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Valerian Root for Insomnia

By Susan T. Marcolina, MD

ALTHOUGH *SLEEPLESS IN SEATTLE* WAS A ROMANTIC COMEDY, insomnia is neither a laughing nor a romantic matter. Insomnia is the most commonly reported sleep problem in industrialized nations worldwide; women and elderly persons are at increased risk.[1] The sequelae of insomnia include diminished productivity and increased susceptibility to accidents from poor concentration, fatigue, and cognitive dysfunction.

Valerian is one of the most well-known soporific herbal therapies, specifically the valerian root extract (VRE). The European variant, *Valeriana officinalis*, is most commonly used and referred to in the scientific literature, although there are more than 250 identified species of this genus. The first reference to the sedative, hypnotic properties of valerian is attributed to the ancient Greek physician and pharmacist Galen (129-199 AD).[2]

Medical Etiologies

To relieve secondary insomnia, psychiatric and medical disorders responsible for it must be effectively treated. Table 1 outlines these disorders. Treatment also should include patient implementation of appropriate sleep hygiene practices *(see Table 2)*. For persistent symptoms, short-term pharmacotherapy may be necessary.

Although pharmacotherapy for primary insomnia is effective, significant side effects occur. Patients complain of daytime sedation or hangover. Dependence may develop with continual use and the possibility exists of fatal overdose if taken in combination with alcohol or drugs. Thus many patients, in search of symptomatic relief, seek alternative, seemingly safer, natural options in the form of herbal therapies.

Pharmacology

Valerian is a perennial herb native to Europe and temperate zones of Asia. The root and rhizome of this plant are used for medicinal preparations. Its chemical composition varies significantly from one species to the next and within plants of the same species. Differences

in growing conditions, root age, harvesting times, and drying techniques also affect chemical composition.

Constituents

In the early 1900s, scientists isolated the essential oil from the rootstock and have since identified more than 150 constituents. The sesquiterpene valeneric acid is an important component of the essential oil, demonstrating substantial sedative and antispasmodic activity. However, it does not fully account for the sedative effects of the root; instead, synergism between the individual chemical constituents probably does. The valepotriate iridoids that compose between 0.2% and 2% of the root are fatty acid esters that have shown some calming activity in animal studies. Alkaloids, such as actinidine, valerianine, and alpha-methylpyrrylketone, are also major constituents of the root, but exist in small amounts and do not contribute to the sedative properties.

Valerenic acid appears to inhibit the enzyme system responsible for the breakdown of gamma-aminobutyric acid (GABA), thereby increasing GABA concentrations and decreasing CNS activity. The valerian root also contains other compounds, such as lignans and GABA, which may account for its sedative properties.[2,3]

Animal Studies

Bos et al found a direct relationship between the valepotriate content of valerian and toxicity of VRE in animal studies. This effect was greatest in species of *Valeria* such as *Valeriana edulis*, which contains the highest level of valepotriates; *Valeriana officinalis* was found to be the least toxic in this regard. Aqueous extractions of valerian contain no valepotriates.[4]

Clinical Studies

Different clinical studies evaluating the efficacy of valerian for insomnia are difficult to compare because different preparations of valerian are used, the numbers of patients are small, validated outcome measures are few, or pre-bedtime variables are poorly controlled. Nevertheless, some information from several studies appears important.

A multicenter, double-blind, randomized study conducted by Vorbach et al randomized 121 patients with non-organic insomnia to receive an alcoholic valerian extract (LI 156) (600 mg/d) or indistinguishable placebo daily for 28 days.[5] Patients were not taking any medications that would interfere with sleep. Sleep efficacy was assessed with four validated rating scales. Patients taking valerian had significantly better results than did those taking placebo on the clinical global impression scale after 14 days and on all additional measures of sleep and mood after 28 days. Two patients from the placebo group and two from the valerian group reported adverse events. Those adverse effects from valerian included headache and next-morning drowsiness.

Leathwood et al compared the effects of 400 mg of a dry 3:1 aqueous extract of valerian root to placebo and a commercial preparation (Hova) that contained 60 mg valerian and 30 mg hop flower extract in 128 participants (some with and some without sleep problems).[6] Each volunteer tested nine samples (three placebo, three valerian, three Hova) presented in a random order and taken 1 hour before bedtime on non-consecutive nights. All participants were instructed to avoid food intake, alcohol, or exercise on the test nights and effects were measured by a questionnaire the following morning. Sleep latency and quality were rated as significantly improved with valerian compared to placebo, particularly by those participants who were poor sleepers. Compared to valerian or placebo, increased drowsiness and nausea were reported with Hova.

Donath et al performed a randomized, double-blind, placebo-controlled, crossover study involving 16 patients (12 female, median age 49 years) with previously established insomnia.[7] The two inclusion criteria were a diagnosis of primary insomnia and the absence of

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Table 1

Causes of secondary insomnia

- Medical
- Psychiatric
- Delirium (e.g., sepsis- or medication-induced)
- Mood disorders
- Pain syndromes
- Anxiety disorders
- Endocrinopathies (e.g., hyperthyroidism)
- Schizophrenias
- Cardiac dysfunction (e.g., CHF, angina)
- Substance dependence/abuse
- Sleep apnea syndrome (central, obstructive)
- Dementia
- Side effects of medications (e.g., theophylline, nicotine, caffeine, steroids)
- Chronic obstructive lung disease
- Restless leg syndrome/periodic limb movements in sleep
- Gastroesophageal reflux

Adapted from: Davidson JRT, Connor KM. *Herbs for the Mind.* New York: The Guilford Press; 2000.

Table 2

Recommendations for sleep hygiene

- Maintain a regular sleep/wake schedule
- Institute a program of daily exercise
- Insulate bedroom from excessive light, noise, heat, and distractions (e.g., television)
- Avoid heavy exercise before bedtime
- Avoid large meals before bed
- Avoid daytime napping
- Avoid long-term use of prescription or OTC sleep medicines
- Avoid tobacco, caffeine, and alcohol prior to bedtime

Adapted from: Davidson JRT, Connor KM. *Herbs for the Mind.* New York: The Guilford Press; 2000.

acute illnesses. The patients underwent eight polysomnographic recordings at baseline, 1, 2, and 4 weeks for placebo and valerian. After a single dose of valerian, no effects on sleep structure and subjective sleep assessment were observed. After multiple-dose treatment, sleep efficiency showed a significant increase for valerian and placebo in comparison to baseline polysomnography. However, compared to placebo, valerian reduced slow-wave sleep latency (21.3 minutes vs. 13.5 minutes, respectively, $P < 0.05$). The study showed low numbers of adverse events during the valerian treatment periods (three vs. 18 in the placebo period). The authors concluded that treatment with a valerian extract demonstrated positive effects on the sleep structure and sleep perception of insomnia patients.

Kuhlmann et al examined the influence of valerian treatment on reaction time, alertness, and concentration in healthy persons.[8] This randomized controlled, double-blind trial enrolled 102 male and female volunteers. The effect initially was examined the morning after a single evening dose of valerian root extract (600 mg), flunitrazepam (1 mg), or placebo, and then after two weeks of evening administration of valerian or placebo. The primary outcome criterion was reaction time, measured with the Vienna Determination Test. Secondary criteria included an alertness test, a tracking test, sleep quality, and safety criteria.

The single administration of valerian did not impair reaction times, concentration, and coordination of study participants compared to placebo. Flunitrazepam caused deterioration in these measured outcomes compared to placebo. Results after 14 days confirmed that there were no statistical differences between valerian and placebo for reaction times and other psychometric testing results. There was a trend toward improved sleep quality for valerian compared to placebo that did not reach statistical significance. Valerian and placebo were not statistically different with regard to adverse effects.

Adverse Effects

Acute side effects may include mild headaches, nausea, nervousness, palpitations, and morning drowsiness. Although most reports describe a lack of residual morning effects on alertness and concentration, some suggest that impaired alertness and information processing does occur. This impairment is dose-dependent and peaks within the first few hours after an oral valerian dose. Therefore, patients should be cautioned against driving or operating dangerous machinery within the first several hours after ingestion.

Several cases of hepatotoxicity involving long-term use of single-ingredient valerian preparations have been reported. Since a variety of dosages were used in the reported cases and higher doses have been safely used, these hepatotoxic reactions may have been idiosyncratic.[9] In addition, Garges reported a case of a patient who had taken VRE for years when he was admitted to the hospital for coronary artery bypass graft surgery. VRE was abruptly discontinued, resulting in a withdrawal syndrome which responded to intravenously administered midazolam, which was gradually tapered.[10]

There is insufficient data to determine the efficacy and safety of VRE in children younger than 18 years of age and in pregnant women; valerian should not be used in these populations.

Drug Interactions

Valerian can potentiate the sedative action of alcohol and other sedative drugs. There is evidence that valerian can inhibit the cytochrome P450 3A4 enzyme; it may increase levels of drugs such as lovastatin, ketoconazole, fexofenadine, etoposide, paclitaxel, vinblastine, and vincristine, which are metabolized by this pathway.[11]

Dosage

In controlled trials of healthy subjects and in patients with sleep disturbances, doses of VRE ranging from 300 to 900 mg were shown to be helpful in promoting sleep, although dosing has not been studied systematically.[3,12]

Formulation

Most pharmacopeia standards recommend that single-ingredient valerian extracts be standardized to at least 0.5% valerenic acid. Valerian products should be stored in closed containers and protected from light and moisture. While valerenic acid and its breakdown products are fairly stable, these and other components of the essential oil degrade over time and in the powdered root form, can degrade by as much as 50% in six months. The valepotriate constituents of VRE are unstable, water insoluble, and susceptible to degradation with temperatures higher than 40° C, humidity, and acid or alkaline exposure.[2]

Regulation

The German Commission E has approved several fixed combinations of VRE and other herbs, including passionflower, chamomile, lemon balm, and hops; however, systematic studies documenting efficacy are lacking.[13]

Conclusion

Standardized potency VRE can be effective for many patients with chronic primary insomnia. Studies have shown an improvement in sleep latency and global functioning (as assessed by validated questionnaires), without significant hangover effects seen with traditionally used sedative hypnotics. One study suggests the possibility of a withdrawal syndrome similar to benzodiazepine withdrawal with abrupt discontinuation. Several case reports have documented hepatic toxicity after long-term usage; therefore, clinical use for individual patients should be limited to 2-6 weeks.

Recommendation

The diagnosis of insomnia requires a careful work-up to determine secondary medical or psychiatric diagnoses. Standardized VRE can be a treatment option for some nonpregnant patients older than age 18 with chronic primary insomnia for 2-6 weeks in conjunction with sleep hygiene measures. ❖

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

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Transcendental Meditation and Prevention of Cardiovascular Disease

By Jane Kattapong, MD

"Well, now that we have seen each other," said the Unicorn, "if you believe in me, I'll believe in you. Is that a bargain?"

Lewis Carroll, *Through the Looking-Glass*

CARDIOVASCULAR DISEASE (CVD), INCLUDING CORONARY heart disease and stroke, is the leading cause of death worldwide.[1] Globally, death rates for CVD have been increasing.[1]

Traditional Western medicine has emphasized pharmacological and interventional treatment to address physical illness. These treatments generally entail the use of tangible pills and devices. Can something we cannot see or touch prevent cardiovascular disease?

Mind-body medicine (MBM) is a field of medicine that addresses the intimate relationship and influences of mind and body upon each other. The earliest acknowledgement of the validity of influences of the mind upon the body in Western medicine practice was the acceptance of the placebo effect.[2] Rather than administering externally generated treatments, MBM utilizes the unseen influences of the mind upon physical disease processes.

MBM Association

One MBM therapy is meditation. Meditation has been defined as "the self-regulation of attention."[2] In general, the practice of meditation is subdivided into two different techniques: concentration meditation and mindfulness meditation. Concentration meditation encompasses transcendental meditation (TM) and the relaxation response. Mindfulness meditation encompasses mindfulness-based stress reduction programs, such as those at Tufts University in Boston. According to Pandya et al, "Meditation … tries to concentrate the mind without tension and creates very peaceful and calm mental status. It is one of the few ways to achieve a state of superconsciousness or self-realization."[3]

Basis and Proposed Benefits

TM is based on traditional Indian vedic philosophy. TM was developed and brought to the United States by Maharishi Mahesh Yogi in the 1960s. The TM technique is taught in the United States through Maharishi Vedic Universities/schools and affiliates and costs about $1,200.[4] According to the Maharishi Mahesh Yogi, "Transcendental meditation opens the awareness to the infinite reservoir of energy, creativity, and intelligence that lies deep within everyone … . By enlivening this most basic level of life, transcendental meditation is that one simple procedure which can raise the life of every individual and every society to its full dignity, in which problems are absent and perfect health, happiness, and a rapid pace of progress are natural features of life."[5]

Mechanism of Action

Many effects on physiological parameters have been reported in the TM medical literature. *(See Table.)* These effects include decreased respiratory rate, decreased skin conductance, decreased total peripheral resistance, increased alpha-wave activity on EEG, increased frontal and occipital lobe blood flow, alterations of hormone levels (including adrenocorticotropic hormone, cortisol, growth hormone, thyroid-stimulating hormone, dehydroepiandrosterone sulfate, prolactin, epinephrine, norepinephrine, and beta-endorphins), decreased serum lipid peroxides, decreased beta-receptor sensitivity, decreased erythrocyte glycolysis, and decreased serum lactate.[6,7]

Specifically regarding CVD risk, TM is believed to have a beneficial effect upon risk factors including hypercholesterolemia, blood pressure, and tobacco use.[8]

Clinical Studies

One randomized, controlled trial examined the effects of regular TM practice on carotid atherosclerosis.[9] In this study, carotid intima-media thickness (IMT) was used as an indicator for coronary atherosclerosis.

Table

Proposed physiological changes associated with transcendental meditation[6,7]

- Decreased respiratory rate
- Decreased skin conductance
- Decreased total peripheral resistance
- Increased alpha-wave activity on EEG
- Increased frontal and occipital lobe blood flow
- Alterations of hormone levels
- Decreased serum lipid peroxide
- Decreased beta-receptor sensitivity
- Decreased erythrocyte glycolysis
- Decreased serum lactate

The study was designed to compare the effects of TM as a stress-reduction intervention with a heart disease education group in African-American subjects. One hundred thirty-eight patients (men and women) were enrolled. All subjects identified themselves as African-American, resided in Los Angeles, and had hypertension. Exclusion criteria included history of complications related to cardiovascular disease or other serious illness. Baseline evaluations included carotid ultrasound to determine IMT. IMT was defined as the distance between the intima-lumen and media-adventitia interfaces at end diastole. Blood pressure, weight, and lipids were determined as secondary outcome measures.

Patients were randomly assigned to either a TM intervention or a CVD risk factor prevention education program. TM was performed as developed by Maharishi Vedic Medicine.[10] The goals of performing TM involve inducing less active thinking processes and creating a state of "restful alertness."[11]

In the TM group, subjects were asked to practice meditation techniques for 20 minutes twice a day while sitting comfortably; in the health education group, patients were asked to dedicate 20 minutes twice a day to any leisure activity, such as reading or exercising. The intervention period was seven months.

In comparison to the health education group, the TM group showed a significant decrease in carotid atherosclerosis ($P = 0.038$). The TM group averaged a decrease of 0.098 mm vs. an increase of 0.05 mm in the control group.

A second small controlled trial examined effects of TM on cardiac signs and symptoms in patients with cardiac syndrome X.[12] Cardiac syndrome X is a term used to categorize patients with angina, positive exercise stress testing, and normal coronary angiograms. Although these patients generally have a good prognosis with respect to event-free survival, they may remain symptomatic despite medical management.[12] Proposed mechanisms contributing to symptoms include anxiety and increased sympathetic activation.

In this trial of TM in cardiac syndrome X patients, nine postmenopausal women with a mean age of 56 years longitudinally served as their own controls. Data were collected regarding cardiovascular status prior to the intervention and three months later. After baseline data were collected, the patients received a three-month training course in TM. After the training period, significant beneficial effects were found, using two-tailed t tests, in time to ST-segment depression on the standard Bruce protocol, maximum ST-segment depression on the standard Bruce protocol, frequency of chest pain episodes, and quality of life.[12] A positive correlation was found in quality of life and regularity of TM practice.

Other studies have demonstrated beneficial effects of TM on high blood pressure and hypercholesterolemia;[13,14] however, these studies have important methodological flaws or have not been reproducible.

Clinical Study Limitations

Several limitations of these studies exist. Study sizes generally were small. There was little provision for determining whether patients actually practiced TM as instructed. The randomized controlled trial described only a specific demographic group; it is unclear if findings in African Americans would be applicable to other groups. Further well-designed studies are necessary to definitively examine the effect of TM on CVD risk.

Other Health Effects

Other studies have addressed health effects of TM. Beth Roth, a nurse practitioner and mindfulness meditation consultant, and Tae-Wool Stanley, a nurse practitioner, conducted a retrospective cross-sectional study of patients who had completed a mindfulness-based stress reduction community intervention.[15] They recorded the number of and reason for health care visits for 47 patients involved in the program, and found that patients had a significant decrease in the number of chronic care visits after completing the program.

In addition, other positive health effects have been proposed. These include beneficial effects on stress, risk of violent death, risk of coronary heart disease, mood disturbances, cancer survival rates, and psychosomatic symptomatology.[3,12,16,17] However, few well-designed studies have been completed to evaluate the effects of TM on these conditions.

Adverse Effects

Little in the way of side effects of TM have been reported. Of potential concern, however, is delaying other, efficacious treatment while TM is being utilized.[18] To minimize risks associated with a delay in effective treatment, conventional treatments and TM can be initiated simultaneously.

Conclusion

Few well-designed controlled clinical trials have examined the effects of TM on cardiovascular risk. The Castillo-Richmond et al study suggests that TM, as a stress reduction technique, has beneficial effects on CVD risk reduction. The cost of this intervention is limited to the resources required to provide instruction and follow-up of the technique. Once patients have received adequate instruction, practice of this technique is

virtually cost-free. Side effects of TM have not been reported.

Recommendation

Although TM cannot be advocated as a substitute for traditional pharmacologic and interventional treatments for CVD risk reduction, this technique certainly appears to be a useful adjunct. TM is a simple, inexpensive intervention that may prevent CVD. This is an intervention that we do not have to see to believe, and can be recommended to patients who are at risk. Although cost effectiveness studies have not been undertaken, TM appears to be worth believing—or at least, examining. ❖

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

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Acupuncture for the Treatment of Dysmenorrhea

By Heather Bufford, MD, and Nassim Assefi, MD

DYSMENORRHEA AFFECTS UP TO 90% OF WOMEN; approximately 15% have severe symptoms.[1] In addition to causing impaired quality of life, dysmenorrhea is associated with significant social impact, including absenteeism from work and school. Annually, this amounts to an estimated loss of $600 million in wages and $2 billion in lost productivity.[2]

Although first-line therapies including non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives often are effective, up to 10% of cases are refractory to such treatment.[1] Acupuncture is an attractive treatment option given its benefits in the treatment of other pain syndromes, safety profile, and acceptability to some women who are reluctant to use medication. However, although the National Institutes of Health Consensus Statement on Acupuncture endorses the potential efficacy of acupuncture for many types of pain, such as acute dental pain, epicondylitis, and fibromyalgia,[3] very little Western-based literature has documented the efficacy of acupuncture for painful gynecologic conditions, including dysmenorrhea.

Table 1

Common causes of secondary dysmenorrhea

- Endometriosis
- Adenomyosis
- Gynecologic tumors
- Cervical stenosis
- Pelvic infections
- Adhesions
- Inflammatory bowel disease
- Irritable bowel disease
- Psychiatric/stress-related

Clinical Features and Pathophysiology

Dysmenorrhea consists of painful cramps in the lower abdomen associated with the onset of menses. Associated features also may include sweating, tachycardia, headaches, nausea, vomiting, diarrhea, and tremulousness.

Primary dysmenorrhea usually begins six months to three years after menarche. Symptoms are typically most severe the first day or two of the menstrual cycle. There is strong evidence linking elevated prostaglandin levels with primary dysmenorrhea, including elevated levels of $PGF_{2\alpha}$ in the menstrual fluid of symptomatic women. In addition, increased myometrial contractility in response to $PGF_{2\alpha}$, and the efficacy of NSAIDs (which inhibit synthesis of prostaglandins) in the treatment of this disorder argue for a prostaglandin relationship.[1,4] Dysmenorrhea also can occur secondary to other gynecologic, gastrointestinal, and psychologic factors *(see Table 1)*.

Diagnosis

Primary dysmenorrhea usually can be diagnosed by history and physical examination. Symptoms often are associated with early menarche, recent menarche, heavy flow, and positive family history. The timing of the pain, cycle length, and social history also can be helpful in differentiating this condition from endometriosis, pelvic inflammatory disease, and other secondary causes. Response to NSAIDs can confirm the diagnosis. Women with late or immediate onset relative to menarche, or severe or refractory symptoms merit careful evaluation by a gynecologist for secondary causes.

Conventional and Alternative Treatments

NSAIDs and OCPs are the conventional therapies for primary dysmenorrhea, alleviating symptoms in 40-90% of patients.[1] Investigational therapies have included transcutaneous electrical nerve stimulation units, nitroglycerin, thiamine, magnesium, omega-3-fatty-acids, and laparascopic presacral neurectomy. Treatment of secondary dysmenorrhea may include surgery, antibiotics, counseling techniques, and acupuncture.

Mechanism of Action

From a Western perspective, the mechanism of acupuncture is unclear. No unique anatomic structures corresponding to the acupoints have been found,[5] but studies have consistently shown that acupuncture alters the concentrations of molecules that mediate pain and inflammatory pathways, such as endorphins, monoamines, and prostaglandins.[6] Acupuncture's documented effects on prostaglandin levels are of specific interest in dysmenorrhea treatment, providing a plausible physiologic mechanism for its effects.

According to traditional Chinese medicine (TCM), there are three major classifications for symptoms consistent with dysmenorrhea: stagnant *qi* (vital energy), cold damp, and deficient blood and *qi*.[7,8] Needling is thought to improve circulation of *qi* and moxibustion (burning of the herb *Artemesia vulgaris*) is thought to warm the meridians and reinforce the effects of acupoint stimulation.

Clinical Data

An English language literature search using "acupuncture" and "dysmenorrhea" as key words revealed one randomized controlled trial (RCT), one prospective trial, and a large body of mostly Chinese articles consisting of case reports, case series, and expert opinions.

The strongest data are from an RCT of 43 women with recurrent pain starting within two years of menarche without evidence of pelvic pathology.[9] Four study groups were followed for one year, including real acupuncture at predetermined acupoints, sham acupuncture with needling at non-acupoints, standard therapy with extra visits to control for attention placebo effects, and usual care. Treatments involved needling at 12 points (either a standardized acupoint or non-acupoint protocol), once weekly for 30 minutes, three weeks of each month for three months. Results showed a significant difference in the proportion of patients with improved symptoms in the acupuncture group (90.9%) as opposed to other groups, and a trend toward significance in the magnitude of improvement. There also was a 41% reduction in the use of oral analgesics in the acupuncture group, with no change in medication use among other groups.

Limitations of this study include lack of investigator blinding (which may bias interpretation of efficacy);

lack of credibility testing to show true blinding of sham acupuncture subjects (the sole physician-acupuncturist-investigator could have given subtle clues to make the sham needle group think they were receiving a placebo treatment); and the use of a non-standard pain scale. However, randomization, use of controls, and objective reduction in pill use make this study more rigorous than any other.

A prospective trial of 48 patients employing acupuncture at seven specified acupoints for five sessions before expected menses resulted in 28 patients (58.3%) with complete relief for at least six months, 12 (25%) with considerable relief, and four (8.3%) with no relief.[10] Limitations of this trial included the lack of a control group, failure to distinguish between primary and secondary dysmenorrhea, potential investigator bias in interpreting results, and lack of standardized pain scales and objective measurements.

The largest case series published in English involved 100 patients.[11] Selection of points varied according to syndrome, as did the use of moxibustion or electroacupuncture. The author of the study reported that 54% of patients had "complete relief" for six months, while 27% showed "marked improvement," 13% were "somewhat improved," and "failure of therapy" occurred in 6% of patients.

In another case series, 49 patients were treated between eight and 13 times with acupuncture according to a TCM diagnosis of dysmenorrhea type.[12] Forty-two patients experienced "complete cure" and another six were "markedly improved." The single failure was complicated by fibroids. In another case series, 32 patients were treated according to TCM diagnosis of dysmenorrhea.[13] Two standard points were used, along with a third that varied by type of dysmenorrhea; moxibustion also was used when indicated. The results showed that 20 patients were considered "cured," and 11 were "effectively treated."

Table 2

Methodological challenges of acupuncture studies[16,17]

- Case definition and discrimination among etiologies
- Appropriate and adequate treatment (sufficient and appropriate points, duration, frequency, manipulation, use of additional stimulation such as electroacupuncture or moxibustion, predetermined vs. individualized regimens)
- Appropriate comparison groups and evaluation of placebo effect
- Blinding of patients and independent physician/acupuncturist assessors (blinding of practitioner is virtually impossible)
- Adequate sample sizes
- Valid subjective and objective outcome measures
- Duration of follow-up

Methodological Challenges

The above case reports, and virtually all clinical trials of acupuncture, have methodological features that confound their interpretation. The methodological challenges of studying acupuncture have been previously described in *Alternative Medicine Alert*[14] and are summarized in tabular form in Table 2.

TCM has at least three different diagnoses for dysmenorrhea, which do not correlate with the Western biomedical model of primary and secondary dysmenorrhea. In most of the dysmenorrhea studies mentioned above, a single acupuncturist-investigator delivered the treatments and assessed the outcomes in all patients. Furthermore, most of the Chinese studies did not use standard, objective pain outcomes, but instead used a gestalt-type clinical impression. These study features lend themselves to bias of interpretation and blinding (in the few cases where patients were given a control treatment).

The ideal acupuncture trial would be randomized and performed with appropriate controls, including needling at non-acupoints (sham acupuncture) and placebo-needling. Such a trial also would blind both patients and investigators assessing patient responses to treatment (dual blinding), with credibility testing to demonstrate patient blinding, as well as an assessment of patient beliefs about the healing powers of acupuncture to evaluate for self-efficacy (effect of positive belief).

The design would standardize treatment in a rational way to incorporate both TCM and Western biomedical classifications of dysmenorrhea, and determine adequate duration, course of treatment, and follow-up. Standardized outcomes such as validated pain scales and objective measures (such as analgesic pill counts and prostaglandin levels in menstrual fluid) should be used. To limit confounding effects, patients should be free of their usual therapies after a medicine wash-out period, or a more pragmatic approach may be to request that they not change any of their ongoing medical therapies.

Adverse Effects

Acupuncture generally is a very safe form of treatment, especially the style in which it is performed in the United States (using disposable needles, limited depth of penetration, and gentle needling techniques). Minor side effects including pain at the insertion site, bleeding, and

fatigue can transiently affect more than 40% of patients. Serious complications, such as infection, pneumothorax, and cardiac tamponade, are extremely rare.[15]

Conclusion

Dysmenorrhea is a very common problem for women that often can be treated easily with standard therapies. However, there are some women who are refractory to conventional medicines or who are not good candidates for standard therapies. It is difficult to assess the efficacy of acupuncture for dysmenorrhea, because there are few rigorously derived data and many challenges to constructing well-designed trials. A single randomized, controlled trial and a large body of mostly anecdotal literature suggest that acupuncture may have an effect beyond that of placebo in ameliorating the symptoms of dysmenorrhea.

Recommendation

Acupuncture may be useful for dysmenorrhea patients who have failed or are not candidates for standard therapy. Given the low side effect profile, referral to a licensed acupuncturist is reasonable for these patients. However, given the paucity of high-quality data, no recommendations can be made regarding the specific type of treatment. The studies indicate that 12 acupuncture treatments should be a sufficient trial for most patients' dysmenorrhea symptoms. ❖

Dr. Bufford is a second-year Obstetrics/Gynecology resident and Dr. Assefi is Attending (Clinician-Teacher), Departments of Medicine and Obstetrics/Gynecology, Complementary and Alternative Medicine Liaison, School of Medicine, University of Washington in Seattle.

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CME Questions

1. Which population group is at highest risk for developing insomnia?
a. Women
b. Elderly patients
c. Children
d. Both a and b

2. Valerian root extract has the potential to cause hepatotoxic side effects.
a. True
b. False

3. Valerian root extract may potentiate the effects of which of the following?
a. Sedative hypnotics
b. Alcohol
c. Etoposide
d. Taxol
e. All of the above

4. **Which of the following cardiovascular disease risk factors may be beneficially modified through regular practice of TM?**
   a. Hyperlipidemia
   b. High blood pressure
   c. Smoking
   d. All of the above

5. **Acupuncture is an attractive treatment option for dysmenorrhea because of its:**
   a. benefit in the treatment of other pain syndromes.
   b. safety profile.
   c. acceptibility to women who are reluctant to use medication.
   d. All of the above

6. **Which class of chemical mediators is thought to be most associated with dysmenorrhea symptoms?**
   a. Endorphins
   b. Monoamines
   c. Prostaglandins
   d. Leukotrienes

7. **Which conventional therapies are used most commonly in the treatment of primary dysmenorrhea?**
   a. Depo-Provera and surgery
   b. Non-steroidal anti-inflammatory drugs (NSAIDs) and oral contraceptives
   c. Oral contraceptives and behavioral therapy
   d. Surgery and physical therapy

Clinical Briefs

With Comments from John La Puma, MD, FACP

Hepatotoxicity Linked to Weight-Loss Supplement

Source: Favreau JT, et al. Severe hepatotoxicity associated with the dietary supplement LipoKinetix. *Ann Intern Med* 2002;136: 590-595.

LIPOKINETIX (SYNTRAX, CAPE GIRARDEAU, MO) is a dietary supplement marketed for weight loss. A possible causal association between LipoKinetix and hepatotoxicity was studied in a case series. Using an outpatient clinic, tertiary care hospital, and U.S. Food and Drug Administration (FDA) databases, seven patients were identified who ingested LipoKinetix and presented with hepatocellular damage between July and December 2000.

All patients developed acute hepatotoxicity within three months of starting LipoKinetix. All reported taking recommended dosages. No patient was taking any other prescription drug. Four were taking other supplements, only one of which was a Chinese herbal formulation. At presentation, symptoms and results of laboratory tests were characteristic of acute hepatitis. All patients recovered spontaneously after LipoKinetix use was discontinued. Three of the seven patients, including one who developed fulminant hepatic failure complicated by cerebral edema, were taking LipoKinetix alone at the time of presentation. Of the four patients who were taking multiple supplements, two resumed taking supplements other than LipoKinetix without incident.

The use of LipoKinetix may be associated with hepatotoxicity. Despite extensive evaluations, no other cause for hepatotoxicity could be identified in the seven patients studied.

COMMENT

Savvy readers know that the Federal Trade Commission has been more active and more capable in regulating supplement manufacturers than the FDA. But few patients know that the FDA has no authority to review supplements—their composition, purity, dissolution, dosage, proof of efficacy, and potential adverse effects or interactions—prior to marketing. These independently analyzed samples did not contain impurities. They did contain, per capsule, norephedrine hydrochloride (25 mg), sodium usniate (100 mg), 3,5-diiodothyronine (100 mg), yohimbine hydrochloride (3 mg), and caffeine (100 mg).

Acute hepatitis and fulminant hepatic failure are serious illnesses. Will they compel Congress to require that supplement companies meet pharmaceutical manufacturing standards?

Probably not. To paraphrase Senator Dirksen (R-IL, 1926-1969), a billion here, a billion there, pretty soon we're talking real money. But not yet. Only $4 billion was spent on supplements last year—almost nothing in comparison with pharmaceuticals. The tragedy is that these supplements often act just like pharmaceuticals—with striking adverse effects.

Because phenylpropanolamine, recently withdrawn from OTC preparations for weight loss, is actually racemic norephedrine, and has been associated with hepatotoxicity in animals, it may be the hepatotoxin. Or, the interaction may simply be idiosyncratic, as the authors suggest. They also offer, as do two editorialists, referral to the MedWatch web site (www.fda.gov/medwatch/report/hcp.htm) and toll free number, (800) FDA-1088.

When this adverse event was reported to the FDA in the fall of 2001, the authors recommended removal from the marketplace. But the FDA had no authority and little leverage to require it, much less to discover how this happened. Case reports and series may not offer proof of causality, but no clinician I know needs further formal pharmacoepidemiology studies to warn patients away from this substance, and ones like it.

Recommendation

Recommend that patients immediately discontinue taking OTC weight-loss agents containing caffeine and ephedrine or ephedrine derivatives, or hormone-containing or hormone-related compounds. Their long-term efficacy and short- and long-term safety have not been proven, and it is unfair to balance that proof on the backs of people who

have obesity as a disease, just when some well-deserved clinical and research attention is about to be made available to them. ❖

Alternative Therapies in Dermatology

Source: Levin C, et al. Exploration of "alternative" and "natural" drugs in dermatology. *Arch Dermatol* 2002;138:207-211.

TO REVIEW SOME OF THE PROMISING natural remedies within dermatology and their potential clinical benefit in supplementing conventional drugs, MEDLINE searches were conducted for the period January 1966 to October 2000. Science Citation Index searches were conducted for the period January 1974 to October 2000.

Primary importance was given to in vivo and in vitro controlled studies, the results of which encourage further exploration. The controls used, the statistical approach to analysis, and the validity of the experimental method analyzed were considered particularly important. Data were independently extracted by multiple observers.

Natural remedies seem promising in treating a wide variety of dermatologic disorders, including inflammation, phototoxicity, psoriasis, atopic dermatitis, alopecia areata, and poison oak. The alternative medications presented seem promising, although their true effects are unknown. Many of the presented studies do not allow deduction of clinical effects. Further experimentation must be performed to assess clinical benefit.

Source: Bedi M, et al. Herbal therapy in dermatology. *Arch Dermatol* 2002;138:232-242.

HERBAL THERAPY IS BECOMING increasingly popular among patients and physicians. Many herbal preparations are marketed to the public for various ailments including those of the skin. Herbal therapies have been used successfully in treating dermatologic disorders for thousands of years in Europe and Asia. In Germany, a regulatory commission oversees herbal preparations and recommended uses. In Asia, herbal treatments that have been used for centuries are now being studied scientifically. Currently, the United States does not regulate herbal products, as they are considered dietary supplements. Therefore, there is no standardization of active ingredients, purity, or concentration. There are also no regulations governing which herbs can be marketed for various ailments. This has made learning about and using these treatments challenging. Information compiled in a practical fashion may enable more patients to benefit from these treatments currently used worldwide.

This review examined herbal medications that show scientific evidence of clinical efficacy, as well as the more common herbs shown to be useful in the treatment of dermatologic disorders. The safety of each herb has been addressed to better enable the physician to know which herbal therapies they may want to begin to use in practice. Common drug interactions and side effects of herbal medicines that may be seen in the dermatologic setting also were studied.

COMMENT

These two articles summarize the state of the evidence-based art of treatment in dermatology.

Levin and colleague take a therapy-centered approach and report data for tea extracts (for preventing and treating UV-induced photodamage differently than sunscreens); hydroxy acids (for improving the appearance of aging skin); gamma linolenic acid (for atopic dermatitis); essential aromatic oils (for IgE-mediated allergic reactions and alopecia areata), vitamins C and E (for preventing nitrate tolerance in healthy volunteers taking transdermal glycerol trinitrate; and for improving photoprotection against UV-induced erythema); and even Quaternium-18 bentonite, a thickening clay in cosmetics (for preventing poison ivy or poison oak contact dermatitis).

Conversely, Bedi and Shenefelt take a disease-centered approach, and explore alternatives for acne, wounds, burns, herpes simplex, bacterial and fungal infections, scabies, condyloma, verruca vulgaris, dermatitis, psoriasis, chronic venous insufficiency, and alopecia. They cover topical treatments from aloe to honey and licorice to garlic. Their citation manager is substantial, and they have done their homework, though they spend very little time on adverse effects.

Together, these papers are complementary and very useful. Daniel M. Siegel, MD, writes an accompanying, thoughtful editorial summarizing the availability of general references both online and in print.

Recommendation

Any clinician who sees patients with dermatologic questions will find this set of papers useful. Among the most effective, least toxic treatments seem to be oral vitamins C and E for prevention of sunburn, and oral vitex for treatment of premenstrual acne, though not in potentially pregnant women; and, topical capsaicin for psoriasis. The most dangerous treatments, and ones to avoid, seem to be Chinese herbal compounds, which may be contaminated with heavy metals, prescription pharmaceuticals, or other substances, and may affect hepatotoxicity; and those compounds with potential interaction with steroids and immunosuppressants—echinacea and astragalus, among others. ❖

In Future Issues:

Saw Palmetto for Benign Prostatic Hyperplasia: An Update

Role of Osteopathic Manipulation in the Treatment of Back Pain