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Alternative Therapy: Focus on Herbal Products

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Pharmacology Literature Reviews

Formulary Update

Alternative therapy encompasses a wide variety of techniques, procedures and medicines that are not used in traditional medical practice. In addition to herbal and homeopathic products, alternative therapy includes acupuncture, chiropractic therapy, yoga, meditation, and nutritional therapy.[1] Alternative therapy is becoming increasingly popular in the United States and is often used by individuals with chronic health conditions. It is estimated that American consumers are spending as much on alternative therapies as hospital care.[2] The exact frequency of alternative therapy use is unknown, but a recent survey of > 1,500 Americans revealed that 34% used at least one alternative therapy in the past year.[3]

Definitions

The National Institutes of Health Office of Alternative Medicine uses the following criteria to define alternative products: 1) sufficient documentation for safety and effectiveness against specific diseases and conditions are lacking; 2) U.S. medical schools do not them include in the curriculum; and 3) insurance providers do not typically reimburse for them.[4]

Many health care providers are unfamiliar with the differences between homeopathic and herbal products. Homeopathy centers around the theory that diseases can be cured using very diluted remedies which produce the same symptoms as the disease. Homeopathic medicines contain minute dilutions of substances derived from animal, plant, or mineral sources; however, these products can also contain prescription agents such as benzodiazepines.[2,5] Herbal medicines are derived or extracted from plants. These medicines have been used for thousands of years, and their use continues to rise.[2,5,6] In fact, annual sales of herbal products in the United States are approximately $1.5 billion.[4]

Regulations

The FDA classifies herbal preparations as dietary supplements; therefore, they are not held to the same stringent standards of purity, efficacy, and safety as are drugs. Therapeutic or health claims on the labels of herbal products are prohibited; however, literature containing unsubstantiated claims and testimonials are often placed near the products. Labels of herbal products must contain disclaimers that the product has not been evaluated by the FDA and is not intended to diagnose, cure, treat, or prevent disease.

Herbal products may not contain any pharmacologically active ingredient or may be toxic because of unstandardized ingredient content. A great deal of variability may exist between manufacturers as well as from batch to batch. Herbal products are claimed to cure numerous disorders ranging from diabetes to obesity, but these claims are often not supported by well controlled clinical trials.[2,6] In addition, herbal products are rarely packaged in childproof containers.[7] In 1996, 400,000 cases of herbal or homeopathic poisonings were reported to poison control centers.[8]

Since herbal products are thought to be "natural", many consumers think that these products are harmless. An herbal expert has identified several products that should be avoided because of associated toxicities (Table 1).[2,6]

Table 1. Unsafe Herbal Products

Name	Toxicity
Borage	Hepatotoxicity; carcinogenicity

Calamus	Carcinogenicity
Chaparral	Hepatotoxicity
Coltsfoot	Carcinogenicity
Comfrey	Hepatotoxicity; carcinogenicity
Ephedra (ma huang)	Hypertension;tachycardia;death
Germander	Hepatotoxicity
Hydrangea	Cyanide poisoning
Licorice	Pseudoaldosteronism
Life root	Hepatotoxicity
Pokeroot	Severe vomiting; death
Sassafras	Hepatotoxicity; carcinogenicity
Yohimbe	Hypertensive crises when given with tyramine-containing foods or sympathomimetics; psychoses

The pharmacology, uses, and safety of three commonly used herbal products are discussed below.

Echinacea

Echinacea, a perennial member of the daisy family, has been used in the United States for hundreds of years. Native Americans used echinacea as a "blood purifer" to counteract blood poisonings. Other uses include treatment of bee stings, leg ulcers, and nasal congestion.[4,9,10] Currently, echinacea is marketed as a stimulator of the immune system and may be used as prophylaxis at the first sign of cold or flu symptoms.

The mechanisms by which echinacea enhances the immune system include: 1) stimulating phagocytosis; 2) increasing motility of leukocytes; and 3) increasing the production of T lymphocytes and interferon.[4] Echinacea has no direct bacteriocidal nor bacteriostatic properties. Several clinical trials have evaluated the efficacy of echinacea root extract for the prophylaxis and treatment of upper respiratory tract symptoms. Unfortunately the studies had methodology flaws and lacked clear diagnostic criteria and standardized dosing regimens.[11,12]

Echinacea is contraindicated in patients with tuberculosis, leukosis, collagenosis, multiple sclerosis, human immunodeficiency virus (HIV), and other autoimmune diseases. Adverse effects of and drug interactions with echinacea are unknown.

Because echinacea can act as a potent nonspecific stimulator of the immune system, it should not be used for more than 6-8 weeks. More research is necessary to fully assess the therapeutic potential of echinacea.[4,9]

St. John's Wort

St. John's wort is a perennial herb that is native to Europe and the United States. Many of its active ingredients have biologic activity; however, the primary active ingredient of St. John's wort is hypericin. Although St. John's wort has antibacterial, antidepressant, and antiviral action, its main use is for the treatment of depression.

Hypericin inhibits monoamine oxidase and the reuptake of serotonin, norepinephrine, and dopamine and binds to GABA receptors *in vitro*. Serum concentrations of hypericin peak approximately 5 hours after oral administration and reach steady-state in 4 days. The half-life of hypericin is approximately 25 hours. Little is known about the metabolism and elimination of hypericin.

A recent meta-analysis examined 23 randomized trials of involving 1,757 mild to moderately depressed outpatients. Eight of these trials used active comparisons (imipramine, amitriptyline, maprotiline, and desipramine,) whereas the remaining trials compared St. John's wort to placebo. The authors concluded that St. John's wort is more effective than placebo and as effective as standard antidepressants. However, the diagnosis of depression was not well defined, the study durations were short, and the antidepressant doses were low.

Adverse effects of St. John's wort include gastrointestinal disturbances, fatigue, pruritis, weight fluctuations, photosensitivity, dizziness, and dry mouth. St. John's wort should not be used in combination with tyramine-containing products, alcoholic beverages, narcotics, amphetamines, sympathomimetics, or any other products that inhibit monoamine oxidase. In addition, concurrent administration with selective serotonin reuptake inhibitors is not recommended.[4,8,13,14]

Following the removal of dexfenfluramine and fenfluramine from the market, weight loss clinics began promoting "herbal fen-phen", a combination of ephedra and St. John's wort. Due to the danger associated with ephedra and the lack of data supporting efficacy in weight loss, the FDA is taking regulatory action to remove these products from the market.[15] The National Institute of Health is sponsoring a study comparing St. John's wort extract to standard antidepressants.[8] Until more information is known, St. John's wort should not be considered an alternative for the treatment of depression.

Ginseng

Ginseng is one of the oldest and most widely recognized herbal products available. The properties of ginseng have been touted as "all healing" for centuries.[16] Ginseng is claimed to have numerous beneficial effects which include

treatment of anemia, atherosclerosis, depression, diabetes, edema, fatigue, hypertension, and ulcers. [2,4,8,9]

Ginsenosides are responsible for the adaptogenic properties of ginseng. An adaptogen is defined as an innocuous substance that causes minimal disorders of physiologic function, has a nonspecific action, and has a normalizing action irregardless of the direction of the pathological state (e.g., functions as a sedative or stimulant). Many clinical trials performed outside of the United States have evaluated ginseng's efficacy for a variety of disorders. However, the trials were fraught with methodology flaws. [2,4,8,9]

Ginseng is contraindicated in asthma, renal failure, Stage 2 or higher hypertension, acute inflammatory or infectious diseases, bronchitis and emphysema, chronic diseases of the gastrointestinal tract (i.e., diverticulitis, gastroesophageal reflux disease), heart failure, arrhythmias, edema, insomnia, anxiety, pregnancy, and breast-feeding. Reported adverse effects of ginseng include insomnia, nervousness, excitation, diarrhea, and skin disorders.[2,4,8,9]

Little is known about drug interactions with ginseng; however, the literature contains two case reports describing ginseng drug interactions. A patient previously well controlled on warfarin therapy experienced a loss of anticoagulant control (subtherapeutic INR) after the initiation of ginseng.[17] In addition, a patient taking both ginseng and digoxin experienced an elevated digoxin level.[2]

Because objective scientific data documenting therapeutic benefits of ginseng are lacking, the role of ginseng as a legitimate therapeutic agent is neither established nor accepted by the medical community.

Natural Product Resources

References that discuss natural products are increasing in number. Table 2 lists available resources for individuals seeking information on natural products.

Table 2. Natural Product Resources

Books
Tyler VE. *Herbs of Choice: The Therapeutic Use of Phytomedicinals*. Haworth Press. 1994.
Tyler VE. *The Honest Herbal: A Sensible Guide to the Use of Herbs and Related Remedies.* Pharmaceutical Products Press. 1993. DerMarderosian A, editor. *The review of natural products.* Facts and Comparisons. 1996.
Society Publications

Herbal Gram and *Herbs for Health* from the American Botanical Council (Austin, Texas)
The Source from the Association of Natural Medicine Pharmacists (Forestville, CA)
Journals
The American Journal of Natural Medicine
Alternative Therapies in Health and Medicine
Alternative and Complementary Therapies
The Journal of Alternative and Complementary Medicine
Internet sites
A Modern Herbal Home Page http://www.botanical.com/botanical/mgmh/mgmh.html
http://www.cathayherbal.com/court/library/

Many Internet sites with information on herbal and alternative therapies. exist. Caution should be taken when interpreting the Internet information as it is not peer-reviewed and may reflect only the opinion of the author.

Conclusion

Herbal products are not regulated as drugs by the FDA; therefore, little is known about their efficacy, appropriate dosages, adverse effects, and drug interactions of these products. Healthcare providers should actively question patients about the use of herbal products, and any use should be documented in the medical record. Pregnant and lactating women should be instructed to avoid herbal products. Parents should also be cautioned to avoid these using these products in infants and young children without medical advice.

As consumer interest in alternative therapy increases, patients will ask healthcare providers for information and recommendations. The paucity of objective, well-designed studies evaluating the effects of alternative therapies may leave healthcare professionals hesitant to respond to questions about these products. Information about herbal products can be obtained from the resources listed in Table 2 or by calling the University of Virginia Drug Information Center at (804) 924-8034.

References

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Pharmacology Literature Review

Gabapentin Stability in Food

Gabapentin is used in both children and adults for the treatment of partial seizures with or without secondary generalization. It is also been found to be effective in treating neurogenic pain syndromes. For patients unable to take full doses or who cannot swallow capsules, this study provides support for administering the capsule contents mixed in table food. Although the study included only 9 adult patients, the results are applicable to pediatric patients. The authors compared the serum concentrations achieved when a 600 mg dose

was given to the patients after fasting, and then when mixed with applesauce, orange juice, and pudding. Each patient served as his/her own control for each of the four administration methods. There were no significant differences in the area under the concentration curve (AUC), maximum serum concentration, or time to achieve maximum concentration among the administration methods tested. There was a trend towards slightly better absorption with foods containing protein. Gidal BE, Maly MM, Kowalski JW, et al. Gabapentin absorption: Effect of mixing with foods of varying macronutrient composition. **Ann Pharmacother 1998;32:405-9.**

Metoclopramide Pharmacokinetics

The pharmacokinetic profile of metoclopramide was studied in 10 premature neonates ranging from 31 to 40 weeks postconceptional age. A single dose of 0.1 to 0.15 mg/kg was given orally to the fasted patients in this study. The average peak serum metoclopramide concentration was 17.7$\pm$6.2 ng/ml. The peak occurred 1 to 3 hours after dosing in most of the subjects. The average volume of distribution at steady state was 6.94$\pm$2.39 L/kg. The average clearance for the group was 0.795$\pm$0.682 L/hr/kg. The results of this study were similar to those published previously in older infants. Based on the results of their own work and previous studies, the authors of this paper recommend a dose of 0.15 mg/kg given orally every 6 hours for infants $\geq$ 31 weeks postconceptional age. Kearns GL, van den Anker JN, Reed MD, et al. Pharmacokinetics of metoclopramide in neonates. **J Clin Pharmacol 1998;38:122-8.**

Pemoline-induced Hepatotoxicity

Although not the first report of this adverse effect, this case serves as a much-needed reminder to clinicians treating children with attention deficit/hyperactivity disorder of the risks of pemoline therapy. The authors describe a 9 year old boy treated with 75 to 112.5 mg/day over a period of approximately seven months. Presenting signs and symptoms on admission were diarrhea, fever, and jaundice. Despite prompt supportive care, the patient progressed to liver failure. He received a liver transplant and was successfully discharged to home. In addition to their case, the authors present a review of the literature on pemoline-induced hepatotoxicity. Adcock KG, MacElroy DE, Wolford ET, et al. Pemoline therapy resulting in liver transplantation. **Ann Pharmacother 1998;32:422-5.**

Topiramate Review

Topiramate is one of the newer antiepileptics in the United States. It is currently approved by the FDA for use as adjunctive therapy in adults with partial-onset seizures; however, it has also been studied in children. The pediatric clinical trials have included both children with partial seizures and Lennox-Gastaut syndrome. This review article includes both the approved and "off-label" uses, as well as a discussion of the pharmacokinetics, adverse effects, and drug interactions of topiramate. The author also presents an interesting cost-benefit analysis, in which the higher cost of topiramate is weighed against reduced monitoring costs. Markind JE. Topiramate: A new antiepileptic drug. **Am J Health-Syst Pharm 1998;55:554-62.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 5/1/98:

1. Budesonide Inhalation Powder (Pulmocort Turbuhaler®) was added to the formulary for the management of asthma in patients < 18 years of age.
2. Sildenafil (Viagra®), a phosphodiesterase inhibitor for the treatment of erectile dysfunction, was rejected for inclusion to the formulary.
3. Tobramycin solution for inhalation (TOBI®) was rejected for inclusion to the formulary. It is available to patients directly through the CF Foundation.
4. The quarterly report of the Adverse Drug Reaction Reporting Program was presented. For more information, please contact Dr. Michelle McCarthy at (804) 924-8034.

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