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Massage to Promote Weight Gain in Premature and Low Birth Weight Infants

By Robert J. Nardino, MD, FACP

TO TOUCH OR NOT TO TOUCH—THAT IS THE QUESTION FACING PARents and caregivers of premature and low birth weight infants. These infants are exposed to a constant barrage of light and sound while they are in Neonatal Intensive Care Units (NICU), in what must be a shocking change from the nurturing environment of the womb. Some have postulated that massage, by reducing the stress caused by the NICU, can promote infant growth and development.

Background

Touch, stretch, and motion stimuli for a nine-month term are thought to be important for infant development, and the premature infant loses access to them abruptly. The lack of usual tactile, visual, and auditory stimuli can result in an impaired intellectual level.[1]

Mechanism of Action

The mechanism by which infant massage may provide benefit is not understood clearly. Reductions in cortisol levels with massage have been reported, but it is unclear whether this plays an important role.[2] Others have not seen this reduction in cortisol, but have demonstrated an enhancement in the activity of the sympathetic nervous system.[3] Improved cognitive development with massage may arise from increased catecholamine activity, resulting in heightened attention and improved memory. Increased secretion of growth hormone also has been reported, suggesting a third hypothesis.[4]

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Massage does not appear to result in increased caloric intake.[5] However, there has been some suggestion that weight gain might result from better conversion of food into energy for growth.

Procedure

There are some variations in the intervention, but the most commonly used regimen is outlined in Table 1. Infant massage entails a systematic stroking, gently but with pressure.

Clinical Studies

In 1969, Solkoff published the first study of massage therapy in 10 preterm infants. The intervention was just five minutes, shorter in duration than the sample massage intervention described in Table 1. Very few data are provided.[6] Several studies at various locales followed, and form the basis for the reviews described below.

A systematic review by Ottenbacher et al in 1987 concluded that interpretation of the studies of tactile stimulation could not be accurately undertaken because the studies were heterogeneous in design, outcome measure, and quality.[7] The authors' analysis included all studies up to that time, including uncontrolled studies. The effect size was much larger in studies that were not randomized properly. Ireland and Olson recently reviewed the existing literature on massage and therapeutic touch in children.[8] They looked at seven studies of massage therapy in preterm infants who did not have other underlying conditions and found consistent beneficial effects on weight gain, activity level, and length of hospitalization. However, while systematic in their search for all relevant studies, they did not attempt a quantitative analysis of the data.

The most thorough and quantitative approach to the body of literature of massage therapy can be found in the Cochrane Collaboration Review published in March 2000.[9] All relevant studies were identified and assessed for the strength of their methods. Thirteen studies were ultimately included for analysis, and their outcomes were combined using weighted averages. Because different studies measured different outcomes, some of the analyses are based on small numbers of patients.

Table 2 shows a summary of differences in selected outcomes between infants receiving massage and infants in control groups. There are statistically significant improvements in several outcomes, including daily weight gain, length of stay, and measures of development. Massage, performed one to three times daily for between four and 10 days, resulted in weight gain ranging from 3-8 g/d in excess of what the control group gained. Benefits in motor and behavioral development were much less consistent. However, the overall interpretation was that there is insufficient evidence to support the use of massage, primarily because the methodologic quality of the studies is weak.

Finally, follow-up of a study by Field et al showed

Table 1

Sample massage intervention

Three 15-minute periods during three consecutive hours, daily for 10 days

Components of the 15-minute session:

1. Five-minute tactile phase: infant placed in prone position, stroked with flat of fingers of both hands (using a gentle pressure, but not too light as to create a tickling stimulus), one minute over each region in sequence:
   - 12 five-second strokes from top of head, down side of face to neck, back to head
   - 12 five-second strokes from back of neck across shoulders and back to neck
   - 12 five-second strokes from the upper back down to the waist and back up
   - 12 five-second strokes from the thighs down to the ankles and back to thighs
   - 12 five-second strokes from the shoulders to the wrists, back to shoulders
2. Five-minute kinesthetic phase: infant placed in supine position, six passive flexion-extension movements lasting 10 seconds to right arm, left arm, right leg, left leg, both legs
3. Five-minute tactile phase identical to phase one

Adapted from: Field TM, et al. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics* 1986;77:654-658.

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Table 2

Selected outcomes from studies comparing massage vs. routine care in preterm/low birth weight infants

Outcome	# of Studies	# of Patients (Exp/Control)	Weighted Mean Difference* (95% CI)	Clinically Meaningful	Consistency
Daily weight gain[5,12,13,15-17]	6	274 (139/135)	5.1 (3.5 to 6.7)	yes	5/6 favored massage
Length of stay[5,12,13,16-18] (days)	7	206 (103/103)	-4.6 (-6.6 to -2.6)	yes	3/7 favored massage
Brazelton Scale: habituation[5,12,13]	3	103 (51/52)	0.8 (0.5 to 1.1)	no	2/3 favored massage
Brazelton Scale: motor maturity[5,12,13]	3	110 (55/55)	0.8 (0.5 to 1.1)	perhaps	1/3 favored massage
Weight at 4-8 mo. follow-up[5,10] (oz)	2	49 (25/24)	0.5 (-0.05 to 1.1)	no	1/2 favored massage

*Studies were weighted based on strength of design

Adapted from: Vickers A, et al. Massage for promoting growth and development of preterm and/or low birth-weight infants. *Cochrane Database Syst Rev* 2000;2:CD000390.

that in addition to improved weight gain, the group of infants receiving massage had better motor and mental development at six months.[9] One other study showed increased weight gain at four months.[10] Further longitudinal studies are needed to support these observations.

Other Studies

Scafidi and Field randomized 28 infants born to HIV-positive mothers to massage or control.[11] These infants were not premature or low birth weight. They found similar results to those in preterm infants—improved average daily weight gain and improvements on Brazelton Scale measurements. A study that investigated the effects of massage on cocaine-exposed preemies was included in the systematic reviews.[12]

Scafidi and colleagues also attempted to determine if certain subsets of infants fared better with massage than others.[13] The idea was to direct the intervention to those patients who most likely would benefit. They found that infants who had higher scores on the Obstetric Complications Scale derived more benefit from massage.

Methodologic Weaknesses

Many of the published studies evaluating massage are of low quality. Even among studies that are randomized, there is no blinding to treatment allocation. Also, the control intervention or usual care is not well defined, and there is no description of efforts to ensure that patients were treated the same in all respects other than the experimental intervention. There is no standardization as to who is administering the intervention. Length of stay data were not reported in several of the studies; failure to report these data suggests that there was no difference, meaning that the results from the studies that did report them may be overestimating the effect.

Adverse Effects

No adverse effects were noted in the published studies. However, there have been observations that marginally stable infants occasionally collapse and develop respiratory distress following a massage session.[14] It is unclear whether there is a threshold for overstimulation and whether there are any significant lasting consequences.

Conclusion

Overall, it is difficult to draw conclusions from the literature on massage in premature and low birth weight infants. The data suggest a possible improvement in short-term weight gain. Data about length of stay, while of importance, may have been compromised by selective reporting. Confirmatory studies with strict methodology to reduce bias and long-term follow-up are needed before massage can be widely adopted. At the same time, it is a noninvasive intervention that in general appears safe to implement. Parents or other non-skilled personnel such as volunteers can administer this intervention. It would seem obvious that premature infants should experience touch, although it is interesting that in the studies that made the comparison, massage yielded benefits in growth that gentle, still touch did not.

Recommendation

The data favoring the use of massage in preterm infants, though weak, do indicate an increase in daily weight gain over the short periods it has been studied. Additionally, massage for any purpose is unlikely to be harmful. Therefore, massage should be considered as an adjunct in the management of premature infants, with the expectation of modest increases in daily weight gain. Whether there are benefits for other aspects of development is inconclusive. It is also uncertain whether it is cost-effective for NICU nurses to administer massage, but it can be performed readily by parents or volunteers. Infants should be medically stable before receiving massage. ❖

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Vitamin C for the Prevention of Asthma

By Susan T. Marcolina, MD

FROM 1982 TO 1992, THE PREVALENCE OF ASTHMA IN THE United States increased 42%, primarily in persons younger than age 20.[1] It is hypothesized that environmental oxidants and dietary antioxidant deficiencies play roles in this trend.[2] Deficiencies of foods containing antioxidants in the American diet and an increased awareness of the role of antioxidants in lung defenses have prompted clinical studies of various antioxidants such as vitamin C.

A water-soluble vitamin, vitamin C or ascorbic acid is an essential micronutrient involved in many biochemical functions. Humans lack the last enzyme in its biosynthetic pathway and thus are unable to synthesize ascorbic acid. Therefore, adequate dietary intake is necessary to provide for bodily needs. Foods rich in vitamin C, primarily fruits and vegetables, are listed in Table 1.

Environmental Oxidants, Vitamin C, and Asthma

The frequency of asthma and allergy symptomatology is strongly associated with increases in air pollutants such as ozone and nitrogen dioxide. The nitrogen oxides in mainstream cigarette smoke constitute the largest inhaled oxidant challenge in humans.[2] In vitro studies show rapid oxidation of vitamin C upon exposure of cigarette smoke to human blood plasma containing the vitamin.[3]

Smokers show higher bronchial reactivity to bronchoconstrictor challenge than nonsmokers. Children of parents who smoke have increased airway responsiveness to cold air and histamine provocation.[4] Active smokers and their children have higher serum IgE and peripheral eosinophil counts than nonsmokers.[5] In a randomized, double-blind, study of 37 male smokers and 38 nonsmokers, Lykkesfeldt et al found that smoking significantly depleted plasma ascorbic acid levels independent of dietary intake.[6]

Pathophysiology

Cyclooxygenase products of arachidonic acid metabolism play a role in the pathogenesis of bronchial

Table 1

Food sources of vitamin C

Source (Portion Size)	Vitamin C (mg)
Strawberries (1 cup sliced)	95
Papaya (1 cup, cubes)	85
Kiwi (1 medium)	75
Orange (1 medium)	70
Broccoli (1/2 cup)	60
Cantaloupe (1/4 medium)	60
Kale, cooked (1 cup)	55
Orange juice (1/2 cup)	50

Adapted from: Levine M, et al. Criteria and recommendation for vitamin C intake. *JAMA* 1999;281:1415-1423.

responsiveness. Vitamin C has been shown to shift this pathway from the synthesis of bronchoconstrictor prostaglandin F2 alpha toward the synthesis of bronchodilator prostaglandin E2.[7]

The presence of eosinophils in blood and bronchoalveolar lavage fluid is linked closely with airway hyperreactivity. Eosinophils, neutrophils, and alveolar macrophages from asthmatic patients produce more reactive oxygen species than those from normal subjects. These reactive oxygen species cause airway smooth muscle contraction[8] and stimulate histamine release from mast cells and mucus secretion.[9]

Slade et al found that vitamin C appears to be the most abundant antioxidant substance in the respiratory tract lining fluids (RTLF), where it may have an important role in protecting against endogenous and exogenous oxidants.[10] Despite links between vitamin C and pulmonary inflammatory mediators, studies of its efficacy in asthma have been conflicting.

Epidemiologic Findings from NHANES I, II, III

Data obtained from the National Health and Nutrition Examination Survey (NHANES) I showed that vitamin C supplementation was associated with increased FEV_1 in a random sample of 2,526 adults. The difference, however, between the mean FEV_1 for the lowest and the highest tertile of vitamin C intake was 40 ml, an amount not clinically significant.[11,12]

A cross-sectional study of 9,074 adults aged 30 years or more, NHANES II examined specific dietary factors. Low vitamin C intake correlated significantly with bronchitis and wheezing symptoms after correction for age, race, sex, and smoking status.[13]

A subsequent study of 19,760 survey participants in NHANES III examined the relationship between vitamin C levels and the use of health care services for respiratory symptoms while controlling for age, race, insurance, income, smoking history, previous diagnosis of asthma, chronic bronchitis, or emphysema. No relationship was found between serum vitamin C levels and the use of health care services.[14]

Kelley et al studied levels of vitamin C in peripheral blood and in fluids obtained from nasal lavage, bronchial wash, and bronchoalveolar lavage in 20 patients with mild asthma and in 20 healthy controls.[15] The asthmatics had significantly decreased levels of ascorbate in bronchial wash and bronchoalveolar lavage fluid ($P < 0.00l$) compared to controls, despite the fact that the asthmatics' plasma vitamin C concentrations were not low. This indicates that plasma measurements of ascorbate alone are not a sufficient indicator of airway antioxidant status. At present, the relationship between plasma and RTLF oxidant pools is unknown.

Clinical Trials in Asthma

Cohen et al conducted a randomized, double-blind, placebo-controlled study.[16] Twenty patients with exercise-induced asthma (EIA) were randomly assigned to receive either 2 g of ascorbic acid or placebo one hour before a seven-minute treadmill exercise session. Pulmonary function testing was performed after an eight-minute rest. The procedure was repeated one week later with each patient receiving the alternative medication. This dose prevented the development of EIA in nine of the 20 patients and reduced airway responsiveness to exercise in two other patients. Four responders who continued receiving oral ascorbic acid, 500 mg/d for two more weeks experienced a protective effect, documented by results of repeated post-exercise spirometry. However, since neither plasma nor RTLF vitamin C levels were checked for each subject, it is impossible to know whether the responders were in fact vitamin C-deficient and whether this affected the results.

Schacter and Schlesinger performed a randomized, double-blind, controlled prospective study in 12 asthmatics.[17] After ingestion of 500 mg of vitamin C, the immediate post-exercise peak expiratory flow rate was significantly improved. Five minutes after exercise, however, only forced vital capacity showed significant improvement compared to placebo.

In a double-blind, randomized, placebo-controlled trial of 16 nonsmoking adults with asthma, Malo et al showed that ingestion of 2 g/d of vitamin C for three days had no effect on histamine-induced bronchoconstriction.[18]

Recommended Daily Dosage

In 1998, after review of pharmacologic data published by the National Institutes of Health on vitamin C kinetics, the Food and Nutrition Board of the National Academy of Sciences derived new classifications for nutrient intake estimates termed Dietary Reference Intakes

(DRI). One of four these reference values is the Adequate Intake or AI—the level just above the better known DRI. This current revised recommendation is 200 mg/d vitamin C from five servings of fruit and vegetables.[19] The AI also can be attained with vitamin supplements.

Levine et al at the NIH performed human pharmacokinetic studies with a wide range of vitamin C daily doses administered to fasting subjects as two divided doses.[19] They found that the active transport mechanism that mediates intracellular accumulation of vitamin C saturated at a plasma concentration of 66 mmol/L, which was achieved with a 200 mg/d oral dosage. Bioavailability at this dose was nearly complete. There was a substantial decrease in bioavailability with an increase in urinary excretion when doses greater than 500 mg/d were studied.

Levine found the half-life of vitamin C to be between two to four hours.[20] In view of its short half-life and the saturability of intracellular transport mechanisms, vitamin C is best administered in divided doses.

Certain clinical circumstances, including smoking, infectious disease states, aging, and post-surgical status, may increase ascorbate requirements.[21]

Formulation

Vitamin C is a labile, water-soluble micronutrient with the amount in food varying with season, shelf-time, and cooking practices.[19] As a supplement, it is available in powder and tablet form in a wide range of dosages. The presence of the United States Pharmacopoeia (USP) insignia on the product label should ensure consumers of consistency and quality of vitamin content.

Adverse Effects

Adverse effects are related to dose. The most common symptoms of diarrhea and abdominal bloating occur when several grams are taken at once. Since oxalate is a product of vitamin C catabolism, daily doses greater than 1 g can predispose to oxalate renal stone formation in susceptible patients.[19] Intravenous vitamin C should not be given to patients with glucose-6-phosphate dehydrogenase deficiency. Oral doses exceeding 6 g/d can precipitate hemolysis in such patients.[22]

Drug Interactions

High-dose vitamin C can interfere with the efficacy of anticoagulants, including warfarin and heparin.[23] It increases absorption of dietary ferric iron.[19] Vitamin C supplements should not be used in persons with hemochromatosis or sickle cell anemia and other conditions that predispose to iron overload. Use of oral contraceptives can lower plasma ascorbate concentrations.[21]

Conclusion

Although the studies of vitamin C for asthma prevention are short, involve small numbers of patients, and have conflicting results, the studies do suggest that it may benefit some asthmatics, particularly those under repetitive oxidant stress such as smokers or those with exercise-induced symptoms. The efficacy of vitamin C for prevention of asthma, however, cannot be predicted.

Recommendation

Physicians should be cognizant of the revised recommendations for adequate vitamin C intake of 200 mg/d, especially for smokers. Patients should try to obtain their vitamin C through consumption of five daily servings of fruit and vegetables or the use of 200 mg of supplemental vitamin C taken in two divided doses. Vitamin C doses in excess of 1 g/d should be avoided since adverse consequences may occur and its efficacy for asthma is controversial. However, since the studies suggest a benefit for some patients with EIA, a one-month trial of 500 mg of vitamin C administered as a twice daily divided dose may be warranted as adjunctive therapy. ❖

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Horny Goat Weed for Erectile Dysfunction

By Michael D. Cirigliano, MD, FACP, and Philippe O. Szapary, MD

COUPLED WITH THE FACT THAT MANY MEN STILL FEEL uncomfortable discussing erectile dysfunction (ED) with their doctors, alternative and "natural" treatments for ED are widely sought. Agents including yohimbe, arginine, *Avena sativa*, and muira puama are employed extensively, though most lack significant scientific data on safety and efficacy.

The herbal agent horny goat weed (*Epimedium sagittatum*, family Berberidaceae), along with several other *Epimedium* species, now joins this group, with a twist. With its suggestive name, the use of horny goat weed is on the rise across the United States and abroad both for ED and as an aphrodisiac. Its rise in popularity and desirability have in fact made it a high-theft item, requiring horny goat weed to be kept under lock and key in many health food stores and pharmacies. Anecdotes and testimonials, sometimes by celebrities, have led many to consider horny goat weed to be the new age "natural viagra."

Background: Erectile Dysfunction

ED is a common disorder affecting men of all ages. The prevalence of some level of ED has been estimated to be approximately 40% in men at the age of 40, and as high as 67% in those at the age of 70.[1] Pharmaceutical agents, along with a number of other modalities, have been developed and are available for treatment, but they are not without side effects and significant cost. Some agents are contraindicated for men with common medical conditions. In many cases, these agents may not be covered by insurance carriers.

Etymology

The term "horny goat weed" is thought to have originated from the observation that goats consuming the plant became much more sexually active than normal. It is also known as "Yin-yang-huo."

Chinese Medicine

Horny goat weed has warming properties and is pleasant to the taste.[2] According to traditional Chinese medicine principles, it is said to warm the kidneys, to strengthen the yang element (virility), and to remove excess moisture and flatulence. Horny goat weed was described in *The Herbal Classic of the Divine Plowman* as a bodybuilding agent, a yang supporter, an agent to reinforce muscles and bones, and a help to the liver and kidney.[3]

Historically, horny goat weed has been used medicinally for a wide variety of ailments including impotence, involuntary ejaculation, fatigue, coronary artery disease, kidney disease, chronic hepatitis, and polio.[4]

Source and Identification

A perennial evergreen indigenous to China and Japan, the herb is found growing on hillsides, in damp shady bamboo groves, or in cliff crevices.[2] The leaves are used medicinally, usually in a decoction. In the spring, light yellow terminal flowers appear. The herb is collected in the summer and autumn, mainly in the provinces of Shaanxi, Liaoning, Shanxi, Hubei,

Sichuan, and Guangxi.[5]

At least 15 *Epimedium* species have been identified. The dried aerial leaves of a number of species, most commonly including *E. grandiflorum*, *E. sagittatum*, *E. pubescens*, *E. wushanesis*, or *E. koreanum*, are used.

Pharmacology

Horny goat weed contains a number of active constituents including flavonoids (more than 20 identified), lignans, phenol glycosides, ionones, sesquiterpenoids, and phenethylol glycosides.[5] It is believed that the active principal components include the glycosides icariin and noricariin.[3] In addition, ceryl alcohol as well as some essential oils and fatty acids may play an active role in the pharmacological properties of horny goat weed.

Mechanism of Action

Increased male sexual function appears to arise from horny goat weed's peripheral vasodilatory and hormonal effects.[3] One study noted that icariin had calcium channel-blocking activity, leading to vasodilation.[6] It is believed that the hypotensive effect of the herb may be related in part to the blockade of sympathetic ganglia, in addition to its effects on calcium channels.[7,8]

The herb's glycosides also have been reported to have sexually stimulating effects on male mice and rats by promoting semen secretion and by stimulating the growth of the prostate, testis, and anus rector muscles.[7] Increases in urinary excretion of androgen precursors, including17-ketosteroids, have been observed, and some investigators believe that horny goat weed effects derive from modulation of cAMP and increased testosterone secretion. Horny goat weed also has been shown to be effective in antagonizing the impotency induced by hydrocorticosterone administration in mice.[9]

Other properties observed in animal studies of the herb include increased coronary blood flow and decreased platelet aggregation. Reports indicate that the glycosides of the herb can increase immune activity and act synergistically with other immune-enhancing agents to stimulate IL-2, IL-3, and IL-6.[3]

Animal Studies

A review of MEDLINE and IBIDS databases revealed 12 basic science-related studies. Several of these support the theory that epimedium has calcium channel-blocking activity, leading to vasodilating qualities and increased blood flow.[6,10]

In one of the best animal studies, the effects of epimedium extract (icariin) and another yang herb, semen cuscutae, were evaluated in 36 male Wistar mice.[11] Animals were divided into four groups including a control group, those receiving a horny goat weed extract, those receiving a semen cuscutae extract, and those receiving hCG. Subdermal injections were administered for six days. Following administration, animal testes, epididymi, and seminal vesicles were weighed. Results indicated that horny goat weed extract increased the weights of the epididymi and seminal vesicles but did not have an influence on testicular weights. Semen cuscutae also was able to increase the weights of the testes and epididymi. The authors concluded that both herbs possessed androgenic hormonal activity and gonadotropin-like actions.

In another animal trial, the herbal product BetterMAN™—a combination product that contains 18 traditional Chinese herbs including *Epimedium sagittatum*—was evaluated in a placebo-controlled trial using rats with experimentally induced ED.[12] Rats were randomized to receive a normal diet vs. a diet high in cholesterol. Eight control animals were fed a normal diet while 24 were fed a 1% cholesterol diet for four months. After two months, BetterMAN was added to the drinking water of 16 of the 24 rats receiving a high-cholesterol diet. Eight rats received daily dosages of 25 mg/kg and eight rats received daily dosages of 50 mg/kg. At four months, erectile function was evaluated with cavernous nerve electrostimulation in all animals. Results indicated that rats developed ED after being fed a 1% cholesterol diet for four months. Erectile response was significantly better in the treated group. Increased levels of basic fibroblast growth factor and caveolin-1 expression in the treated group was thought to protect the cavernous smooth muscle and endothelial cells from the harmful effects of high serum cholesterol.

Clinical Studies

Few sound clinical data describe the safety and efficacy of horny goat weed for ED or as an aphrodisiac, despite widespread use. An extensive search of the literature revealed no English language trials. Communication with members of the Herb Research Foundation, however, did identify four human clinical trials involving horny goat weed. All were in Chinese, requiring translation.

In the first of these trials, 50 patients with ED were treated with an oral, combined preparation of epimedium and semen cuscutae.[13] In this case series, 50 men with ED ranging in age from 20-60 years were treated as outpatients. All patients in the study reportedly had experienced ED for seven months to 16 years. Treatment involved taking the ground powder of epimedii and cuscuta (15 g each) in a 5 g dose tid with "cooking wine." Treatment lasted on average for 20 days. In addition, supplementary treatment included perineal and genital

massage as well as bathing in medicinal water and other Chinese herbs for 20 minutes every evening. Entry requirements for the study included no intercourse for 100 days prior to participation.

Results indicated that 38 patients achieved total recovery, which accounted for 76% enrolled; eight patients experienced some improvement (18%). Four patients noted no improvement (8%) for a total effectiveness rate of 92%. The treatment period ranged between seven and 48.5 days. Follow-up visits with 20 patients found no recurrence of symptoms for two years.

In the second study, 30 patients with kidney disease (17 males and 13 females) ranging from 19 to 43 years of age were evaluated.[14] Patients were given "Yishen Soup," which was comprised of 12 Chinese herbs including epimedium. Patients were treated for 20 to 84 days. Improvement was defined as either resolution of clinical symptoms or improved "urine" parameters and blood urea nitrogen. Those patients having a "tendency" toward impotence were noted to have an improvement of symptoms with treatment. According to the authors, 16 cases achieved clinical recovery, with 11 showing improvement and three showing no effects.

In the third trial, the effects of epimedium on a number of clinical and laboratory parameters were evaluated in 34 patients with renal failure on hemodialysis.[15] Twenty-one males and 13 females (average age of 38) were enrolled. Patients receiving epimedium were noted to have improvement in both renal and sexual function, especially patients under 40 years of age. Patients were treated for four months but were noted to show improvement even after one dose.

In the final trial, 22 hemodialysis patients were treated with an *Epimedium sagittatum* decoction.[16] In this trial, 12 other patients receiving hemodialysis served as controls and did not receive the extract. There is no mention as to the selection of controls or a matching placebo. Techniques of blinding and randomization were not revealed. It was found that those patients in the treatment arm had "improvement" in sexual performance and an improved quality of life.

All the mentioned studies have significant limitations including small sample size, lack of uniform diagnosis, use of multiherbal preparations, use of co-interventions (massage), and lack of appropriate controls or random assignment.

Adverse Effects and Drug Interactions

Horny goat weed appears to be safe in animals when taken for short periods of time in recommended dosages. At an oral dose of 450 g/kg, normal activity of mice was not altered and toxic reactions were not observed during three days of observation. The LD_{50} of the concentrated decoction of the herb in mice was 36 g/kg by intraperitoneal administration.[7]

A manual of traditional Chinese medicine lists adverse effects; it appears that these have been observed in animals, but the source is unclear.[17] Extended use of Japanese epimedium (*Epimedium grandiflorum*) has resulted in dizziness, nausea, vomiting, dry mouth, and nosebleed.[17] Large doses of Japanese epimedium have been noted to cause respiratory arrest and exaggeration of tendon reflexes to the point of spasm.[17] Given the paucity of documented safety data in humans, horny goat weed use is contraindicated in pregnancy.

No known drug interactions have been identified. Patients on vasodilating agents, however, should be aware of the theoretical possibility of hypotension when combining horny goat weed with them.

Formulation and Dosage

A number of herbal preparations utilizing epimedium alone or in combination with other herbal remedies are available. Several standardized formulations use a 5% icariin flavonoid marker. This "standardization," however, is not necessarily the active principal. The usual recommended daily dosage is between 0.5 mg and 1.5 mg.

Conclusion

Unfortunately, most of what is known about horny goat weed comes from basic science studies and involves human data from inadequate case series. Given the limited amount of human data available regarding epimedium for ED and as an aphrodisiac, its use cannot be recommended. Its rising acceptance in the U.S. population is concerning, given the *Epimedium* species' vasodilating properties, which may be contraindicated in patients on antihypertensives and nitrates. A randomized clinical trial is needed to help clarify the value of this popular herb.

Recommendation

Based on the present data, the use of horny goat weed for ED or as an aphrodisiac should be discouraged. Primary care providers should focus their efforts on screening their patients for ED and use standard, effective, proven therapies. ❖

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Reader Question

Comment: I am a board certified urologist who incorporates complementary medicine into my daily practice. I found the article by Teresa Klepser and Nicole Nisly, "Chondroitin for the Treatment of Osteoarthritic Pain" (*Alternative Medicine Alert*, August 2000 pp. 85-88) to be very informative. However, the authors apparently are unaware of research which suggests that chondroitin sulfate may cause prostate cancer to spread or recur following treatment.[1] Although the exact mechanism is unknown, when chondroitin sulfate binds with versican—a growth-stimulating protein that is found within the prostate—the resulting chondroitin sulfate-versican complex can stimulate the spread of prostate cancer.[2] Although the data are preliminary, I encourage men with prostate cancer, and those who are at risk of developing prostate cancer, to avoid chrondroitin sulfate until there is a definitive answer.

Mark W. McClure, MD, FACS
Raleigh, NC

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Response: *We appreciate your comments regarding our article and the references you site regarding the possibility that chondroitin sulfate may cause prostate cancer to spread or recur post-treatment. The information presented is intriguing, and certainly requires further investigation. We agree that until more conclusive information is available, males who are at risk of developing or who already have prostate cancer should avoid chondroitin. In those patients, glucosamine may be an alternative option.*

Teresa Klepser, PharmD
Assistant Professor, Division of Clinical and Administrative Pharmacy, College of Medicine
Nicole Nisly, MD
Assistant Professor, Department of Medicine
University of Iowa, Iowa City

CME Questions

4. **Massage therapy for preterm infants has demonstrated which of the following benefits?**
   a. Improved coordination
   b. Improved intestinal motility
   c. Improved daily weight gain
   d. All of the above

5. **Limited evidence suggests the following long-term effects of massage:**
   a. improved weight gain.
   b. improved motor function.
   c. improved cognitive development.
   d. All of the above

6. **Humans have the ability to synthesize ascorbic acid.**
   a. True
   b. False

7. **Smokers are at risk for developing asthma because of:**
   a. increased bronchial reactivity.
   b. increased levels of eosinophils.
   c. increased levels of inflammatory mediators in airways.
   d. All of the above

8. **Horny goat weed may cause the following side effects:**
   a. nausea.
   b. vomiting.
   c. dry mouth.
   d. dizziness.
   e. All of the above

9. **Horny goat weed may improve erectile dysfunction by the following mechanism:**
   a. increasing testosterone levels through cAMP.
   b. reducing estrogen levels.
   c. reducing blood flow via vasoconstriction.
   d. increasing blood pressure and heart rate.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Dangers of Products Containing Ephedra

Source: Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;343:1833-1838.

"DIETARY SUPPLEMENTS THAT CONtain ephedra alkaloids (sometimes called ma huang) are widely promoted and used in the United States as a means of losing weight and increasing energy. In the light of recently reported adverse events related to use of these products, the Food and Drug Administration (FDA) has proposed limits on the dose and duration of use of such supplements. The FDA requested an independent review of reports of adverse events related to the use of supplements that contained ephedra alkaloids to assess causation and to estimate the level of risk the use of these supplements poses to consumers.

"We reviewed 140 reports of adverse events related to the use of dietary supplements containing ephedra alkaloids that were submitted to the FDA between June 1, 1997, and March 31, 1999. A standardized rating system for assessing causation was applied to each adverse event.

"Thirty-one percent of cases were considered to be definitely or probably related to the use of supplements containing ephedra alkaloids, and 31 percent were deemed to be possibly related. Among the adverse events that were deemed definitely, probably, or possibly related to the use of supplements containing ephedra alkaloids, 47 percent involved cardiovascular symptoms and 18 percent involved the central nervous system. Hypertension was the single most frequent adverse effect (17 reports); followed by palpitations, tachycardia, or both (13); stroke (10); and seizures (7). Ten events resulted in death, and 13 events produced permanent disability, representing 26 percent of the definite, probable, and possible cases.

"The use of dietary supplements that contain ephedra alkaloids may pose a health risk to some persons. These findings indicate the need for a better understanding of individual susceptibility to the adverse effects of such dietary supplements."

Source: Gurley BJ, et al. Content versus label claims in ephedra-containing dietary supplements. *Am J Health Syst Pharm* 2000;57:963-969.

The ephedra alkaloid content of 20 ephedra-containing supplements was determined by high-performance liquid chromatography. Contents of (-)-ephedrine, (+)-pseudoephedrine, (-)-methylephedrine, (-)-norephedrine, and (+)-norpseudoephedrine were measured.

Ephedra alkaloid content varied considerably among products. Total alkaloid content ranged from 0.0-18.5 mg per dosage unit. Ranges for (-)-ephedrine and (+)-pseudoephedrine were 1.1-15.3 mg and 0.2-9.5 mg, respectively. (+)-Norpseudoephedrine, a Schedule IV controlled substance, was often present. Significant lot-to-lot variations in alkaloid content were observed for four products. For one product, lot-to-lot variations in the content of (-)-ephedrine, (+)-pseudoephedrine, and (-)-methylephedrine exceeded 180%, 250%, and 1,000%, respectively. Half of the products exhibited discrepancies between the label claim for ephedra alkaloid content and actual alkaloid content in excess of 20%. One product was devoid of ephedra alkaloids.

Assays of 20 ephedra-containing dietary supplements showed that alkaloid content often differed markedly from label claims and was inconsistent between two lots of some products.

COMMENT

Manufacturers and distributors of Metabolife 356®, Dexatrim®, and other popular over-the-counter ephedra-containing agents should read these arti-

cles, because it may help them avoid liability. Clinicians should read them because it may help their patients avoid stroke, myocardial infarction, and even death—without exaggeration.

These data demonstrate what most clinicians have heard by anecdote—hypertension, stroke, seizures, and death have been attributed to ephedra-containing compounds. What's worse is that it's not predictable how much ephedra or a metabolite is in any one given formulation—from nothing at all to, more commonly, 1,000% of expected. Lot-to-lot variation in any supplement is disturbing, but especially so in a deadly one.

Perhaps the only disease about which it is socially acceptable to taunt the victim, obesity is as frustrating to patients as it is to doctors. Patients who want to lose weight and seek a physician's help in so doing are among the most motivated of all patients. It takes courage to make this request of a doctor, since patients realize that doctors know little about obesity treatment and have less time than ever for the behavior modification that is needed and effective.

Yet physician encouragement does not take long at all, and is much more helpful than any over-the-counter or prescription medication. Instead of medications, ask patients to do just two things to start: First, always sit while eating, and second, never eat out of the refrigerator. These two steps help people recognize ways to identify and control portion size, and to value the flavor and quality of the food they are about to inhale.

Recommendation

There are just no two ways about it: Ephedra alkaloids not only are unpredictably quantified in over-the-counter preparations, but are dangerous. In part they're dangerous because of the demonstrated wild variance in concentration, and in part because of their sympathomimetic effects. Insist that patients avoid them...no exceptions. ❖

Aromatherapy: Evidence-Based Medical Care?

Source: Cooke B, Ernst E. Aromatherapy: A systematic review. *Br J Gen Pract* 2000; 50:493-496.

"AROMATHERAPY IS BECOMING increasingly popular; however, there are few clear indications for its use. To systematically review the literature on aromatherapy in order to discover whether any clinical indication may be recommended for its use, computerized literature searches were performed to retrieve all randomized controlled trials of aromatherapy from the following databases: MEDLINE, EMBASE, British Nursing Index, CISCOM, and AMED. The methodological quality of the trials was assessed using the Jadad score. All trials were evaluated independently by both authors and data were extracted in a pre-defined, standardized fashion. Twelve trials were located: six of them had no independent replication; six related to the relaxing effects of aromatherapy combined with massage. These studies suggest that aromatherapy massage has a mild, transient anxiolytic effect. Based on a critical assessment of the six studies relating to relaxation, the effects of aromatherapy probably are not strong enough for it to be considered for the treatment of anxiety. The hypothesis that it is effective for any other indication is not supported by the findings of rigorous clinical trials."

COMMENT

Another report from the most prolific and one of the most principled and evidence-based shops in alternative medicine evaluation located at the University of Exeter, this critical assessment is unlikely to turn the cosmetics, spa, and beauty businesses on their heads. It does, however, suggest that the scientific basis for aromatherapy is yet to be developed.

Concentrated essential oils are aromatic plant extracts massaged into (or at least, on to) the skin. Whether inhaled essential essences are at work on the limbic system, or its the magic hands of a therapist that calms clients, or both, no one knows.

Ten of the 12 randomized clinical trials were positive, though there was wide variance in their interventions, frequency, duration, and indication. Six studies were identified for reduction of anxiety and improvement in well-being. Follow-up was minimal, and only one trial of these latter six was double-blind (though blinding here would be tough).

The introduction of aromatherapy in cancer care, palliative care, and midwifery begs the question of whether aromatherapy is a medical intervention or just a relaxing, safe way to spend 15 minutes to an hour. Whether employers will want to include aromatherapy as a covered benefit will determine whether their employees (our patients) will be able to access it regularly and readily in a doctor's office or in a day spa.

Aromatherapy does improve anxiety, at least temporarily. It makes people feel better, giving them something alluring to smell and offering hands-on, paid-for, personal attention. Is that medicine? Yes, if it is therapeutic, and though the data are soft, it appears to be for that indication. But is it evidence-based medical care? You decide.

Recommendation

Should you recommend rosemary- or lavender-containing neck pillows, microwaved for two minutes, for tension headache sufferers, instead of two beers or a prescription anxiolytic? If it appeals to your patient, and if she can microwave safely and can afford the pillow at the drugstore—yes, absolutely. ❖

In Future Issues:

Acupuncture for Migraine

Chromium for Weight Loss

Yoga for Musculoskeletal Disorders

Supplement to *Alternative Medicine Alert*
February 2001

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

The B Vitamins: Part I

Vitamin B_1 (thiamin)

IT IS ESTIMATED THAT 45% OF AMERICANS DO NOT CONSUME ADEQUATE AMOUNTS OF VITAMIN B_1. Deficiencies manifest most commonly as disorders of the neuromuscular, gastrointestinal, and cardiovascular systems. Beriberi is the classic deficiency syndrome and is seen most commonly in Asian countries. In the United States, deficiencies are seen most frequently in severely malnourished infants, the elderly, and adults who diet chronically, suffer alcoholism (Wernicke-Korsakoff syndrome), and eat heavily processed- or refined-food diets.

Dietary Reference Intakes (DRI)

0.2 mg/d for children 0-6 mo	0.9 mg/d for children 9-13 y
0.3 mg/d for children 7-12 mo	1.2 mg/d for men 14 y and older
0.5 mg/d for children 1-3 y	1.0 mg/d for women 14-18 y
0.6 mg/d for children 4-8 y	1.1 mg/d for women 18 y and older

Active Constituents

Vitamin B_1 must be phosphorylated to be metabolically active. It combines with two molecules of phosphoric acid to form the important co-enzyme thiamine pyrophosphate (TPP).

Food Sources

All plant and animal foods contain vitamin B_1, but in very low concentrations. The richest sources include brewer's yeast, organ meats, and whole cereal grains. Severe deficiency may require parenteral replacement.

Mechanism of Action

- As co-enzyme TPP, performs oxidative decarboxylation reactions in the Krebs cycle and transketolation reactions in the pentose phosphate shunt.
- Plays a major role in the conversion of glucose into biological energy.
- Necessary for the maintenance of nerve tissues, nerve function, and nerve transmission.
- Necessary for the maintenance and proper functioning of muscles, especially the heart.
- Required for the synthesis of acetylcholine, the primary neurotransmitter involved in thought and memory processes.
- Involved in fatty acid synthesis.

Clinical Uses

- To reduce the occurrence of cataracts.
- To treat diabetic neuropathy.

Adverse Effects/Toxicity

As a water-soluble vitamin, vitamin B_1 toxicity is very rare and most likely would require IV or parenteral administration. Overdose would require multiple gram dosages. Rare reports of hypersensitivity can be found in the literature.

Interactions/Nutrient Depletion

- Vitamin B_1 is heat sensitive and is destroyed easily during cooking.
- Tea may contain anti-thiamin factors, but this is not a problem in usual food intakes.

- Raw fish may contain microbial thiaminases.
- Vitamin B_1 levels are depleted by diuretic drugs and GI conditions such as diarrhea, and malabsorption due to lactose intolerance and celiac disease.
- Alcohol interferes with the absorption of vitamin B_1, which is necessary for the metabolism of alcohol.
- Drugs that deplete vitamin B_1 include: aminoglycosides, bumetanide, cephalosporins, chlortetracycline, demeclocycline, doxycycline, ethacrynic acid, fluoroquinolones, furosemide, macrolides, minocycline, oxytetracycline, penicillins, phenytoin, sulfonamides, tetracyclines, torsemide, and trimethoprim.
- Deficiency symptoms usually are neurologic (fatigue, depression, irritability, memory loss, mental confusion, loss of reflexes in legs, defective muscular coordination, and nerve inflammation, including "pins and needles" and numbness), cardiovascular (edema, muscular weakness, sore calf muscles, heart palpitations, rapid pulse rate), or gastrointestinal (indigestion, weight loss, and anorexia) in nature.

Vitamin B_2 (riboflavin)

Vitamin B_2 deficiency most commonly affects the skin, eyes, and mucous membranes of the GI tract. Approximately 34% of Americans consume less than the recommended amounts. Like vitamin B_1, infants, alcoholics, and elderly persons on highly processed diets are at greatest risk of vitamin B_2 deficiencies.

Dietary Reference Intakes (DRI)

0.3 mg/d for children 0-6 mo
0.4 mg/d for children 6 mo-1 y
0.5 mg/d for children 1-3 y
0.6 mg/d for children 4-8 y
0.9 mg/d for children 9-13 y
1.2 mg/d for men 14 y and older
1.0 mg/d for women 14-18 y
1.1 mg/d for women 19 y and older

Food Sources

Dietary sources of vitamin B_2 include liver, milk, dairy products, meats, dark green vegetables, eggs, avocados, oysters, mushrooms, fish (e.g., salmon and tuna), and enriched breakfast cereals.

Mechanism of Action

- Facilitates the metabolism of carbohydrates, fats, and proteins.
- Combines with phosphoric acid to become part of two flavin co-enzymes: flavin mononucleotide (FNfN) and flavin adenine dinucleotide (FAD). FNfN and FAD bind more than 100 flavoprotein enzymes, which catalyze oxidation-reduction reactions in cells.
- Plays a critical role in the conversion of carbohydrates to ATP in the production of energy.
- Has important antioxidant activity by itself and as part of the enzyme glutathione reductase.
- Is necessary for growth and reproduction.
- Is necessary for healthy skin, hair, and nails.

Clinical Uses

- To prevent migraine headaches.
- To reduce the occurrence of cataracts.

Adverse Effects/Toxicity

Vitamin B_2 is water-soluble and not appreciably stored in the body. There is no known toxicity.

Interactions/Nutrient Depletion

- Approximately 15% of vitamin B_2 is absorbed if taken alone, vs. 60% when taken with food.
- Vitamin B_2 is heat stable, but very photosensitive.
- Drugs that deplete vitamin B_2 include: acetophenazine, aminoglycosides, amitriptyline, amoxapine, cephalosporins, chlorpromazine, chlortetracycline, chlomipramine, demeclocycline, desipramine, doxepin, doxycycline, fluoroquinolones, fluphenazine, imipramine, macrolides, mesoridazine, methdilazine, methotrimeprazine, minocycline, nortriptyline, oral contraceptives, oxytetracycline, penicillins, perphenazine, prochlorperazine, promazine, promethazine, protriptyline, sulfonamides, tetracyclines, thiethylperazine, thioridazine, trifluoperazine, trimethoprim, trimipramine.
- Symptoms of deficiency include dermatologic (cheilosis, seborrheic dermatitis, and angular stomatitis) and ophthalmologic (red, teary, burning, itching, and photosensitive eyes) manifestations.

Resources

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February 1, 2000

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Sincerely,

Brenda L. Mooney

Brenda L. Mooney
Vice President and Group Publisher
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