex, and pretest percentage of fat mass. Several secondary analyses were performed and the authors stated that all findings were consistent with the primary analysis.

Strengths/Limitations: This well-designed trial had very thorough statistical analyses and met power. The treatment dose was at the extreme low end of a previously determined dose-response curve. Treatment and placebo groups had a significant difference after randomization in regard to total body fat mass of men (2.6% vs. 5.9%, respectively). Because of various mechanical problems, several patients' DXA readings were estimated on the basis of other measurements. In addition, medication compliance was monitored, however, dietary compliance was not.

Level of Evidence: Level I, several major limitations.

Comments: Subjects were asked to "maintain a stable physical activity level" throughout the trial, but no information was provided about exercise or activity levels of the groups. Although the investigators did adequately address problems found in earlier studies, other procedural concerns are evident. Lack of monitoring of dietary compliance gives rise to the possibility of great differences between the groups and is a serious limitation, as is the low dose used.

Clinical Impact: At this time, *G. cambogia* extract is not recommended as an aid to weight loss due to lack of documented efficacy. A larger, rigorously designed trial using a higher dose needs to be performed to either confirm lack of efficacy or characterize any possible benefit. ❖

In Future Issues:

St. John's Wort for Depression
Are Natural Vitamins Better?
Glucosamine Sulfate and Osteoarthritis

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Applying Evidence-Based Medicine to Dietary Supplements

By Patrick J. Bryant, PharmD

DECISIONS MADE STRICTLY ON PERSONAL EXPERIENCE, INSTEAD OF EVIDENCE FROM WELL-controlled, randomized trials with adequate sample size, often overestimate the efficacy and underestimate the safety risks associated with drugs.[1] In order to more accurately estimate safety and efficacy, evidence-based medicine (EBM) is experiencing increased use in conventional medicine practice. It is our intent to bring to you this same rigorous critical evaluation of the dietary supplement literature through this publication.

By applying only information supported with sound evidence in the literature, we ensure that the knowledge we act on and pass onto our patients/customers, in addition to other health care practitioners, is valid and accurate. EBM concepts are especially important in the study of dietary supplement information since, unlike prescription medications, dietary supplements are not required to undergo review and approval by the FDA. The studies conducted on the safety and efficacy of dietary supplements are never critically evaluated by FDA reviewers and scientific experts on the FDA Advisory Panel. With an EBM review of the available information on a specific dietary supplement, you can at least be assured that some critical evaluation regarding efficacy and safety has occurred.

The EBM Process

Various processes exist to conduct an EBM review. We will use a process originally described by Cook and Guyett[2] that we have modified to simplify application to clinical practice. This process involves the following steps.

Step 1: Identify, retrieve and, if necessary, translate into English the body of scientific literature associated with a particular dietary supplement.

Step 2: Perform a standardized, disciplined, and rigorous critical evaluation of those clinical studies that have the best design and largest sample sizes. This evaluation is performed in an identical manner for each EBM review using a standardized checklist of characteristics required for a scientifically sound study.

Step 3: Identify the major limitations of each trial from the critical evaluation. The key considerations may be major strengths or limitations, and include: dosage, length of study, power, sample size, inclusion criteria, blinding, randomization, evaluation measurements, appropriate statistical tests, and conclusions.

Step 4: Assign a Level of Evidence rating to each trial based on the critical evaluation and identified limitations. (*See Figure 1.)* The term "clinical impact," as used in the rating, takes into account not only the statistical power of the trial, but the sample size and the amount of patient exposure for the disease state. For example, a trial of a treatment for common cold symptoms that includes 100 patients may meet statistical power and be considered to have a

fair sample size, yet has low clinical impact because 100 patients is a small percentage of the millions of patients who suffer common cold symptoms each year. Conversely, a trial in 50 patients with a disease that occurs in only 5,000 patients per year might be a high clinical impact study. There are no hard-and-fast rules about the numbers for determination of clinical impact; much depends on professional judgment.

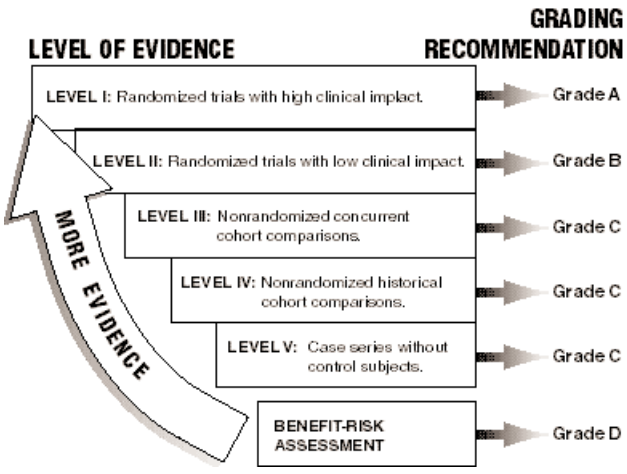
Step 5: In situations where very little published scientific literature exists on a dietary supplement, a Benefit-Risk Assessment will be conducted. This assessment process is identical to that used when this issue exists with prescription drugs. The available data first will be reviewed to assess safety. Any known or possible benefits to the patient will then be weighed against the known or possible risks determined from the safety evaluation.

Product safety information to be considered in this situation will include purity, formulation standardization, known pharmacological effects, and known or theorized adverse events. Patient considerations also factor into this assessment, such as the severity, duration, or self-limiting nature of the disease or condition for which the product is to be used, origin of diagnosis (by health care practitioner or self-diagnosis), concomitant disease states, and concomitant prescription or OTC medications. In addition, the likelihood of harm if treatment with the supplement does not aid the condition, masks another condition, or prevents the patient from seeing a health care practitioner will be considered.

Step 6: Develop recommendation for use of the particular dietary supplement and assign a Grade of Recommendation based on the Level of Evidence which helps the reader determine the strength of the conclusion based on the available evidence in the literature.

Figure 1

Level of evidence and grading recommendation



The Goal of EBM

The goal of this EBM evaluation is to provide an objective assessment of the efficacy and safety of a dietary supplement, taking into account the strength of the evidence used. From this assessment, a recommendation will be developed taking into consideration the use of the dietary supplement in the clinical setting.

How to Use EBM Reviews

There is a tremendous amount of information available on the more commonly used dietary supplements. The primary problem is that much of that information is anecdotal or has little to no scientific support. Utilizing that information to make clinical decisions on therapeutic plans, educate or consult health care practitioners, and counsel patients/customers is difficult, if not impossible. Use of an EBM review allows all health care practitioners to begin the decision-making process at the same level of knowledge. From there, other factors to the decision-making process depend on what is to be accomplished. It is important to add a clinical perspective to the formula as well as to understand the needs and beliefs of the consumer, especially if the goal is to incorporate this knowledge into an acceptable plan for an individual patient.

Key to all this is the understanding that, unlike prescription medications, the pharmacist and physician are not the "gatekeepers" in providing dietary supplements to the consumer; the consumer is the "gatekeeper." The physician is usually even further removed from the situation than the pharmacist. In some situations, the pharmacist is at least present at the point of sale and can influence the consumer's purchase of the dietary supplement. The pharmacist must handle this responsibility much the same way as with OTC medications and therefore must be knowledgeable about the objective scientific evidence that exists for various dietary supplements. It is our hope and goal that the EBM reviews in this newsletter will assist pharmacists and other health care providers in acquiring that necessary knowledge. ❖

References

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