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Guided Imagery as Supportive Therapy in Cancer Treatment

By Roberta Lee, MD

MANY CHALLENGES FACE THE CLINICIAN PROVIDING "SUPPORTIVE care" to cancer patients. Psychological problems and deterioration of quality of life caused by severe nausea, cachexia, and pain are just a few of the hurdles faced by those fighting this disease. Guided imagery, a cognitive intervention, has been implemented with increasing frequency as a therapeutic option for many encountering these difficulties.[1,2]

Definition

Achterberg has defined imagery as "the thought process that invokes and uses the senses: vision, audition, smell, taste, the senses of movement, position, and touch. It is the communication mechanism between perception, emotion, and bodily change."[3] Guided imagery is a psychological and behavioral device that equips individuals to harness their ability to imagine and visualize all of the senses. Using self-selected images, patients can communicate with physiological processes of which they are not consciously aware.[4]

History

The practice of imagery in medicine has a long history. The ancient Greeks described trance experiences that were used as vehicles for treatment of mental or physical illness. In the 18th century, Franz Mesmer identified hypnosis, a cousin to guided imagery, as a formal phenomenon of psychotherapeutic interest.

In the mid-1950s, the American Medical Association and the American Psychiatric Association recognized hypnosis as a therapeutic tool. Approximately 10 years later, the technique of guided imagery was developed through the collective efforts of psychologists and physicians including Carl and Stephanie Simonton, Irving Oyle, Roberto Assagioli, Jean Achterberg, Frank Lawlis, and Martin Rossman.

Mechanism of Action

The potential therapeutic mechanisms for guided imagery have not been determined precisely. Green and Green, early pioneers in guided imagery research, proposed the first psychoneurological theories

Volume 2 • Number 6 • June 1999 • Pages 61-72

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about the relation of imagery to healing. These researchers postulated that when the mind chooses and recreates an image of a desired physical, emotional, or mental behavior, a hierarchical self-regulating feedback mechanism takes over. This mechanism involves the cerebral cortex, the limbic system, and the hypothalamus, and affects the autonomic nervous system.[4]

The imagery sequence begins with the patient creating a mental image that, when stimulated in a deeply relaxed state, accesses the limbic system. The limbic system accepts the image as a course of action to be implemented. If the imagery includes changes in the involuntary autonomic nervous system, the limbic system "programs" the hypothalamus to bring about the physiological changes.[4]

Other mechanisms have been proposed for the use of imagery in controlling pain. In the gate control theory, pain stimuli are transmitted through the substantia gelatinosa in the dorsal horn of the spinal cord, which may act as a gating mechanism. Transmission of painful stimuli are blocked at the gate before reaching higher levels of conscious awareness. This theory acknowledges influences of cognitive control or higher CNS processing of pain control.[5]

Another theoretical perspective about imagery and pain control involves a model of stress and coping. The self-regulation model of pain control proposed by Leventhal and J. E. Johnson suggests that a person experiencing a stressful or noxious stimulus may initiate coping efforts that regulate responses to both sensory stimuli and emotional distress. Thus, a cognitive strategy such as guided imagery may decrease the anxiety response to stressful stimuli and to both sensory and emotional responses to pain.[6]

Technique

Guided imagery and hypnosis may be confused. Guided imagery is hypnotic, but involves interaction between the guide and the patient during the session. The patient is more "passive" in hypnosis, which does not require interaction.

The modern use of a therapeutic imaging session usually entails 20 to 30 minutes. The session begins with a relaxation exercise to help focus attention and "center" the mind. In the relaxation phase, the practitioner coaches the patient to relax "progressively" different parts of the body (e.g., first the feet, then the ankles, the knees, and so on). Once a state of total body relaxation is achieved, the practitioner suggests the introduction of an image of a serene, comforting environment.

For example, a typical dialogue might be: "Keep your eyes closed while you take a few deep, easy breaths, and imagine yourself in the most peaceful, beautiful serene place you can conjure up. Think of a time when you felt relaxed and peaceful—perhaps a walk in the park or a day on the beach. Focus on the sights, sounds, smells, and physical sensations associated with this time. Focus on this for about five minutes."

A number of options are possible after relaxation is established. Active imagery—the recruitment of the five senses—can be used to conjure up positive images designed to alleviate pain, relieve nausea, or even help patients become more in touch with their feelings about a chronic illness. In these examples, the image becomes a symbol that patients use to achieve a therapeutic response.

Clinical Studies

Imagery intervention and its clinical applications in oncology have focused on four areas: efficacy in pain control; ability to improve quality of life through psychological support; influences on immunity; and influences on surgical outcome.

Cancer pain involves complex physiologic and psychological mechanisms that often necessitate a combination of clinical interventions to achieve effective management. Hypnotic (imagery) intervention in pain control has demonstrated that imaging techniques may be

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

PUBLISHER: Brenda Mooney.

MANAGING EDITOR: Leslie G. Coplin.

ASSOCIATE MANAGING EDITOR: Paula L. Cousins.

GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.

POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: 1-800-688-2421.

Customer Service E-Mail Address: customerservice@ahcpub.com

Editorial E-Mail Address: leslie.coplin@medec.com

World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States

$219 per year (Student/Resident rate: $119).

Outside the United States

$249 per year plus GST (Student/Resident rate: $130 plus GST).

Back Issues

$36 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials. This program has been reviewed and is acceptable for up to 20 Prescribed hours by the American Academy of Family Physicians. Term of approval is for one year from beginning of distribution date of July 1, 1998, with option to request yearly renewal.

For CME credit, add $50.

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Conflict of Interest Disclosure

Physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. La Puma is Director of C.H.E.F. Skills Research. Dr. Ofman has the following relationships: Consultant for Zynx Health, Inc., Cedars-Sinai Health System; Research for Astra USA, Johnson & Johnson, Janssen. Dr. Barrette, Dr. deLeon, Dr. Dietz, Dr. Klepser, Dr. Nisly, Dr. Schiedermayer, and Dr. Sorrentino have no relationships with companies related to the field of study covered by this CME program.

helpful. A meta-analysis of all research articles published between 1960 and 1988 on the topic of cognitive strategies for pain modification showed that in more than 85% of the studies, cognitive interventions (such as hypnosis, guided imagery, and progressive relaxation) were significantly more effective in attenuating pain than no treatment.[7]

Even cancer patients in remission and those without need for chemotherapy or radiotherapy may have a poor quality of life. It is reported that even after years of complete remission, patients experience great apprehension about possible recurrence.[8]

Lyles et al reported that patients practicing "guided relaxation/imagery" felt less emotional distress, nausea, and physiological arousal following chemotherapy infusion than controls. In this study, 50 cancer patients receiving chemotherapy (25 by push injection and 25 by drip infusion) were assigned to one of three protocols for their chemotherapy treatments: progressive muscle relaxation plus guided imagery; therapist control, in which a therapist provided support and encouragement but not systematic relaxation training; and no treatment control. During the training sessions, patients who received relaxation training reported feeling significantly less anxious and nauseated during chemotherapy, showed less physiological arousal (as measured by pulse rate and systolic blood pressure), and experienced less anxiety and depression immediately after chemotherapy.[9]

Imagery and its effect on immunity have recently attracted the interest of researchers. A study by Kiecolt-Glaser et al examined the impact of imagery on natural killer cell function. Their treatment subjects were medical students with normal immune function. The students in the treatment arm were taught hypnosis and progressive relaxation. The controls were students with no relaxation training. Natural killer cell function and other cellular immune functions were measured after the students took their exams. Those who practiced the techniques routinely had significantly better immune function during exposure to the stress of exams.[10]

Gruber et al measured natural killer function and mixed lymphocyte responsiveness in patients with stage 1 breast cancer over an 18-month period. Subjects were provided with relaxation, guided imagery, and biofeedback training. The guided imagery tape provided a short segment on relaxation asking patients to place themselves in a relaxed setting where all things were possible. General guidelines were then given to patients regarding the immune system and the development of health promoting processes within their bodies. No specific imagery was suggested to the patients. The findings showed significant effects in natural killer cell activity ($P < 0.017$) and mixed lymphocyte responsiveness ($P < 0.001$). No significant psychological changes were detected. However, reductions were seen in psychological inventory scales measuring anxiety.[11,12]

Surgical outcome with the use of imagery has been another focus of clinical research. In one randomized controlled study, the value of a brief preoperative hypnosis experience was explored with a sample of 36 head and neck cancer surgery patients. Fifteen patients volunteered for hypnosis and 21 received the usual care (no hypnosis). Within the hypnotic intervention group, hypnotizability was negatively correlated with surgical complication and there was a trend toward negative blood loss during surgery and postoperative complications.[13]

Adverse Effects

Imagery techniques involve the skillful use of imagination which interplays in complex ways with the psyche. Not all cancer patients are ideally suited for this type of intervention. In some instances the use of guided imagery has had a significant destabilizing psychological effect or "abreaction."[14]

Contraindications/Poor Candidates

Psychotic patients have poor outcomes with imaging techniques. Those patients who have fundamental spiritual beliefs that prevent introspection seem to do poorly with this intervention.[14] Patients who have experienced deep psychological, physical, or sexual trauma should not be casually introduced to this technique.

Availability

Learning guided imagery requires a time commitment and specific training. Currently, individuals who have been certified in guided imagery can be identified by contacting the Academy for Guided Imagery. This institution provides a structured curriculum and certification process involving guided imagery. The training involves up to 150 hours of observed instruction before qualifying for certification. Psychiatrists are not routinely trained in imagery, but may sometimes elect such training. Psychologists, physicians, social workers, and nurses among others may include imagery in their services.

Conclusion

Especially as an alternative to sedating medication in improving quality of life, guided imagery is of interest. The scientific data to support its use are not conclusive, but it may provide a means for patients to regain a sense of control over their lives in the face of crisis. After training, patients are able to evoke the imagery on their own (with audio or visual aids) at any time.

Recommendation

Guided imagery appears to be generally safe and potentially beneficial in providing symptomatic relief to some cancer patients. Guided imagery may allow some cancer patients to reduce anxiety and lessen symptoms of nausea and pain through use of their own sensory recruitment. ❖

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Chaste Tree Berry for Premenstrual Syndrome

By Teresa Klepser, PharmD and Nicole Nisly, MD

BETWEEN 20-50% OF WOMEN SUFFER FROM PREMENSTRUAL tension at some time during their lives.[1] Many women experience premenstrual symptoms such as nervousness, irritability, depression, bloating, breast tenderness, weight gain, skin problems, and digestive problems. Various therapies have been studied for the management of premenstrual symptoms including hormones, vitamins, dopamine agonists, non-steroidal anti-inflammatory drugs, diuretics, magnesium, calcium, lithium, exercise, and lifestyle modification.

One herb that may be useful in treating premenstrual syndrome is chaste tree berry, also commonly called chasteberry and monk's pepper.[2] Chaste tree berry is from the fruit of *Vitex agnus-castus* that grows along the Mediterranean coastal region and in central Asia. The berries have a pepper-like taste and smell and are used as an inexpensive substitute for the black pepper spice.[3]

The chaste tree berry gets its name from the belief that the plant would inspire chastity. To help with chastity, monks would eat the berries or seeds as a spice to decrease sexual desire.[2,3] It is also believed that chaste tree berry is useful in passing afterbirth and increasing milk secretion.[4] Chaste tree berry has been used in Europe for many years to treat female reproductive tract disorders such as menstrual abnormalities, premenstrual syndrome, menopausal complaints, and infertility.[5,6]

Indications

Vitex agnus-castus is approved in Germany for use in disorders of the menstrual cycle, premenstrual syndrome and mastodynia.[2,7]

Constituents

Vitex agnus-castus contains a wide variety of bioactive compounds, including iridoid glycosides, flavonoids, progestins, and volatile oils.[2] (*See Table 1 for progestin components of* Vitex agnus-castus.) Although many compounds have been identified in *Vitex agnus-castus*, few are known to be active, including aucubin, luteolin 7-O-(6'-p-benzoylglucoside), casticin, testosterone, α-pinene, sabinene, β-pinene, β-myrcene, ρ-cymene, terpinene-4-ol, α-terpineol, and caryophyllene epoxide.[8]

Mechanism of Action

Some of the active ingredients in vitex—including

α-pinene, β-pinene, caryophyllene-oxide, chrysosplenol, luteolin-7-glucoside, and orientin—are believed to possess anti-inflammatory effects.[8] Ascaridole, myrcene, and ρ-cymene are believed to have analgesic properties; 1,8-cineole, α-pinene, α-terpineol, ascaridole, bornyl-acetate, citronellol, and limonene are thought to have sedative properties; and terpinen-4-ol is believed to be a diuretic.[8] Testosterone may be the only active hormone.[9] Studies show that vitex may have dopaminergic properties.[10] However, it is unknown which active ingredients possess the dopaminergic properties and how these properties affect premenstrual syndrome symptoms.

Laboratory and Animal Studies

In vitro studies show that vitex binds to dopamine receptors and inhibits the secretion of prolactin from the rat pituitary gland.[2,5,11] Vitex does not appear to inhibit the pituitary's production of luteinizing hormone or follicle stimulating hormone.[11] Animal studies have also shown an increase in lactation and mammary enlargement.[2] No in vivo human studies to support this finding and no published studies that analyze the pharmacokinetics of vitex could be found.[7]

Clinical Studies for Premenstrual Syndrome

A 1992 study evaluated the efficacy of vitex liquid extract in 1,542 women, aged 13-62 years, with a diagnosis of premenstrual syndrome. These women received 40 drops of vitex liquid extract every morning for an average of 25.3 days. Questionnaires were given to the patients and their gynecologists to rate each patient's symptomatic response to vitex. Physicians rated vitex as "very good" or "good" 92% of the time. In contrast, 57% of the patients reported improvement in symptoms and 33% noted complete relief of their symptoms.[12]

A randomized, placebo-controlled, intention-to-treat trial compared the safety and efficacy of Agnolyt® (a vitex capsule formulation) with pyridoxine (vitamin B_6).[1] The study included 175 women, aged 18-45 years, with premenstrual tension.

For three menses, women were given one capsule of vitex dried fruit extract (3.5-4.3 mg) plus one placebo capsule daily or one placebo capsule on days 1-15 of the menstrual cycle and 100 mg of vitamin B_6 twice daily on days 16-35 of the menstrual cycle. End points assessed included the premenstrual tension syndrome scale, six typical premenstrual symptoms, and the clinical global impression scale. A sample size of 100 women in each group was calculated; however, 175 women were enrolled and only 127 women completed the trial and were included in the efficacy analysis. Twenty women terminated the study prematurely; 12 in the vitex group and eight in the B_6 group; no explanation was given.[13]

Vitex and vitamin B_6 produced similar reductions in the premenstrual tension syndrome scores (-47.7% vs. -48%, respectively). In the vitex group, 77.1% of the patients reported improvement in the clinical global impression scale compared to 60.6% of the vitamin B_6 patients.[12] Eighty percent of the women received "adequate" efficacy when assessed by the investigators. However, when efficacy was assessed by the patients, 36% of the vitex group reported having no complaints, compared to 21.1% of the vitamin B_6 group. The absence of a placebo group, the inability to achieve calculated sample size, and the uneven baseline for the two groups make this study less than definitive.[13]

Of the 175 women enrolled, adverse events occurred in 17 patients; 12 women in the vitex group and five women in the vitamin B_6 group. Side effects included gastrointestinal and lower abdominal complaints, allergic and acneiform skin reactions, and temporary headaches. No serious side effects occurred.[6,14]

Another randomized, double-blind, placebo-controlled trial evaluated the efficacy of vitex in 52 women with menstrual cycle disturbances secondary to latent hyperprolactinemia. Women were given 20 mg of Strotan®, an aqueous-alcoholic extract of vitex fruit, once daily for three months. Women who received vitex had a significant reduction of prolactin release and a significant reduction of their premenstrual syndrome symptoms compared to placebo.[15]

Table 1

Progestins found in *Vitex agnus-castus* leaves and flowers

progesterone (leaf)
hydroxyprogesterone (leaf)
testosterone* (leaf)
epitestosterone (leaf)
androstenedione (flower)

*Compound thought to have biologic activity

Source: Chaste Tree. In: *The Review of Natural Products.* St. Louis, MO: Facts and Comparisons: 1998.

Adverse Effects

Side effects may include gastrointestinal and lower abdominal complaints, allergic reactions (i.e., itching and rash), headache, and increased menstrual flow.[2] Early menstruation following delivery is noted as a rare side effect.[4] Side effects have been reported in fewer than 2% of patients.[4]

Table 2

Sample *Vitex agnus-castus* prices

Brand	Formulation	Recommended Dose	Price/Count
Enzymatic Therapy Inc.	225 mg chaste tree berry (*Vitex agnus-castus*) extract standardized to contain 0.5% agnuside (1,130 mcg/capsule) per capsule	1-2 capsules daily	$16.95/60 capsules
Nutritional Dynamics	150 mg chasteberry fruit standardized to contain 0.5% agnuside and 0.6% aucubin per capsule	1 capsule daily	$15.95/60 capsules
Nature's Herbs	100 mg chasteberry fruit and seeds (*Vitex agnus-castus*) concentrate standardized for a minimum of preferred 0.9-1.1% glycosides (a unique active component of which a minimum is 0.5% agnuside) per capsule. Combined with a base of dong quai root and Siberian ginseng	4 capsules daily	$11.99/60 capsules
Nature's Answer Chasteberry 0% alcohol	Chaste tree berry extracted using alcohol and water or other menstruums to capture active constituents; alcohol removed via cold extraction process	6-8 drops in water tid	$9.90/1 oz

Source: Online mail-order firms

Contraindications/Precautions

Vitex is contraindicated in pregnancy, lactation, and in women receiving hormone replacement therapy.[2,7] Although vitex contains progestins, the long-term effects of such "natural hormones" (e.g., the development of various hormone-medicated neoplasms) is unknown.

Drug Interactions

No drug interactions have been reported in the literature. However, dopamine-receptor antagonists, such as haloperidol, may weaken or block the effects of vitex.[7]

Dosage/Formulations

There are a variety of recommended preparations and dosages. Vitex is available as aqueous-alcoholic extracts (50-70% V/V) from the crushed fruit, tinctures, tea, or capsules.[4,7] Some preparations are formulated to give an average daily dose of 20-40 mg of berries. The daily dose of crushed fruit may then be divided and administered two or three times daily.[4] Vitex extract containing 175-225 mg is recommended to be standardized to contain 0.5% agnuside;[15] however, agnuside is thought to be an inactive ingredient. In Germany, the aqueous-alcoholic extracts are recommended. Results may be seen as early as four months or as late as 18 months.[4]

Herbalists recommend 1-2 ml of the tincture tid or 40 drops of a standardized tincture daily.[4,16] However, no strength for the tincture is given. Tea should be ingested three times a day.[16] The amount of vitex in tea is unknown. A cream preparation is also available that contains vitex and wild yam.

Many products containing vitex also contain other herbs such as black cohosh, dong quai, wild yam, Siberian ginseng, and licorice. Many of the combination products are not standardized. (*See Table 2 for price comparison.*)

Conclusion

Traditionally and historically, *Vitex agnus-castus* has been used in the treatment of female reproductive tract disorders. The clinical evidence is weak regarding the use of vitex in the treatment of premenstrual syndrome, but side effects appear to be rare and safety high.

Recommendation

Vitex may be an option for women who have tried vitamin B_6 and calcium, and who do not wish to use prescription hormonal treatment. However, it may be difficult for patients to find a standardized product. Although the effective dose remains unknown, most information suggests using a product that contains 20-40 mg of the dried berry extract standardized to contain 0.5% agnuside. Patients should be aware that results may take up to 18 months. However, systemic side effects should be minimal. ❖

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Guarana for Cognitive Enhancement

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

As the pressures of modern life continue to increase, people are seeking "natural products"—often presumed to be safer than synthetic counterparts—to help them combat fatigue and enhance mental performance. The herbal remedy guarana, which has a high caffeine content and historical use as a "cerebral stimulant," is becoming more popular in the United States.

Despite guarana's long history of use, especially in South America, few clinical studies have been undertaken to study its safety and efficacy. Those that do exist involve small numbers of patients and are of marginal quality. Despite this lack of clinical evidence, guarana's use continues to grow. Clinicians must be aware of this herb's actions and potential side effects.

History

Guarana is prepared from the dried crushed seed paste of the plant *Paullinia cupana* or *Paullinia sorbilis* (Family: *Sapindaceae*).[1] These plants are native to the Amazon Basin in Brazil.[2] Guarana was reportedly first discovered by the Maues-Sateres Indian tribe and has been used as a tonic and stimulant for thousands of years.[3] Native peoples have used guarana during periods of fasting to tolerate dietary restrictions, for dysentery, and as an aphrodisiac.[1] In the 19th century, guarana became popular as a stimulating drink in France,[4] and in 1880 the product was introduced as an official drug in the U.S. Pharmacopoeia, where it remained listed until 1910.[4] It later appeared in the National Formulary.

Pharmacology

Currently, guarana is classified as a food additive and dietary supplement. The herb's pharmacological activity is primarily due to its content of methylxanthine alkaloids.[5] Its phytochemical constituents include caffeine, hypoxanthine, saponins, tannins, xanthine, and timbonine.[6] Related alkaloids, including theophylline and theobromine, have also been identified but are found only in the bark, flowers, and leaves of the plant and have not been found in the seeds.[1] The high doses of saponins and tannins found in the plant have been demonstrated to have antioxidant properties.[7]

Some studies have noted guarana's ability to inhibit platelet aggregation following IV or oral administration,[8]

possibly from decreased platelet thromboxane synthesis.[9]

Proposed Mechanisms of Action

It is thought that guarana's major medicinal effects are due to its extremely high caffeine content.[10] Guarana has been found to contain between 2.6-7% caffeine by dry weight.[10] This compares to coffee beans which contain between 1-2% caffeine and dried tea leaves which contain between 1-4% caffeine.[1]

Some have speculated that the stimulant effect of guarana is more gradual and sustained than that given by an equivalent dose of caffeine,[11] the duration of action of which ranges from one to three hours. Guarana has a caffeine-tannin complex that is postulated to affect the dissolution rate of caffeine from guarana in the GI tract and slow absorption by the gut wall. This theory remains unproven.[11]

Some researchers claim that part of the revitalizing effects of guarana may be due to its antioxidant action.[12] These actions have been noted in vitro with inhibition of spontaneous lipoperoxidation.[12]

The use of guarana as a component in herbal weight loss preparations stems from numerous investigational studies showing the ability of the sympathetic stimulant ephedrine, when coupled with caffeine, to have a synergistic effect on increasing metabolic rates with subsequent increased energy expenditure (thermogenesis), and to have lipolytic effects.[13] These effects have resulted in a modest but statistically significant weight loss in both animal and human trials when combined with diet.[13]

Animal Studies

Several animal studies have examined various aspects of the herb and its physiological effects. One study compared behavioral effects in rats and mice subsequent to acute and chronic guarana administration.[12] These effects were compared with those produced by *Panax ginseng* administration. In this study, guarana was noted to have some antioxidant effects with resultant inhibition of spontaneous lipoperoxidation. Groups of animals treated with guarana in doses of 2,000 mg/kg showed no significant difference when compared to control groups for the parameters of motor activity, tremor, or salivation.

In another study, mice given a suspension of guarana in a dose of 0.3 mg/ml showed a significant increase in physical capacity when subjected to a stressful situation such as forced swimming after three to six months of guarana treatment.[16]

Clinical Trials

Despite its widespread use by the public, there are few human clinical trials looking at the safety and efficacy of guarana. Several small studies in humans have attempted to assess the effects of guarana on the cognition of normal volunteers with negative results. In one small study, three groups of normal volunteers ranging in age from 20 to 35 were given either placebo, 25 mg caffeine, or 1,000 mg of guarana containing 2.1% caffeine daily.[14] Subjects were treated for three days. Neuropsychological testing, assessment of quality of sleep, and a State-Trait Anxiety Inventory (STAI) evaluation assessing level of anxiety were all performed before and after treatment. After four days, no reproducible improvement in cognition was noted in any group. Interestingly, no adverse effects on sleep or anxiety were noted either. The authors concluded that the negative results may have been due to the short duration of treatment.

In another study, the effects of long-term administration of guarana on the cognition of normal, elderly volunteers were studied.[15] Forty-five patients were divided into three groups either receiving 1,000 mg of guarana containing 2.1% caffeine, 25 mg of caffeine, or matching placebo for 150 days. All volunteers underwent immediate and recent memory assessment along with assessment of psychomotor performance at the beginning of the study, and at the third and fifth months of treatment. Volunteers were also evaluated using a sleep assessment scale and anxiety assessment scale. Results showed that guarana did not cause statistically significant memory effect. During the study, four patients taking guarana developed side effects including tachycardia, insomnia, and epigastric discomfort. One patient taking caffeine developed epigastric discomfort while one receiving placebo complained of insomnia.

Adverse Effects and Drug Interactions

Some researchers have raised the possibility that guarana may have dose-dependent genotoxic, mutagenic, and carcinogenic effects.[17] Since guarana contains greater than 10% tannins, there is some concern of increased risk of carcinogenesis with long-term use.[17] Increased incidence of cancers of the upper GI tract have been reported in some black tea drinking populations, a beverage with equally high tannin content.

Despite these concerns, no published reports describing severe toxicity from guarana have been noted.[1] Much more is known about side effects of caffeine however. Caffeine effects typically include restlessness, nervousness, excitement, insomnia, diuresis, GI disturbances, tachycardia and even cardiac arrhythmias.[18] Long-term use may exacerbate fibrocystic breast disease and may lead to a caffeine dependence and withdrawal syn-

Table 1

Sample guarana prices

Brand	Formulation	Recommended Dose	Price/Count
Excel	455 mg guarana extract, 100 mg caffeine	1 capsule daily	$14.99/60 capsules
Dr. Clayton's	425 mg Amazonian guarana per tablet	1-2 tablets daily	$11.95/125 tablets
Source Naturals	900 mg guarana per tablet (equivalent to 35 mg naturally occurring caffeine per tablet)	1-4 tablets daily	$10.98/100 tablets
Natrol	200 mg guarana extract 4:1 per capsule (equivalent to 32 mg caffeine per capsule)	1-2 capsules daily	$7.95/90 capsules
Kal	800 mg guarana per tablet	3-6 tablets daily	$5.99/60 tablets

Source: Online mail-order firms

drome.[18] The one-time lethal dose for caffeine is estimated at 5-10 g, but fatal poisoning by caffeine is rare.[19] Dosages greater than 1 g can lead to untoward effects; signs of intoxication can be seen at doses greater than 250 mg.[20]

In our own practices, side effects associated with the use of preparations containing guarana have included excessive nervousness and insomnia requiring discontinuation. In one such patient, herbal sedatives including valerian root and kava were self administered to counteract the stimulant effects noted with the use of guarana. Subsequent office visits resulted in discontinuation of all supplements and resolution of symptoms.

Drug Interactions/Contraindications

Given the high caffeine content found in guarana, a number of well-known drug interactions may occur. Cimetidine decreases caffeine clearance by 30-50% which may lead to increased side effects.[21] Benzodiazepines may be rendered less effective.[21] MAOIs combined with excessive caffeine ingestion have led to elevations in blood pressure. Lithium levels may be lower if caffeine is ingested in large doses.[21] Certain quinolone antibiotics significantly inhibit caffeine elimination and may lead to increased caffeine side effects.[21] Concomitant use with phenylpropanolamine and pseudoephedrine, ingredients commonly found in decongestants, has also led to significant increases in blood pressure.[21] Verapamil also is noted to inhibit metabolism of caffeine.

Use of guarana is contraindicated in pregnancy and lactation[21] and in children and adolescents. Patients with a history of anxiety or other psychological disorders, hypertension, and heart disease should avoid use of caffeine products.

Formulation and Dosage

Guarana preparations can be purchased with a wide range of dosages. Preparations may contain guarana alone or in combination with other nutritional supplements for weight loss including ma huang, *Panax ginseng*, bee pollen, gotu kola, and chromium. Dosages can range from 250-1,200 mg with caffeine content ranging from 20-200 mg. Prices range from $4.99 for 30 tablets of guarana to $44.99/month for combination products. Guarana adds a bitter taste when added to commercially available soft drinks. (*See Table 1 for price comparison.*)

Regulation

Guarana is approved by the FDA as generally recognized as safe as a food additive for flavoring. It is not included in the Commission E monographs. Other herbal supplements for weight loss, including ma huang (ephedra), have been closely monitored by the FDA and have been associated with at least 44 deaths nationally, according to MedWatch.

Conclusions

No published scientific data support the use of guarana for cognitive enhancement. Although there are some data suggesting that the combination of ephedrine and caffeine may have a modestly beneficial effect for short-term weight loss, short-term agents have a notorious history. Well-designed, long-term clinical trials are required. Given potential carcinogenesis from the concentrated tannin content and a highly variable caffeine content, guarana poses fundamental questions of safety and efficacy.

Recommendation

The use of guarana as a natural energizer and weight loss aid alone or in combination with other herbals, especially ma huang, cannot be recommended and should be discouraged as potentially harmful. A lack of significant scientific data proving safety and efficacy along with

apparent potential for harm precludes its use. Patients using these products should be counseled regarding alternate, safer means for increased energy such as multidisciplinary lifestyle modification programs. ❖

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CME Questions

31. Guided imagery and hypnosis are psychological and behavioral techniques that both involve interaction between therapist and patient.

a. True
b. False

32. Which of the following has *not* been reported as a side effect of chaste tree berry?

a. Rash
b. Increased menstrual flow
c. Lower abdominal complaints
d. Blurry vision
e. Headache

33. Which of the following drugs may weaken the effects of *Vitex agnus-castus*?

a. Bromocriptine
b. Aspirin
c. Haloperidol
d. Atenolol

34. The major active constituent of guarana is:

a. cocaine.
b. caffeine.
c. tannins.

35. Guarana has been shown to cause all of the following except:

a. fatigue.
b. inhibition of platelet aggregation.
c. tachycardia.
d. stimulation.

Writing Therapy to Reduce Asthma and RA Symptoms

Source: Smyth JM, et al. Effects of writing about stressful experiences on symptom reduction in patients with asthma or rheumatoid arthritis: A randomized trial. *JAMA* 1999;281:1304-1309.

TO DETERMINE IF WRITING ABOUT stressful life experiences affects disease status in asthma or rheumatoid arthritis (RA) patients using standardized quantitative outcome measures, we conducted a randomized controlled trial between October 1996 and Dec-ember 1997. A volunteer sample of 112 patients with asthma (n = 61) or RA (n = 51) enrolled; 107 completed the study.

As the intervention, patients were assigned to write either about the most stressful event of their lives (n = 71; 39 asthma, 32 RA) or, as a control, about their plans for the day (n = 41; 22 asthma, 19 RA).

Asthma patients were evaluated with spirometry and RA patients were examined by a rheumatologist at baseline, and at two weeks, two months, and four months. The evaluations were done blind to the experimental condition.

Of evaluable patients four months after treatment, asthma patients in the experimental group showed improvements in FEV_1 (63.9% at baseline to 76.3% at four months; $P < 0.001$); controls showed no change. RA patients showed reduced mean disease severity from 1.65 to 1.19 (28% on a scale of 0 [asymptomatic] to 4 [very severe] at four months; $P = 0.001$); controls showed no change. Combining all completing patients, 33 of 70 (47.1%) experimental patients had clinically relevant improvement; nine of 37 (24.3%) controls also improved ($P = 0.001$).

COMMENT

Every writer knows that writing can be therapeutic, even if it hurts. But only when it hurts?

These Stony Brook investigators excluded patients with a defined psychiatric disorder, in psychotherapy, or on mood-altering medications (including prednisone, >10 mg/d). Patients were told that the investigators were interested in the patients' experiences of stress. The patients did not discuss their writing with staff or other participants and wrote in private for 20 minutes on three consecutive days a week after completing baseline disease severity assessments, which were comparable.

Nearly all patients were Caucasian, well-educated (mean two to three years of college), and averaged a mean annual family income of $66K (RA) and $50K (asthma). Nearly all used medication regularly. Less than 10% of each group smoked, and 49% of each group got regular exercise.

The authors report that observation of participants in similar writing sessions show "considerable emotional upset during the writing sessions." These patients most commonly wrote about the death of a loved one, serious problems of a close other, and problems in relationships.

Not noted was whether and how medication regimens changed over time; to what mechanism physicians attributed patients' assessed improvement; what patients thought of the intervention; or which symptoms specifically improved. Asthma patients' FEV_1 ratings improved at two weeks and at each follow-up visit; RA patients' current clinical status assessment did not improve until four months.

Many physicians regularly receive long letters from patients describing household events and personal problems. The possibility of actually prescribing such writing assignments and asking patients to write expressively as part of their chronic disease management is intriguing and refreshing.

Recommendation

Structured, systematic trials assessing the usefulness of expressive writing are a logical, important next research step. Taking a pen in hand is low cost, noninvasive, and personal. Providing a writing tablet and 20 minutes free of other distractions are generous gifts. Prescribed by a caring clinician, the combination seems low risk and potentially therapeutic. ❖

Dangers of Asian Patent Medicines

Source: Adult lead poisoning from an Asian remedy for menstrual cramps—Connecticut, 1997. *MMWR Morb Mortal Wkly Rep* 1999;48:27-29.

A CASE OF ADULT LEAD POISONING attributed to an Asian remedy for menstrual cramps, "Koo Sar" pills, is reported. A 33-year-old Cambodian woman, her husband and their two children were screened at a free lead-screening event sponsored by a nursing school community health promotion center. The husband had a blood lead level (BLL) of <10 mcg/dL, and the children, aged eight and two years, had BLLs of 2 and 3 mcg/dL respectively. The woman, however, had a BLL of 44 mcg/dL and a confirmatory BLL two weeks later of 42 mcg/dL. The woman reported no symptoms associated with lead poisoning (e.g., muscle pains or weakness, headaches, or loss of appetite).

The woman had taken six red "Koo Sar" pills daily for seven days of each month to treat menstrual cramps. The Connecticut Department of Public Health (CDPH) analyzed her BLLs, which declined to 28 after one month, 21 after two months, 19 after three months, and 12 after six months. The CDPH regards adult BLLs <10 mcg/dL as normal. Lead was found in the pills in concentrations ranging from 1.2-12.5 parts per million (ppm), assayed in three different state health department laboratories. The pills were manufactured in Hong Kong and the accompanying

literature was written in Chinese. The insert states, "These medical pills are good for general disability;" one pill is to be taken twice daily with warm water.

No other cases of lead poisoning associated with Koo Sar pills have been reported to California, Connecticut, New York, or any of the other 24 states covered by the Adult Blood Lead Epidemiology and Surveillance program. No recall has been initiated.

COMMENT

The contamination of Asian patent medicines has been reported previously, but lead poisoning from one has not been reported. Ko found that 24 of 260 Asian products gathered from California retail herbal stores contained a median of 30 ppm of lead (*New Engl J Med* 1998;339:847). The *MMWR* speculates that the red dye used to color the Koo Sar pills contains the lead.

As this patient's case demonstrates, laboratory evidence of lead poisoning is readily documented, and is slow to disappear. Whether we have to rely on patients to come to screening centers, or continue to think of lead when anemia and lethargy are presenting complaints is up to bodies like the FDA and the FTC.

Recommendation

We have previously suggested that "Physicians who counsel patients who seek to use traditional Chinese medicine made in Asia should warn them of the high prevalence of toxic ingredients." (See *Alternative Medicine Alert*, November 1998, p. 132.) We also have advised against recommending any individually prepared Chinese herbal creams, as they may contain steroids. (See *Alternative Medicine Alert*, May 1999, p. 60.) Given the adulteration of many traditional Chinese medicines, we believe that physicians should advise their patients not to take Asian-made patent medicines of any kind until they are manufactured, labeled, and regulated for safety, purity, and consistency. ❖

L-arginine for Cardiac Patients

Source: Lerman A, et al. Long-term L-arginine supplementation improves small-vessel coronary endothelial function in humans. *Circulation* 1998;97:2123-2128.

CORONARY ENDOTHELIAL DYSFUNCtion is characterized by an imbalance between endothelium-derived vasodilating and vasoconstricting factors. The present double-blind randomized study was designed to test the hypothesis that six-month supplementation of L-arginine, the precursor of the endothelium-derived vasodilator nitric oxide (NO), reverses coronary endothelial dysfunction to acetylcholine in humans with nonobstructive coronary artery disease.

Twenty-six patients with recurrent chest pain but without significant coronary artery disease on coronary angiography and intravascular ultrasound were randomized to either oral L-arginine or placebo, 3 g tid. Endothelium-dependent coronary blood flow reserve to acetylcholine was assessed at baseline and after six months of therapy. There were no baseline differences between the two study groups in clinical characteristics or in coronary blood flow. After six months, the coronary blood flow in arginine subjects increased compared with placebo subjects (149+/-20% vs. 6+/-9%, $P < 0.05$). This was associated with a decrease in plasma endothelin concentrations and an improvement in patients' symptoms scores.

Oral L-arginine supplementation for six months in humans improves coronary small-vessel endothelial function in association with a significant improvement in symptoms and a decrease in plasma endothelin concentration. This study proposes a role for L-arginine as a therapeutic option for patients with coronary endothelial dysfunction and nonobstructive coronary artery disease.

COMMENT

How much coronary disease is nonobstructive? Much. What is endothelial dysfunction? Probably the mechanism of exercise-induced myocardial ischemia. It may be the mechanism of nonobstructive myocardial perfusion defects.

These Mayo Clinic authors hypothesized that L-arginine reverses coronary endothelial dysfunction in patients with angina and normal arteriograms. The investigators catheterized qualifying, consenting patients referred for recurrent chest pain, and excluded anyone with diffuse disease and anyone with a 40% or greater lesion. Those with an attenuated increase or actual decrease in coronary blood flow in response to an infusion of acetylcholine, and a normal coronary flow reserve in response to adenosine were recruited and randomized to L-arginine or control. Patients took no other medication, vitamins or amino acids. Six months later, the patients were catheterized again. Their chest pain was assessed monthly, and improved at the end of six months (as did that of the placebo group).

Whether arginine improves cardiac function and symptoms by enhancing production of NO or other vasoactive factors such as endothelin, or by slowing the progression of coronary atherosclerosis, no one knows. Unfortunately, arginine has been reported to activate herpes virus replication and interact, in animal models, with tumor growth.

Recommendation

Long-term controlled studies—longer than six months—are needed to determine the effects of arginine supplementation. Cardiac patients who want to add 3 g tid to a low-fat, antioxidant-rich, high-fiber diet, a regular aerobic exercise program, and their daily aspirin should be monitored closely. ❖

In Future Issues:

Yohimbine for Impotence
L-Carnitine for Congestive Heart Failure
Omega-3 Fatty Acids for Stroke Prevention