State of Complementary and Alternative Medicine in Cardiovascular, Lung, and Blood Research
Executive Summary of a Workshop

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Abstract—The National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine recently cosponsored a workshop on the use of complementary and alternative medicine (CAM) in cardiovascular, lung, and blood research. In view of the increasing use of CAM by the general public, it is imperative to promote credible research by the established biomedical community. The goal of this workshop was to enhance the exchange of information and ideas between alternative medicine practitioners and scientists in cardiovascular, lung, and blood research and to foster collaborative research among these researchers. The workshop focused on 5 areas of research, including a historical and cultural perspective of CAM, methodological issues in clinical trials, herbal medicine, chelation therapy, mind/body (meditation) therapy, and acupuncture. CAM has become widely used without rigorously proven efficacy and safety. To protect the public, it was recommended that the fundamental mechanistic research for these CAM approaches be vigorously pursued and that any large-scale clinical trial be carefully executed to avoid any waste of resources and any unnecessary risk. It was felt that standardization of botanical products and procedure-based CAM intervention, such as acupuncture and meditation, is essential for meaningful basic and clinical research. Although botanical products properly consumed are perceived as generally safe, potential herb-drug interactions are a major safety concern. Clearly, many challenges need to be addressed by the scientific community before the public can be assured of the proper use of CAM. (Circulation. 2001;103:2038-2041.)

Key Words: acupuncture ☐ medicine, herbal ☐ cardiovascular diseases ☐ alternative medicine ☐ meditation

A workshop entitled “Complementary and Alternative Medicine in Cardiovascular, Lung and Blood Research,” which was sponsored by the National Heart, Lung, and Blood Institute and the National Center for Complementary and Alternative Medicine (NCCAM), was convened June 12 through 13, 2000 in Bethesda, Maryland. This workshop was co-chaired by Kenneth Wu, John Longhurst, and Eric Gershwin. In addition to the 20 speakers, the workshop was attended by nearly 100 participants.

The objective of this workshop was to promote the exchange of information and ideas, to identify opportunities, and to foster collaboration among scientists who are interested in using complementary and alternative medicine (CAM) in cardiovascular, lung, and blood research. The workshop focused on 5 areas of research, including a historical and cultural perspective of CAM, methodological issues in clinical trials, herbal medicine, chelation therapy, mind/body (meditation) therapy, and acupuncture.

Background and History
Wayne Jonas provided a historical and cultural overview of CAM. CAM approaches in health maintenance have recently become highly popular in the United States, with >40% of the population using it in some way at an annual expenditure of $30 billion. This trend is partly prompted by increasing appreciation of the importance of the “whole person” in health and the skepticism of the general public about orthodox medicine.

Several CAM therapies have been shown to be effective for specific ailments (see the National Institutes of Health [NIH] Consensus Conference on Acupuncture and NIH Technology Assessment Conference on Integration of Behavioral and Relaxation Approaches Into the Treatment of Chronic Pain and Insomnia), and many more remain untested and unproven. Therefore, care in using alternative approaches is imperative. Complete evaluation of complementary medicine must include both scientifically rigorous and clinically pragmatic perspectives when assessing its value or danger.
A recent survey on the use of alternative care providers was reported by Barbara Altman. It has become clear that most people who use CAM do so without informing their primary care physicians and that few physicians are knowledgeable about CAM. CAM therapies encompass a diverse and growing assortment of healthcare approaches. These approaches, which are often used in conjunction with conventional medicine, include acupuncture, biofeedback, chiropractic, herbal medicine, massage, and meditation.

William Harlan stressed the need to use the randomized, controlled trial as the “gold standard” to determine the efficacy and effects of CAM. However, recognizing the broad use of CAM, observational studies by CAM practitioners should not be disregarded. For many CAM therapies, no reliable information exists concerning the numbers and types of patients who use them, delivery and dosage, patient condition before and after treatment, and relevant side effects. These issues can be investigated adequately in observational studies. Such studies form the basis of further studies, provide information on the consistency of the delivery of a therapy, and give an estimate of the effect size. Although recent reviews suggest that observational studies may provide the same answer as a randomized, controlled trial, it is premature to equate the 2 types of studies as sources of confident and specific information about the value of a therapy. The uniqueness of many CAM therapies, such as the special need for standardization and characterization of botanicals and the need to insure their purity and absence of potentially harmful contaminants in these botanicals also presents special challenges in designing any rigorous clinical trials, ensuring the safety of patients in the trial, and determining the potential reproducibility of the trial.

Stephen Straus described the role of the NIH in the support of research in CAM. In 1991, Congress mandated the establishment of the Office of Alternative Medicine at the NIH. This office was elevated to the status of Center in 1998, with a current funding of $70 million a year. The goals of the NCCAM are to invest in research, both through investigator-initiated projects and solicitations, to expand the cadre of researchers by training and recruiting established scientists, to compile data on CAM approaches, and to disseminate pertinent information about CAM more effectively to the community. The philosophical difference between the practitioners of ancient approaches and mainstream researchers is a major challenge. The extensive use of untested CAM practices by the US public has dictated that NCCAM make clinical research its highest priority and the centerpiece of its research portfolio. Currently, NCCAM has supported clinical trials on such topics as St John’s wort in depression, gingko biloba and dementia, gingko biloba and vascular function in peripheral artery disease, shark cartilage and cancer, acupunture in osteoarthritits and cardiovascular disorders, and glucosamine/chondroitin and arthritis. Recently, NCCAM initiated the Frontier Medicine Research Program, which covers areas in which there have been few, if any, rigorous attempts at research. These include Reiki for rehabilitation after cardiac surgery and distance healing (prayer) for AIDS.

### Botanicals

Varro Tyler gave the opening talk on herbal medicine. As much as a third of the US population has used herbal medicine, spending nearly $4 billion in 1998. The most popular remedies are echinacea, St John’s wort, garlic, and ginkgo biloba. The use of herbal medicine continues to increase rapidly. Because current law allows herbs to be sold as dietary supplements, herbal products are not subject to any regulation, and their purity, safety, and efficacy are not controlled. Unfortunately, the quality of herbal products is extremely variable. In fact, many products available on the market do not even contain any of their purportedly active ingredient(s). Therefore, in the interest of public health, it would be reasonable for the Food and Drug Administration (FDA) to allow drug approval only with associated mandatory quality and safety standards based on “reasonable” efficacy.

Norman Gillis discussed the protective effect of ginseng against lung injury caused by free radicals. Using cultured cells and an intact lung model, it was shown that ginseng or its active ingredient, ginsenosides, promotes vasodilation and prevents injury by enhancing the biosynthesis of nitric oxide in the endothelial lining of the lung. Eric Gershwin examined the possible relationship between dietary changes and the increased prevalence of asthma in the United States. The use of food coloring, excessive dietary salt in processed food, and reduced zinc intake due to lower red meat consumption can potentially contribute to the severity of asthma. In addition, the replacement of animal fats with vegetable oils in the American diet may have changed the lipid composition in the body, causing a different distribution of fatty acid metabolites, many of which modulate ion transport, mucus secretion, and smooth muscle contraction. Although some of these dietary changes have been beneficial in the prevention of cardiovascular disease, their potential impact on asthma is complex and remains to be examined. Consumption of microorganisms in yogurt is thought to help reduce susceptibility to a variety of diseases. Dietary magnesium is also a contributing factor to bronchodilation. Some herbs, such as ginseng and ephedra, have been shown to be effective in relieving the severity of asthma. Therefore, CAM approaches incorporating the use of dietary supplements may be beneficial in the management of asthma.

Garlic is one of the most studied herbs in the United States. The ability of garlic supplements to lower elevated serum cholesterol levels and reduce atherosclerotic plaque formation is equivocal, with early trials demonstrating an effect but more recent trials failing to confirm these observations. One possible cause for these discrepancies is differences in the garlic preparations tested. Considerable evidence indicates that allicin is essential to garlic’s hypolipidemic and antithrombotic effects. Efficient release of allicin requires high alliinase enzymatic activity. Larry Lawson found that several preparations used in the recent negative studies released very low concentrations of allicin. He suggested that these low levels are a result of low alliinase activity in the tested products or alliinase instability in the acidic conditions found during digestion in the stomach. Therefore, the release of allicin from a product needs to be standardized under U.S. Pharmacopieia–defined gastrointestinal
conditions and verified before beginning a clinical trial. A meta-analysis of all existing randomized trials investigating the effects of garlic on cardiovascular factors was performed by Ron Ackerman and Cindy Mulrow. They confirmed the short-term benefits of garlic on lipid lowering and antiplatelet effects. However, no significant effect on blood pressure or glucose level was found.

A highly standardized extract of ginkgo biloba, EGB761, is widely used in Europe for treating disorders due to vascular insufficiency, including diminished cognitive function associated with aging. Many products containing ginkgo biloba extracts, some of uncertain purity or standardization, are also being widely used in the United States. John Farquhar presented evidence indicating that ginkgo biloba may have either an anti-platelet aggregation or an antioxidant effect, which could be responsible for some of its beneficial effect on the vascular system. Three major active ingredients have been identified in ginkgo biloba, and at least one of these has been shown to enhance endothelial cell-derived NO levels in an in vitro study. The question has been raised whether the NO effect is due entirely to decreased NO breakdown (due to ginkgo’s known in vitro antioxidant action) or by a direct stimulation of NO synthase. A mechanistic study of ginkgo’s vascular effects is currently in progress in patients with peripheral vascular disease.

Chelation Therapy
Chelation therapy for metal poisoning has been used for many years. One agent, ethylenediamine tetra-acidic acid (EDTA), was found by clinical observation to benefit patients with vascular and degenerative diseases. However, no clinical trials have confirmed its potential benefit. Ted Rozema, who has used this therapy to treat cardiovascular diseases for nearly 2 decades, suggested that calcium chelation may be responsible for this effect of EDTA. He recommends a major research effort, including clinical trials, to resolve the controversy. This recommendation was supported by a number of other speakers.

Iron is required for cell growth and, in particular, DNA replication. Iron chelators, such as deferoxamine, have been shown to have an antiproliferative effect. Lawrence Horwitz discovered a novel chelator, exochelin, which was isolated from Mycobacterium tuberculosis bacteria. Because of its solubility in lipids, exochelin is 10 times more effective than deferoxamine in arresting the growth of vascular smooth muscle cells. The proliferation of vascular smooth muscle cells is characteristic of restenosis after angioplasty. Furthermore, excessive iron stores are associated with myocardial infarction. Exochelin, with its reversible growth inhibition and lack of cytotoxicity, may be used as a therapeutic agent for several cardiovascular complications.

Mind-Body Medicine
Stress is a major contributor to high rates of cardiovascular disease morbidity and mortality. The transcendental meditation (TM) program is the most widely researched standardized meditation technique for stress reduction. Robert Schneider and colleagues conducted a randomized, controlled trial of stress reduction with TM for hypertensive black Americans. This trial was the first to show that TM can be effective in reducing blood pressure, with high cultural acceptability and compliance in a high-risk minority population. Follow-up randomized trials and other controlled studies have reported reductions in other cardiovascular disease risk factors, such as smoking, alcohol abuse, psychosocial stress, and oxidized lipids. Furthermore, recent studies have demonstrated reductions in myocardial ischemia and regression of carotid atherosclerosis in subjects randomized to the TM program compared with controls. Clinical outcome studies have reported reduced rates of cardiovascular disease morbidity and mortality in TM practitioners compared with controls. The cost-effectiveness of the TM program in the prevention and treatment of cardiovascular disease is also emphasized. Vernon Barnes further showed that a decrease in vasoconstrictive tone during TM may be the hemodynamic mechanism responsible for reducing blood pressure. Changes of the levels of stress-related neuromodulators, such as cortisol, catecholamines, and serotonin, have also been found to occur during or after TM practice.

Acupuncture
Lixing Lao reviewed the history and the safety of acupuncture. At a NIH Consensus Development Conference on acupuncture in 1997, conference panel members recognized promising aspects of acupuncture research, affirmed acupuncture’s efficacy in certain conditions, such as pain relief and treatment for nausea, and noted encouraging research on acupuncture treatments for asthma, bronchitis, myocardial infarction, and rehabilitation from stroke. Appropriate use of acupuncture by trained practitioners seems to be very safe. During the last 35 years, only 80 cases of complications and adverse effects of acupuncture have been reported in the United States, and there were an estimated 5.4 million patient visits in 1997 alone. Zang-Hee Cho reported his use of positron emission tomography and functional MRI in the mechanistic study of the neural basis of acupuncture. These techniques detect changes in blood flow and oxygenation relating to neural activity in the brain. Specific activation of certain brain regions, including some of the pain perception centers such as the limbic area and hypothalamus, can be demonstrated during the application of acupuncture. It was suggested that a neural imaging center dedicated to CAM research is highly desirable.

Recent evidence suggests that hypertension and certain cardiovascular diseases can be improved by treatment with acupuncture. Peng Li defined the neuronal pathways responsible for the long-lasting effect of electroacupuncture on blood pressure in a rodent model and demonstrated that low-frequency electroacupuncture activates opioid receptors and provides a therapeutic effect on hypertension. Conversely, high-current electroacupuncture activates the cholinergic system and leads to increased blood pressure, which alleviates shock and bradycardia. Using a feline model, John Longhurst demonstrated that stimulating a well-recognized acupoint over the median nerve on the ankle reduces the extent of myocardial ischemia. Acupuncture seems to act through the direct stimulation of sensory nerves to release endorphins and opiates. Although acupuncture has been used as a treatment for hypertension in China and Russia, it has yet
to gain acceptance in the United States. Using a randomized,
doubled-blind, crossover design, Norman Kaplan hopes to
show that acupuncture at certain acupoints produces long-
lasting blood pressure reductions in hypertensive patients but
not in normotensive subjects. To be of clinical value, acu-
puncture must provide an antihypertensive effect that persists
far beyond the actual procedure.

Recommendations

During the final discussion, it was emphasized that in most
cases, CAM has become widely used without rigorously
proven efficacy and safety. To protect the public, there is an
increasing demand to accelerate the initiation of large scale
clinical trials with major expenditure. It was argued that
without rigorous research to understand the fundamental
mechanisms for these CAM approaches, the clinical trials are
often wasteful in time and resources and even risky. It was
thought that a few alternative therapeutic approaches cur-
rently in use by the public are premature. However, without
compelling and overwhelming evidence to prove their inef-
ficiveness, it is unlikely that the public will be dissuaded
from further use. At the same time, it would be equally
difficult to justify the need to have a large scale and costly
trial simply to prove the ineffectiveness of certain ap-
proaches. Clearly, many challenges need to be addressed by
the scientific community before the public can be assured of
the proper use of CAM. The recommendations resulting from
the discussion fall under 2 broad categories.

Standardization

Standardized formulations of botanical products have not
occurred in either the US market or the research arena. Before
supporting clinical trials on botanical remedies, several issues
regarding the characterization of botanical products must first
be addressed, including whether to use whole extract or a
specific fraction, the method of extraction (eg, alcoholic, tea,
pressed juice), and the chemical and genetic standardization
of the product. Reliable and well-characterized products will
assure the quality of study outcomes. The recent release of a
draft of the FDA Guidance for Botanical Drug Products
(http://www.fda.gov) should help guide the development of
reliable products for research.

Procedure-based CAM (eg, acupuncture, meditation, mas-
sage, etc.) has a separate set of questions. Most types of
procedure-based CAM are not clearly defined interventions,
as are synthetic drugs or some types of herbal remedies.
Procedure-based CAM interventions are used in many differ-
ent ways and are geared toward the individual patient; this
creates a situation in which the prescribed set of treatments
used for one patient may not be appropriate for another
patient presenting with the exact same signs and symptoms.
This variability greatly increases the complexity of designing
high-quality research. For instance, taking acupuncture as an
example, can we test whether a standardized set of needling
points is more appropriate for treating hypertension than
individualized treatment? Assuming a standardized set of
points is applicable, what “dose” of acupuncture should we
use to treat hypertension, ie, how long and frequent are the
treatment sessions, and how many sessions do we need? It is
essential to answer these basic questions before proceeding to
large clinical trials.

Safety

Many CAM therapies have been used for generations, if not
centuries, and they are often the first line of treatment for
individuals without access to conventional Western medicine,
suggesting some level of safety. Although most botanical
products are probably safe when used properly by trained
practitioners, some products are toxic at high doses and others
may have potentially adverse effects in some susceptible
individuals. In addition, the widespread usage of herbal
remedies, the high probability that herbal remedies and
pharmaceutical drugs are being used together, the general
potential for herb-drug interactions, and the recently pub-
lished reports of adverse herb-drug interactions support the
need for further research in this area. Particularly needed are
more data on the uptake, bioavailability, pharmacodynamics,
and mechanisms by which herbal remedies might exert their
effects.
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