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5-Hydroxytryptophan (5-HTP) for Treatment of Depression

By Teresa Klepser, PharmD, and Nicole Nisly, MD

SEVENTEEN PERCENT OF AMERICANS HAVE A MAJOR DEPRESSIVE disorder in their lifetime. More than 10% have had an episode within the past 12 months.[1] Females have two or three times the prevalence as males, and adults 25-44 years have the highest prevalence. Between 10-20% of institutionalized patients have depression.

These objective data have lead to the widespread use of antidepressants, some of which enhance neurotransmission. Although prescription medications may provide some symptomatic relief, many are associated with a list of unwanted side effects and drug interactions.

Several dietary supplements have been suggested for use in the management of depression. St. John's wort, S-adenosylmethionine (SAMe), tyrosine, 5-hydroxytryptophan (5-HTP), and ginkgo are among them. This review will focus on 5-HTP, a dietary supplement manufactured from the seeds of the African plant *Griffonia simplicifolia*,[2] metabolized to serotonin, and touted to enhance neurotransmission and alleviate depression.

Pathophysiology of Depression

Most theories suggest an insufficiency of brain monoamine neurotransmitters such as norepinephrine (NE), serotonin, and dopamine. The biogenic amine hypothesis suggests that depression is caused by an inadequate monoamine neurotransmission. The permissive hypothesis suggests that decreased levels of serotonin allow depression to occur and that decreased levels of NE actually cause depression. The dysregulation hypothesis emphasizes a dysregulation of homeostasis of neurotransmitters, instead of an increase and decrease in the neurotransmitters' activities. The role of dopamine in depression is unclear but may be indirectly involved in antidepressant activity.

Indications

People use 5-HTP to aid in the treatment of depression, fibromyalgia, insomnia, binge-eating associated with obesity, attention deficit disorder, and chronic headaches.[3] 5-HTP has an orphan

INSIDE

drug indication for the treatment of post-anoxic myoclonus, also known as Lance-Adams' syndrome, a rare complication of successful cardiopulmonary resuscitation. The syndrome is clonic movement secondary to the hypoxia. There is some clinical evidence to support the use of 5-HTP in the treatment of anxiety, obesity, fibromyalgia, cerebellar ataxia, palatal myoclonus, segmental myoclonus, Ramsay-Hunt syndrome, and tardive dyskinesia.[4]

Pharmacokinetics

5-HTP is absorbed in the small intestine and peak concentrations are noted within one to two hours following oral administration. Following ingestion, 5-HTP easily crosses the blood-brain barrier and enters the central nervous system. The half-life of 5-HTP is approximately four hours so steady state will be reached within one day. 5-HTP has a shorter half-life than prescription antidepressants, such as fluoxetine (Prozac®) two to three days, sertraline (Zoloft®) one day, paroxetine (Paxil®) 21 hours, and amitriptyline (Elavil®) 15 hours. Therefore, patients may see a response sooner with 5-HTP than with prescription antidepressants. Approximately 25% of the administered drug is eliminated by first-pass metabolism. The major metabolite is serotonin.[5]

In some studies, researchers administered a decarboxylase inhibitor (carbidopa or benzerazide) with 5-HTP to prevent the conversion of 5-HTP to serotonin in the gut and other peripheral organs. Such a combination allows more 5-HTP to be converted to serotonin in the brain.[5]

Mechanism of Action

5-HTP is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of serotonin. The rate-limiting step in the synthesis of serotonin is the conversion of L-tryptophan into 5-HTP by the enzyme tryptophan hydroxylase. To make more serotonin, it is more efficient to supply 5-HTP than to supply tryptophan (conversion rate 70% vs. 1-3%), because the body uses a large percentage of dietary L-tryptophan to make other compounds, such as kynurenine and vitamin B_3.[4] These differences make dietary 5-HTP more efficient than L-tryptophan at increasing serotonin levels in the brain. Serotonin has been shown to be involved in the regulation of sleep, depression, anxiety, aggression, appetite, temperature, sexual behavior, and pain sensation.[3]

Clinical Studies

In the 1970s and early 1980s, studies showed 5-HTP to be more effective than placebo in managing patients with depression. Several small studies also have compared 5-HTP to standard antidepressants.

Angst et al conducted two open dose-finding studies with L-5-HTP in combination with benzerazide, and a double-blind trial comparing L-5-HTP plus benzerazide vs. imipramine in 30 patients with depression.[6] In the double-blind trial, patients received either a mean dose of 800 mg L-5-HTP and 375 mg benzerazide or 150 mg imipramine daily for 20 days. Endpoints included Hamilton Rating Scale for Depression (HRDS), the AMP-system (scale 5 = somatic-depressive syndrome; scale 8 = retarded-depressive syndrome; scale 11 = automonic syndrome; scale 12 = neurological syndrome), a Global Rating Scale of Severity of Depression, and a Brief Rating Scale for the Behavior on the ward. The AMP-system and HRDS showed no significant difference in efficacy between L-5-HTP and imipramine in the double-blind trial. L-5-HTP caused mainly gastrointestinal side effects; imipramine caused mainly dryness of the mouth and tremor that seemed to be dose dependent.

A randomized, double-blind, double-dummy, multicenter Swiss study evaluated 63 subjects with major depression.[7] Each received either 100 mg 5-HTP (oxitiptan, Triptum) or 50 mg fluvoxamine tid for six weeks. Endpoints included the HRDS, a self-assessment scale, the Clinical Global Impression (CGI), and adverse events. Equal benefit was found between 5-HTP and fluvoxamine. 5-HTP was slightly more effective at reducing

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depressed mood, anxiety, physical symptoms, and insomnia, but the differences were not statistically significant. 5-HTP caused fewer and less severe side effects with the most common complaint being mild digestive distress.

Although 5-HTP may be beneficial when given in combination with a monoamine oxidase inhibitor (MAOI) to patients who are unresponsive to MAOI therapy alone,[8] this strategy is not endorsed universally. Nolen et al compared L-5-HTP to tranylcypromine, a MAOI, in a controlled, open, crossover study to evaluate the treatment of depression that was resistant to serotonin reuptake inhibition.[9] Fifteen of the 26 patients responded to tranylcypromine, whereas none of the 17 patients responded to L-5-HTP.

Nardini et al evaluated the combination of L-5-HTP and a tricyclic antidepressant (chlorimipramine) in 26 depressed inpatients in Italy.[10] Patients were randomized to receive 300 mg/d L-5-HTP or placebo for one month. Each patient also received 50 mg/d chlorimipramine. Endpoints included the HRDS, Zung's Depression Status Inventory (ZDSI), and CGI. HRDS scores in both groups improved during the month; however, the combination group had a greater improvement (no P value given). For the ZDSI, the improvement in patients with endogenous depression receiving combination therapy was statistically significant. As for the CGI, 12 of the patients receiving combination therapy had marked or fair improvement, whereas seven patients receiving chlorimipramine had marked or fair improvement.

Van Praag et al evaluated the effectiveness of preventing relapse of depression when 5-HTP was used prophylactically after a therapeutic course of a tricyclic antidepressant.[11] Twenty patients were treated for depression with clomipramine for three to six months. Three to four weeks after clomipramine was discontinued, patients were randomized to receive either 200 mg/d 5-HTP plus 150 mg/d carbidopa, or placebo. The relapse rate for 5-HTP was statistically significantly lower on the HRDS.

Unfortunately, many of these generally positive studies have limitations, including small sample sizes, short durations of therapy, open-label trials, no placebo arm, poor definition of depression, and inclusion of patients with bipolar depression. Also, studies used either 5-HTP or L-5-HTP, and it is unknown whether there is a therapeutic difference between 5-HTP and L-5-HTP.

Adverse Effects

The most common side effects associated with 5-HTP are dose-related and include nausea, vomiting, diarrhea, and anorexia. Reported central nervous side effects include euphoria, hypomania, restlessness, rapid speech, anxiety, insomnia, aggressiveness, and agitation. These symptoms resolved upon discontinuation of 5-HTP.

Regulation

The U.S. Food and Drug Administration (FDA) in 1998 issued a statement confirming the presence of impurities in some 5-HTP products currently marketed as dietary supplements.[12] One of the impurities, known as "Peak X," has been associated with more than 1,500 cases of eosinophilia-myalgia syndrome, including 38 deaths in 1991. Eosinophilia-myalgia syndrome is a serious systemic illness associated with increased eosinophils and severe muscle pain. More than 95% of these cases were traced to L-tryptophan supplied by Showa Denko K.K. of Japan. However, the FDA could not conclude that other brands of L-tryptophan were not a cause or contributor to eosinophilia-myalgia syndrome. As a result, tryptophan supplements were pulled off the market. There is at least one case of eosinophilia-myalgia syndrome with 5-HTP. However, based on this, it is difficult to establish a link between eosinophilia-myalgia syndrome and 5-HTP. At this time, the FDA encourages health care practititioners to report adverse events to FDA's MedWatch program by phone (1-800-FDA-1088), fax (1-800-FDA-0178), or mail (FDA, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787).

Which of the following is a reported side effect of 5-HTP?

a. Sedation
b. Hiccups
c. Anxiety
d. Blurry vision
e. Hypertension

Contraindications and Precautions

According to one report, 5-HTP may cause seizures in children with Down syndrome.[2] Although safety in children has not been proven, children have been given 5-HTP in studies without any apparent harmful effects.[2] Safety in pregnant or nursing women and those with liver or kidney disease has not been established.[2] Patients who have peptic ulcer disease, platelet disorders, and/or renal disease should not take 5-HTP, mainly because tryptophan has been associated with scleroderma, autoimmune thrombocytopenia, and eosinophilia-myalgia syndrome.[5] Since 5-HTP is eliminated renally, patients who have renal disease should not take 5-HTP. These cautions are based on in vitro and animal data.

Drug Interactions

Concurrent use of 5-HTP with MAOIs or reserpine is not recommended since the combination may increase the risk of hypertensive reactions. The latter agents should be discontinued for at least two weeks before 5-HTP is initiated. Some studies, however, have demon-

strated additional benefit when the combination of tryptophan and a MAOI was used.[13] Tricyclic antidepressants, serotonin reuptake inhibitors, and the pain medication tramodol should be discontinued before 5-HTP initiation, as these drugs raise serotonin levels, and dangerously, may induce serotonin syndrome.[2] Methysergide, cyproheptadine, and other serotonin receptor agonists may decrease the therapeutic effects of 5-HTP.[5]

Another safety issue with 5-HTP involves an interaction with carbidopa, used for Parkinson's disease. Several reports suggest that the combination can create skin changes similar to those that occur in scleroderma.[2]

Dosage and Formulation

The usual starting dose of 5-HTP for the orphan drug indication of treating post-anoxic myoclonus is 25 mg qid; this may be increased by 100 mg/d every three to five days to reach a dose between 600 and 1,000 mg/d.[5] An orphan product that has been approved for marketing is available through the normal pharmaceutical supply channels. Some health insurers will pay the cost of orphan products that have been approved for marketing.

A recommended dose of 5-HTP in the management of depression has not been determined. The doses used in clinical studies have ranged from 150-300 mg/d[14] to 100-200 mg tid.[2] Some studies administer a decarboxylase inhibitor, such as carbidopa, in addition to 5-HTP to prevent peripheral conversion of 5-HTP. Carbidopa usually is given as 150 mg/d. Patients may see some response during the first week of use.

Conclusion

5-HTP has been studied for treating depression. Clinical data to support its use for this indication are positive, but flawed. Side effects appear to be rare as long as the product does not contain "Peak X," an impurity that has been associated with eosinophilia-myalgia syndrome. Unfortunately, 5-HTP as a dietary supplement is not regulated by the FDA, so there is no guaranteed quality.

Recommendation

At this time, 5-HTP may be considered an option for the treatment of depression. However, patients who have peptic ulcer disease, platelet disorders, and/or renal disease should not take 5-HTP. 5-HTP should not be taken with other antidepressants or serotonin receptor agonists. Patients should be aware of the possibility of 5-HTP products containing impurities. ❖

Which of the following drugs may interact with 5-HTP?

a. Paroxetine
b. Metoprolol
c. Medroxyprogesterone
d. Penicillin
e. Atorvastatin

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Cellasene™ and Endermologie® for Cellulite

By Susan T. Marcolina, MD

EIGHTY-FIVE PERCENT OF POST-PUBERTAL FEMALES HAVE cellulite, a condition characterized by irregular dimpled tissue on the upper outer thighs, lower buttocks, and posterior upper thighs. This dimpling, also known as the "mattress phenomenon" was found by Nurnberger and Muller to be demonstrable in the lateral thigh skin in almost all women using the pinch test. They defined the pinch test as tangentially applied pressure to the skin of the buttocks and lateral thigh. The authors staged cellulite according to pinch test results.[1] (*See Table 1.*)

By Madison Avenue aesthetics, cellulite is unattractive. Hence, women's magazines abound with articles and advertisements featuring products and therapies that will eliminate cellulite. These therapies generally have little scientific validation and are costly, though Endermologie® may have some effectiveness.

Clinical Histopathology of Cellulite

Studies by Nurnberger and Muller, published in 1978, showed a sexual dimorphism in the subcutaneous and connective tissue structure of the thigh. Such differences are demonstrable in fetal skin after the eighth month of gestation and coincide with the time the fetal testicles become hormonally active.[2] Rosenbaum et al recently verified these gender-specific differences and examined affected and unaffected areas of thigh in healthy adult volunteers. The authors found no evidence of differences in adipose tissue physiology, blood flow, or biochemistry to account for the anatomic phenomenon of cellulite.[3]

Etiology

Although cellulite is not related to obesity, excess weight accentuates the condition.[4] The dermis is thinner in females than in males and reaches maximal thickness by age 30 with subsequent diminution. With the aging process, the septa of connective tissue between the adipocytes become thinner, the adipocytes hypertrophy, and fat appears within the dermis.[1]

Cellasene and Endermologie Therapies

Italian chemist Dr. Gianfranco Merizzi introduced his invention, Cellasene™, at a Manhattan press conference in March 1999 as the new cure for cellulite. Cellasene is manufactured in Italy by Medestea Internationale and is distributed in the United States by Rexall Sundown.[5]

LPG Endermologie is a patented machine-assisted massage system developed in France in the 1970s by Louis Paul Guitay. He invented this device for use in remodeling and loosening scar tissue in burn and trauma patients. In the course of its use, physicians noted the improvement in the appearance of cellulite. LPG Endermologie USA (Fort Lauderdale, FL) markets two units, the original Endermologie System 1 and the new Cellu M6®, which offers pulsatile suction and the ability to program and store information about individual treatments.[6,7]

Endermologie Procedure

LPG Endermologie involves kneading the skin with an electrically powered, hand-held machine containing two rollers. As the rollers exert positive pressure to massage the skin between them, negative pressure from the suction lifts up the skin fold bringing it between the rollers.[8] A technician moves the machine over the hips, stomach, legs, and buttocks, which are covered with a nylon stocking to decrease friction and prevent direct skin contact.

Clinical Trials—Cellasene

Medestea Internationale sponsored two clinical studies in Italy.[9] The first was an open-label trial performed on 25 healthy female volunteers with a mean age of 38. Circumferential hip, right thigh, and right ankle measurements were taken by tape measure before and after receiving one Cellasene softgel tid for eight weeks.

The data showed that all the women had a reduction in their anthropometric measurements. The ultrasonographic estimates of subdermal thickness also were reduced compared to baseline.

In the second study, a single-blind, placebo-controlled

Table 1
Staging categories of cellulite

Stage	Characteristics of Thigh and Buttock Skin
0	Smooth skin when standing or lying; negative pinch test
I	Smooth skin standing or lying with positive pinch test demonstrating mattress phenomenon
II	Positive mattress phenomenon spontaneously when standing
III	Mattress phenomenon spontaneously positive in sitting and lying positions

Adapted from: Nurnberger F, Muller G. So-called cellulite: An invented disease. *J Dermatol Surg Oncol* 1978;4:221-229.

trial, 25 women (mean age 30.9 years) in the treatment group and 15 women (mean age 33.9 years) in the placebo group had the same measurements taken as in the first study. All subjects completed the trial. Diet and physical activity remained constant during both trials. The Cellasene treatment group showed a reduction in hip and thigh circumference and ultrasound measurements showed a slight reduction in subdermal thickness after eight weeks. Neither study was published in a peer-reviewed journal. Problems with the studies include the lack of blinding of the investigators, limitations of reproducibility with tape measurement, and lack of either study evaluating the changes in cellulite appearance.

Lis-Balchin performed a parallel, placebo-controlled, two-month clinical study of Cellasene in 21 women. Seven of the 11 treatment subjects gained weight, as did eight placebo subjects. Only three of the women in the Cellasene group had improvement in cellulite appearance vs. two in the placebo group.[10]

Rexall Sundown and Medestea Internationale sponsored a 20-week, double-blind, placebo-controlled clinical study of 200 women at the University of Miami; this study concluded in February 2000. The university released a statement that the results were inconclusive "due to subject nonadherence with and significant deviations from the protocol requirements."[11]

Clinical Trials—Endermologie

In an open-label clinical pilot study, Ersek studied 22 women between the ages of 22-48.[12] Each study patient was prescribed 14 LPG Endermologie sessions (45 min each) once or twice per week with a trained LPG technician. Measurements of the circumference of waist, hips, thighs, knees, and calves for each patient were taken and averaged into a mean. Patients' weights also were recorded. Identical weight and circumference measurements were collected for each patient at sessions 1, 7, and 14. A mean body circumference loss was determined for each of the five parameters measured above. These parameters were averaged into a mean index of overall loss.

The 22 patients in this study completing at least seven treatments experienced a mean index of overall loss of 1.38 cm. Of these 22 patients, 19 exhibited a weight loss of 0.612 kg during this time period, while two showed a mean weight gain of 0.655 kg. Despite the weight gain, they still had a mean index of overall loss in body circumference of 1.15 cm.

For the six patients completing all 14 Endermologie treatments, their mean index of overall loss was 2.84 cm with an average weight loss of 0.321 kg.[12]

Chang et al continued this study using 85 patients, 46 of whom completed at least seven sessions while 39 completed all 14 sessions. Although the study results varied widely, a general correlation was noted between body circumference loss and weight loss for patients who completed seven and 14 sessions, with greater improvement seen in those completing the 14-treatment course.[8]

Dabb used Endermologie for the reduction of cellulite in 24 small-volume liposuction patients treated over a two-year period. Each patient had a medical evaluation and participated in an exercise and nutrition program. Each had one or more sessions of small volume liposuction, followed by a series of Endermologie treatments limited to the area involved in the liposuction. Periodic body composition analyses assessed compliance with diet and exercise regimens.

Of the 24 patients who completed the study, 22 patients reported satisfaction with attainment of treatment goals. The two patient treatment failures gained weight and were noncompliant with their original dietary and exercise regimens.[13]

Table 2
Herbal ingredients of Cellasene

Herbal Ingredients	Botanical Name	Portion of Plant Used
Borage seed oil	*Borago officinalis*	Seeds
Bladderwrack	*Fucus vesiculosis*	Thallus
Sweet clover extract	*Melilotus officinalis*	Leaves and flowering tips
Ginkgo biloba extract	*Ginkgo biloba*	Leaves
Grape seed extract	*Vitis vinifera*	Seeds
Soya lecithin	*Glycine max*	Seeds

Adapted from: Cellasene. Available at: www.cellasene.com/pages/product.htm. Accessed July 14, 2000.

Formulation

Cellasene features what Medestea terms Lipovascolen™, a proprietary blend of natural herbal extracts, each listed in Table 2.

Dosage

The manufacturer recommends taking three Cellasene softgels per day for eight weeks followed by one softgel daily for another eight weeks.[14] A minimum of 14 Endermologie sessions (35 min each, once or twice weekly) is recommended, followed by once monthly maintenance sessions.[6,8,12]

Adverse Effects

Cellasene is marketed as a food supplement so there is

limited information about the proportions of component herbs it contains. Each softgel contains 240 µg of iodine, derived from bladderwrack (*Fucus vesiculosis*) extract.

The German Commission E bladderwrack monograph specifies that ingestion of an iodine dosage over 150 µg/d may induce latent hyperthyroidism or exacerbate existing hyperthyroidism.[15] Bladderwrack has been reported to accumulate cadmium and lead in various plant parts because of heavy metal content of seawater. Conz et al reported the case of an 18-year-old who consumed a product containing *Fucus vesiculosis* for weight loss and presented with acute renal failure, which resolved within one year after discontinuation of this product.[16]

The coumarin derivatives in sweet clover extract can potentiate the effects of warfarin anticoagulants and should not be used in patients on this medication. *Ginkgo biloba* also has anticoagulant effects as its ginkgolide components are potent inhibitors of platelet-activating factor.[17]

The results and experiences of Endermologie treatment for patients are technician dependent. If the vacuum pressure exerted with the device is too great, petechiae, ecchymoses, and pain can result.[18]

Cost

Cellasene retails for approximately $40 for a two-week supply.[14] Each 35- to 45-minute Endermologie session costs between $80-$100.[12]

Regulation

Cellasene is marketed as an over-the-counter dietary supplement. In July 2000, the Federal Trade Commission (FTC) filed a lawsuit in federal district court charging Rexall Sundown, Inc. with making false and unsubstantiated claims in marketing Cellasene.[19] The FTC alleges that statements from the product label, such as as Cellasene "helps eliminate cellulite" and "fights cellulite from the inside," are unsubstantiated. In addition, the FTC alleges that Rexall Sundown falsely represented that it had clinical evidence establishing efficacy of Cellasene. The FTC will seek full refunds for U.S. consumers that could exceed $54 million.[19]

Endermologie was licensed by the FDA as an approved device for “temporary improvement in the appearance of cellulite” in April 1998. In March 2000, the FDA approved the device for an additional indication of a temporary reduction in the circumferential body measurements of cellulite treated areas. The advisory committee based their recommendations for approval on studies done by Ersek, Chang, and Dabb.[8,12,13]

Conclusion

Cellulite and its unattractive appearance are a nuisance to many women. There is insufficient clinical evidence, however, to support the use of Cellasene to treat cellulite.

Endermologie appears to offer a promising alternative of care for body remodeling, in conjunction with diet and exercise, and it may be an adjunct to liposuction. Its effects may vary with operator proficiency. The clinical studies to date show a wide range of results.

Recommendation

Given the dearth of any blinded, placebo-controlled trials that demonstrate its efficacy in the reduction of cellulite, coupled with the concerns about long-term, significant iodine consumption, Cellasene should be avoided.

Endermologie may be an effective adjunct to an overall fitness program including weight loss, regular exercise, and a low-fat diet for the reduction of cellulite. More studies within a carefully controlled research setting must be performed, however, before our patients spend the time and incur the expense of treatment. ❖

Which of the herbal ingredients of Cellasene can potentiate the effects of oral anticoagulants?

a. Borage seed oil and grape seed extract
b. *Ginkgo biloba* and sweet clover
c. Sweet clover
d. None of the above

Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA.

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Echinacea for Colds

By V. Jane Kattapong, MD, MPH

"The most high hath created medicines out of the earth, and a wise man will not abhor them."

Ecclesiasticus 38:4

As WINTER IS NEARLY HERE, MANY OF US ANTICIPATE patients' questions regarding the usefulness of echinacea as a treatment for the common cold.

Since 1994, when Congress enacted the Dietary Supplement Health and Education Act, echinacea has become one of the most popular herbal remedies in the United States. Since this topic was first addressed in these pages by Udani and Ofman,[1] only a small amount of new evidence has become available. However, these data may provide us with additional advice to offer patients who ask about the usefulness of echinacea.

Traditional Uses

A member of the daisy family (Asteraceae), echinacea also is known as the purple coneflower. There are nine different species of echinacea in the United States and southern Canada. American Indians have used echinacea preparations as antiseptics and analgesics for hundreds of years. Echinacea has been used as a treatment for colds, tonsillitis, toothaches, intestinal pain, snake bites, rabies, seizures, wound infection, sepsis, and cancer.[2-4]

One hundred years ago, echinacea was the best-selling native medicinal plant in the United States;[3] however, its use in the United States declined greatly after the development and distribution of antibiotics. In the last six years echinacea has become wildly popular; in 1998, retail sales of echinacea preparations in the United States totaled nearly $70 million.[5]

Modern Uses

Echinacea has enjoyed even greater popularity in Europe, especially in Germany.[6] More than 500 different echinacea-containing products were available in Germany in 1996.[7] Modern-day European uses for echinacea are similar to traditional Native American uses; proposed indications for echinacea have included colds, upper and lower respiratory tract infections, chronic arthritis, cancer, yeast infections, bacterial infections, chronic fatigue syndrome, skin diseases, wounds, ulcers, and chronic pelvic infections.

Mechanism of Action

Echinacea is believed to act either via immunomodulatory enhancing properties or via direct inhibition of virus replication.[8] The plant is composed of seven active constituents, including polysaccharides, flavonoids, essential oils, polyacetylenes, alkylamides, caffeic acid derivatives (such as echinacoside), and miscellaneous chemicals.[1] Immunologically active components are believed to be polysaccharides, glycoproteins, caffeic acid derivatives, and alkamides.[9]

Clinical Trials

A literature search revealed four well-designed, controlled studies in the medical literature evaluating echinacea as a treatment for the common cold.

In the first study, adult volunteers from the Medical University of South Carolina community were recruited

to receive exposure to rhinovirus type 23.[8] After the initial virus challenge, the 117 subjects received either an echinacea preparation or placebo for five days. The echinacea preparation was standardized to contain 0.16% cichoric acid and minimal amounts of echinacosides and alkamides. No significant differences were seen between the treatment and control groups in incidence of rhinovirus infection, clinical colds, symptoms, or severity of symptoms. No side effects of echinacea were reported in this study.

In a similar study, Melchart treated 302 volunteers with either an *E. purpurea* extract or placebo for 12 weeks.[10] No significant difference was found between incidence of common colds or symptom severity between the two groups.

In the third study, Grimm randomly assigned 108 patients with a history of more than three colds or respiratory symptoms in the preceding year to receive either *E. purpurea* extract or placebo.[7] Subjects received 4 ml echinacea or placebo bid for eight weeks. However, it is unclear if the concentrations of active ingredients were equivalent in each of the aliquots.

There were no significant differences between the two groups in number of colds or respiratory infections, median duration of colds or respiratory infections, or severity of infections. There was no significant difference between the two groups in incidence of side effects. In the treatment group, reasons for study withdrawal included nausea (n = 1), constipation (n = 1), bad taste of medication (n = 1), and unspecified (n = 1). In the placebo group, reasons for withdrawal included sweating and paresthesia (n = 1), bad taste of medication (n = 1), and unspecified (n = 1).

In the fourth study, Henneicke-von Zepelin enrolled 263 patients presenting to one of 15 study sites.[11] Patients with an acute common cold were randomized to receive placebo or a combination herbal remedy containing echinacea and other herbal ingredients. A composite score was created to incorporate intensity of cold symptoms, general well being, and severity of illness. An analysis of efficacy parameters demonstrated significantly greater efficacy for the herbal remedy. It is impossible to determine whether any of the effectiveness was derived from the echinacea or one of the other herbal ingredients. In addition, the validity of the efficacy score was not established.

Other Literature

The bulk of the limited research on echinacea is in German; very little research on echinacea has been undertaken in the United States. Although few well-designed, controlled studies demonstrate echinacea's efficacy as a common cold treatment, other weaker clinical evidence from Germany suggests that echinacea may decrease severity and duration of colds and upper respiratory infections if started at the time symptoms begin and continued for 7-10 days.[12] Reviews of existing clinical studies found that the bulk of the literature contained methodological flaws, but suggest that echinacea may have efficacy for treating, but not preventing, colds and upper respiratory infections.[13,14]

Echinacea Preparations

A systematic review of the literature regarding echinacea's effectiveness as a cold remedy meets with a serious obstacle: lack of product standardization. Preparations vary according to plant species and plant components, as well as variability between different plants in concentrations of active components.

E. angustifolia, *E. pallida*, and *E. purpurea* are the three echinacea species used medicinally. Both the processing and application methods introduce sources of variability. A product may be prepared from one or several plant components such as the root, upper parts, or the whole plant. The mode of application may result in local or systemic activity, via oral, injectable, or topical preparations.[7] This lack of standardization hinders attempts to assess efficacy definitively.

Oral preparations include a tincture (made with alcohol or myrrh), freeze-dried extract in tablet form, capsules, and teas. No information is available regarding comparability of the bioavailability of active ingredients in these various preparations.

Adverse Events and Contraindications

Few serious adverse events associated with echinacea have been reported. Commonly reported side effects have included gastrointestinal symptoms such as nausea, diarrhea, and constipation. In addition, skin rash has been reported when used topically. Relatively little information exists in the literature regarding toxicity or drug interactions with echinacea.[15]

Echinacea has no known mutagenic properties.[1] Of concern, however, are life-threatening episodes of anaphylaxis, as well as acute asthma, urticaria, and angioedema reported in association with echinacea use.[16,17] Unpublished case reports presented at the American Academy of Allergy, Asthma and Immunology annual meeting in March 2000 suggest that allergic reactions to echinacea may result from IgE-mediated hypersensitivity, and may be more common in patients with atopy.[16] Because of its immunomodulatory effects, echinacea generally is thought to be contraindicated for individuals with AIDS, HIV infection, or autoimmune

disorders, although this contraindication has not been well established.[12,18] In addition, individuals with allergies to members of the daisy family probably should avoid echinacea.[19] Echinacea should be avoided in pregnant or lactating women because of a lack of information regarding safety.

Conclusion

Limited well-designed, controlled studies have evaluated the efficacy of echinacea as a cold remedy. A literature review revealed four controlled studies addressing this topic. Of these four, only one suggested utility of echinacea as a cold remedy, and this study used an echinacea preparation containing a combination of other herbal ingredients. Very limited evidence suggests that echinacea may be useful for limiting severity and duration of cold symptoms after onset, but that it is not effective for preventing colds. Future research should devote particular attention to using a standardized, well-characterized echinacea preparation and should incorporate methods to ensure quality control.

Recommendation

Only a small number of controlled studies have evaluated the effectiveness of echinacea as a treatment for the common cold. Insufficient evidence exists for or against echinacea to recommend it as efficacious. Since there have been few reported side effects, and fewer therapeutic alternatives, it may be reasonable to encourage some interested patients to give it a try. Since echinacea has immunomodulatory effects, it cannot be recommended for individuals with allergies to the daisy family, autoimmune disorders, AIDS, or HIV infection; for pregnant or lactating women; or for patients with atopy. ❖

Limited evidence suggests echinacea may be useful for:

a. preventing colds.
b. limiting severity and duration of colds.
c. both preventing and limiting severity and duration of colds.
d. neither preventing nor limiting severity and duration of colds.

Dr. Kattapong is a board-certified neurologist and a principal in MediCat Consulting, a health services consulting firm in Tucson, AZ.

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With Comments from John La Puma, MD, FACP

Walnuts for Reducing Cholesterol Levels

Source: Zambón D, et al. Substituting walnuts for monounsaturated fat improves the serum lipid profile of hypercholesterolemic men and women. A randomized crossover trial. *Ann Intern Med* 2000;132:538-546.

IT HAS BEEN REPORTED THAT WALNUTS reduce serum cholesterol levels in normal young men. To assess the acceptability of walnuts and their effects on serum lipid levels and low-density lipoprotein (LDL) oxidizability in free-living hypercholesterolemic persons, we designed a randomized, crossover feeding trial. We studied 55 men and women (mean age, 56 years) with polygenic hypercholesterolemia at a university hospital's lipid clinic. We gave them a cholesterol-lowering Mediterranean diet and a diet of similar energy and fat content in which walnuts replaced approximately 35% of the energy obtained from monounsaturated fat. Patients followed each diet for six weeks.

Forty-nine persons completed the trial. The walnut diet was well tolerated. Planned and observed diets were closely matched. Compared with the Mediterranean diet, the walnut diet produced mean changes of -4.1% in total cholesterol level, -5.9% in LDL cholesterol level, and -6.2% in lipoprotein(a) level. The mean differences in the changes in serum lipid levels were -0.28 mmol/L (95% confidence interval [CI], -0.43 to -0.12 mmol/L) (-10.8 mg/dL [-16.8 to -4.8 mg/dL]) ($P < 0.001$) for total cholesterol level, -0.29 mmol/L (CI, -0.41 to -0.15 mmol/L) (-11.2 mg/dL [-16.3 to -6.1 mg/dL]) ($P < 0.001$) for LDL cholesterol level, and -0.021 g/L (CI, -0.042 to -0.001 g/L) ($P = 0.042$) for lipoprotein(a) level. Lipid changes were similar in men and women except for lipoprotein(a) levels, which decreased only in men. LDL particles were enriched with polyunsaturated fatty acids from walnuts, but their resistance to oxidation was preserved.

We find that substituting walnuts for part of the monounsaturated fat in a cholesterol-lowering Mediterranean diet further reduced total and LDL cholesterol levels in men and women with hypercholesterolemia.

COMMENT

The Mediterranean diet has much to recommend it—flavor, familiarity, fun, good fats. The whole traditional Mediterranean diet, however, which derives 40-45% of its calories from fat, especially olive oil, is not a tenable American option. Affluent and eager as we are, most of us simply would add olives and olive oil, fish, and nuts to our currently over-the-top caloric intakes. And because the average American adult already eats 216 calories/d more than he or she did 25 years ago, that would be too much.

But components of the traditional Mediterranean diet (fish, green vegetables, very little red meat, and eggs) are individually deserving of special attention, and scientists are trying hard to find the magic bullet in food. Gratefully, these investigators gave whole walnuts (untoasted, but they were practicing science, not cooking), and substituted them for the monounsaturates (i.e., olive oil) in the Mediterranean diet.

Average LDLs dropped from 196 mg/dL to 174 mg/dL on walnuts vs. 185 mg/dL on the control diet.

It's no surprise that polyunsaturated walnut fat is better than butter, cream, cheese, and beef. But to substitute walnuts' polyunsaturated omega-3 fats for monounsaturated ones, and to lower cholesterol with whole foods, other than fresh garlic—that's new! That's exciting! And to get to eat more nuts—that's good too!

But not too many more—14 walnut halves, or fewer if they're large, and you're up to an ounce. An ounce is a serving, and packs 180 calories—the same as 4 teaspoons of olive oil. In this study, people ate 8-11 walnuts daily, and remained in statin territory. But eating nuts is a start, and it is something that patients can do that is positive and helpful.

Could other nuts do this? Yes, probably. Pecans have been studied recently; 3/4 cup, which have more monounsaturates than polys, lowered LDLs by 6% over eight weeks. Whether the mechanism is antioxidant-related is unknown. But the effect seems to be independent of simply limiting saturated fat.

Recommendation

Nuts are good medicine. Toast 'em if you got 'em. Then eat an ounce at a time and skip the olive oil that day. ❖

Mercury Poisoning from Mexican Beauty Cream

Source: Weldon MM, et al. Mercury poisoning associated with a Mexican beauty cream. *West J Med* 2000;173:15-18.

THE STUDY HAD TWO AIMS: (1) TO describe demographic characteristics, patterns of use, and symptoms associated with mercury poisoning among persons who used a Mexican beauty cream containing mercurous chloride and (2) to estimate the prevalence of cream use in Texas near the Mexico border. We designed a case series and cross-sectional survey in border communities of Arizona, California, New Mexico, and Texas. We studied those persons who had used the cream and contacted a health department in response to announcements about the cream. These persons participated in the Survey of Health and Environmental Conditions in Texas Border Counties and Colonias, 1997. We assessed urine mercury concentrations, self-reported symptoms, and prevalence of cream use among households and the persons within them. Of 330 cream users who contacted their

health department, 96% were women, and 95% were Hispanic. The mean urine mercury concentration was 146.7 µg/l (median 79 µg/l; reference range: 0-20 µg/l). Eighty-four percent had concentrations of greater than 20 µg/l. In 5% of 2,194 randomly selected Texas households near the Mexico border, at least one person had used "Crema de Belleza-Manning" (Laboratorios Vida Natural, S.A., Tampico, Tamaulipas, Mexico) in the previous year. We conclude that most cream users had increased urine mercury concentrations. Cream use was common in Texas near the Mexico border. Physicians should consider toxicity in patients with neurologic symptoms of unclear cause and use public health departments when investigating unusual illnesses.

COMMENT

Beauty always has a price, and many men are willing to pay it. But it is immoral that women should have to pay it with their nervous systems.

Substantially banned by the FDA in over-the-counter (OTC) topical salves for decades, mercury is toxic. Symptoms of fatigue, nervousness/irritability, severe headaches, insomnia, tingling, burning, and tremors were elicited in well over one-third of women who responded to public notices and were tested for mercury. No control, comparison group, or systematic physical examination was recorded.

Most of these women used the cream two to three times daily, primarily as a skin lightener, but also as acne treatment and a moisturizer. Nearly 80% had purchased the cream in Mexico. Median use was 4.0 years.

Mercury-containing creams and lotions are available in Hispanic communities throughout the United States, usually in flea markets or herb shops, as in this study. Asian communities, with herbalists and markets that stock Chinese patent medicines, also commonly offer OTC mercury-containing potions, salves, and pills.

Recommendation

Unusual neurologic or cognitive symptoms in women with skin concerns should bring to mind mercury intoxication. Ask women to bring in face and beauty creams and send them to the lab for analysis, after measuring the patient's mercury levels. ❖

In Future Issues:

Acupuncture for Depression

Ipriflavone for Osteoporosis Prevention

Nicotine Adenine Dinucleotide (NADH) for Parkinson's

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Supplement to *Alternative Medicine Alert*
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ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

What Makes a Good Multivitamin? And Who Needs One?

IN A PERFECT WORLD, PATIENTS WOULD GET AN ADEQUATE AMOUNT OF ESSENTIAL NUTRIENTS from a well-balanced diet. However, for a variety of reasons—including nutritional deficiency, pregnancy, advanced years, and lifestyle—many patients simply are unable to meet these recommended standards and may require dietary supplementation.

This handout commences a series devoted to examining appropriate multivitamin use. We begin with an overview of who should take a multivitamin and the components of a good multivitamin. Subsequent handouts will address specific nutrients, their physiological effects and safety profiles, and special needs populations, including children, women, and the elderly.

What Can a Multivitamin Do?

Research has shown that adequate levels of folate can prevent neural tube disorders in the developing fetus. However, demonstrating that multivitamin supplementation prevents chronic disease has been another matter—made difficult by many contributing confounders, such as diet, family history, and environmental issues.

Clinical trials and observational studies suggest an association between multivitamin use and disease prevention, but no clear causal relationship has been shown. For example, among the nearly 90,000 participants in the Harvard Nurses' Health Study, the women who took multivitamins for 15 years reduced their risk of colon cancer by as much as 75%.[1] The data also suggest that multivitamins may reduce the risk of breast cancer in certain women. Conversely, results from the National Health and Nutrition Examination Survey found cancer mortality and overall mortality were similar in regular users and nonusers of dietary supplements.[2]

Who Needs to Take a Multivitamin?

How many of your patients take multivitamins? According to a survey conducted by the American Dietetic Association (ADA), nearly half of Americans consume vitamin and mineral supplements on a daily basis.[3]

A well-balanced diet can provide adequate levels of most vitamins and minerals as well as fiber and phytochemicals. Often, people who eat a nutritious diet don't need to supplement with a multivitamin. Ironically, many studies have shown that people who have higher intakes of nutrients from food are the very people who are most likely to take a multivitamin.[2-4]

As reflected in the ADA study, regular vitamin and mineral supplementation increases with age and is associated with more frequent intake of fruit and vegetables.[3,5] Multivitamin use also seems to be most prevalent among those who believe their health is affected by diet.[6]

Try as many patients might, however, only 28% of Americans have made significant adjustments in their eating behavior.[3] The vast majority have failed to achieve a healthy, nutritious diet or have made no effort at all. In addition, many people have special dietary concerns and may not be able to get adequate levels of nutrients from the food they eat. These people may include the elderly, children, pregnant women, the physically active, and those with absorption problems or chronic illnesses. In these situations, dietary supplementation may be necessary.

What Constitutes a Good Multivitamin?

Currently, the Food and Nutrition Board of the National Academy of Sciences is evaluating and revising the Recommended Daily Allowances (RDAs). New recommendations, called Dietary Reference Intakes (DRIs), have been established for those nutrients that have undergone this review process.

The chart below reflects the most current data available, using RDAs for those nutrients awaiting DRI review. Consumers should select a multivitamin that contains nutrient levels appropriate for their age and gender. ❖

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Table

Recommended Dietary Allowances (RDA) and Dietary Reference Intakes (DRI)

1989 RDA								2000 DRI																		
Age	Energy (kcal)	Protein (g)	Vitamin A (µg RE)	Vitamin K (µg)	Iron (mg)	Zinc (mg)	Iodine (µg)	Life Stage Group	Calcium (mg/d)	Phosphorous (mg/d)	Magnesium (mg/d)	Vitamin D (µg/d)	Fluoride (mg/d)	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin (mg /d)	Vitamin B_6 (mg/d)	Folate (µg/d)	Vitamin B_{12} (µg/d)	Pantothenic acid (mg/d)	Biotin (µg/d)	Choline (mg/d)	Vitamin C (mg/d)	Vitamin E (mg/d)	Selenium (µg/d)
Infants								**Infants**																		
0-6 mo	650	13	375	5	6	5	40	0-6 mo	210	100	30	5	0.01	0.2	0.3	2	0.1	65	0.4	1.7	5	125	40	4	15
6 mo-1 y	850	14	375	10	10	5	50	7-12 mo	270	275	75	5	0.5	0.3	0.4	4	0.3	80	0.5	1.8	6	150	50	6	20
Children								**Children**																		
1-3 y	1300	16	400	15	10	10	70	1-3 y	500	460	80	5	0.7	0.5	0.5	6	0.5	150	0.9	2	8	200	15	6	20
4-6 y	1800	24	500	20	10	10	90	4-8 y	800	500	130	5	1	0.6	0.6	8	0.6	200	1.2	3	12	250	25	7	30
7-10 y	2000	28	700	30	10	10	120																			
Males								**Males**																		
11-14 y	2500	45	1000	45	12	15	150	9-13 y	1300	1250	240	5	2	0.9	0.9	12	1.0	300	1.8	4	20	375	45	11	40
15-18 y	3000	59	1000	65	12	15	150	14-18 y	1300	1250	410	5	3	1.2	1.3	16	1.3	400	2.4	5	25	550	75	15	55
19-24 y	2900	58	1000	70	10	15	150	19-30 y	1000	700	400	5	4	1.2	1.3	16	1.3	400	2.4	5	30	550	90	15	55
25-50 y	2900	63	1000	80	10	15	150	31-50 y	1000	700	420	5	4	1.2	1.3	16	1.3	400	2.4	5	30	550	90	15	55
51+ y	2300	63	1000	80	10	15	150	51-70 y	1200	700	420	10	4	1.2	1.3	16	1.7	400	2.4	5	30	550	90	15	55
								70+ y	1200	700	420	15	4	1.2	1.3	16	1.7	400	2.4	5	30	550	90	15	55
Females								**Females**																		
11-14 y	2200	46	800	45	15	12	150	9-13 y	1300	1250	240	5	2	0.9	0.9	12	1.0	300	1.8	4	20	375	45	11	40
15-18 y	2200	44	800	55	15	12	150	14-18 y	1300	1250	360	5	3	1.0	1.0	14	1.2	400	2.4	5	25	400	65	15	55
19-24 y	2200	46	800	60	15	12	150	19-30 y	1000	700	310	5	3	1.1	1.1	14	1.3	400	2.4	5	30	425	75	15	55
25-50 y	2200	50	800	65	15	12	150	31-50 y	1000	700	320	5	3	1.1	1.1	14	1.3	400	2.4	5	30	425	75	15	55
51+ y	1900	50	800	65	10	12	150	51-70 y	1200	700	320	10	3	1.1	1.1	14	1.5	400	2.4	5	30	425	75	15	55
								70+ y	1200	700	320	15	3	1.1	1.1	14	1.5	400	2.4	5	30	425	75	15	55

Adapted from: National Academy of Sciences. *Dietary Reference Intakes 2000: Applications in Dietary Assessment.* Washington, DC: National Academy Press; 2000:198-200. More information is available at: http://books.nap.edu/books/0309071836/html/198.html#pagetop and http://www.nal.usda.gov/fnic/dga/rda.pdf.