

# IMPLEMENTING A RESEARCH AGENDA FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE\*

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**Key Words** complementary medicine, alternative medicine, research

■ **Abstract** Complementary and alternative medicine (CAM) consists of diverse clinical interventions that are practiced because of their popularity rather than the prior demonstration of safety and efficacy required for conventional agents. CAM therapies can be grouped into five categories: biologically based therapies, manipulative and body-based interventions, mind-body interventions, “energy” therapies, and alternative medical systems. The present evidence that individual CAM interventions are efficacious is largely anecdotal, but hundreds of small trials have yielded positive results. For a few modalities, existing data are either very encouraging or else sufficient to conclude that they are ineffective. CAM interventions are presumed to be safe, yet they may not be, particularly in the case of botanical agents with inherent toxicities, significant drug interactions, or potent adulterants. The public health questions regarding CAM can only be addressed through a research agenda that defines which interventions have favorable therapeutic indices. Implementation of this agenda involves adequate characterization and standardization of the product or practice, with rigorous investigation to demonstrate its safety, mechanism of action, and efficacy.

## PRESENT STATUS OF COMPLEMENTARY AND ALTERNATIVE MEDICINES

Complementary and alternative medicine (CAM) consists of clinical interventions that are practiced because of their popularity. In contrast, conventional treatments must be demonstrated to be safe and effective before registration authorities approve them for use. Alternative interventions are used in place of conventional treatments; complementary interventions are used with conventional treatments.

The 20 most common CAM therapies used in the United States in the 1990s are listed by Kessler et al. (1). The many diverse CAM therapies are frequently

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grouped into five overlapping categories: biologically based therapies, manipulative and body-based interventions, mind-body interventions, “energy” therapies, and alternative medical systems.

## Biologically Based Therapies

Biologically based therapies entail administration of botanical or animal products, vitamins, minerals, and amino acids. These agents reflect some of mankind’s first attempts to improve the human condition. The personal effects of the “ice man” included medicinal herbs (2). By the Middle Ages, thousands of botanical products had been inventoried for their medicinal effects. Many of these, including digitalis and quinine, form the basis of contemporary medicines.

In the United States, botanicals/herbs, vitamins, minerals, and amino acids have been formally classified and regulated as dietary supplements since the Dietary Supplement and Health Education Act (DSHEA) of 1994 (3). The difference between a dietary supplement and a drug depends on the use of the agent, not on the nature of the agent itself. If an herb, vitamin, mineral, or amino acid is used to resolve nutritional deficiency or to improve or sustain the structure or function of the body, the agent is considered a dietary supplement. If the agent is used to diagnose, prevent, treat, or cure a disease, the agent is considered a drug.

The distinction between the use of a product for a “structure-function” indication and its use for a therapeutic aim is something of an exercise in semantics. For example, administering calcium for the declared purpose of counteracting diminished plasma calcium levels or to “improve bone health” would be considered as giving a dietary supplement. On the other hand, administering calcium to treat or prevent the disease osteoporosis would be considered as giving a drug. Similarly, menopause is viewed as a normal, age-related physiological process; thus, black cohosh would be a botanical dietary supplement when administered to improve bodily function in menopausal women. However, treating osteoporosis with this same botanical would be considered administering a drug.

These semantic distinctions are important because under law, dietary supplements can be marketed without prior approval of their safety and efficacy by the US Food and Drug Administration (FDA), whereas prior approval is required for drugs. Thus, the passage of DSHEA in 1994 permitted countless botanicals, amino acids, vitamins, and minerals to be sold in grocery stores and health food stores without regulatory review.

Although all dietary supplements are grouped together, botanicals and animal products differ from vitamins, minerals, and amino acids in being complex mixtures. Plant extracts, for example, consist of literally thousands of components. CAM practitioners use the whole extract for treatment, as opposed to identifying an active compound within the extract to be purified and used as a single agent. The use of whole extracts, rather than the active component alone, to treat

human diseases is based on the assumption that components in an extract combine additively or synergistically to produce the total therapeutic effect.

Biologically based therapies have been used to treat diseases of all human organs. For a few of them, data are already sufficient to warrant large-scale trials. For example, multicenter trials are in progress for the following botanicals: *Ginkgo biloba* for prevention of dementia, St. John's wort for depression, saw palmetto and *Pygeum africanum* for benign hypertrophy of the prostate, glucosamine and chondroitin sulfate from animal tissues for a musculoskeletal disorder (osteoarthritis), shark cartilage for lung cancer, and vitamin E and selenium to prevent prostate cancer. These examples illustrate that in general, the diseases for which biological products are directed tend to be chronic ones.

The vast number of biologically based approaches being applied to disorders of various bodily systems renders it impossible to draw sweeping conclusions about their efficacy. A survey of dietary supplements used to prevent or treat infectious diseases illustrates the range of existing data regarding the clinical efficacy of CAM biologicals. For infectious diseases, biologically based treatments range from being effective or likely effective in specific situations, to being of undetermined efficacy, to being proven ineffective.

Among the effective botanical modalities for infectious diseases, artemisinins are a striking success. For severe malaria, artemisinins kill parasites more rapidly (48 h and 72 h in two studies) than does standard therapy with quinine (60 h and 90 h) (4, 5).

As an example of an approach that is likely to be effective in selected settings, cranberry prevented urinary tract infections in women in one prominent study. The number of infections was reduced from 18 per 50 control women to 8 per 50 treated women (6). However, the treatment was not an effective prophylaxis for children with neurogenic bladder, for whom 75% of both controls and treated subjects experienced infection (7). Similarly, vitamin A supplementation statistically reduced the duration of measles pneumonia in vitamin A-deficient children from 8.5 days to 6.3 days (8), but it did not reduce the duration of respiratory syncytial virus pneumonia in US children, who are far less likely to be vitamin-deficient (9). Studies of *Echinacea purpurea* conflicted regarding its ability to treat or prevent viral colds. One study found that prophylactic administration of 4 ml of fresh expressed juice of whole flowering echinacea plants, twice a day for eight weeks, did not reduce statistically the incidence of natural colds (74% in placebo, 65% in the echinacea group) (10). Another study found that 5 ml of pressed juice, twice a day for 10 days, was effective treatment in that the duration of cold symptoms (6 days) was statistically diminished compared to placebo (9 days) (11).

Finally, careful study proved some biological interventions ineffective. Contrary to popular belief, vitamin C prophylaxis does not diminish the incidence or duration of the common cold (12, 13), nor does treatment with "megadoses" of vitamin C (daily administration of ~300 times the recommended daily allowance) reduce the duration or severity of cold symptoms (14).

## Manipulative and Body-Based Therapies

Manipulative and body-based approaches include chiropractic or osteopathic manipulation and many forms of massage.

Spinal manipulation has been used since the time of the ancient Greeks (15), but it was incorporated into two specific healing disciplines in the American heartland of the late nineteenth century: chiropractic and osteopathic medicine. The essence of chiropractic is “spinal adjustment,” in which force is applied to the spine with therapeutic intent. “Dozens of adjusting techniques exist, and discussions about their relative merits make up much chiropractic academic discourse” (15). The force is generally delivered by hand. The medical indication is low-back pain in 60% of cases, and head, neck, and extremity complaints for most other cases. The rationale for spinal manipulation has been postulated to be alleviation of an entrapped facet, repositioning of a disk fragment, alleviation of stiffness induced by fibrotic tissue, or modification of neuronal activity.

Chiropractic is literally a hands-on rather than a high-technology approach and is frequently performed along with other CAM approaches such as massage, acupuncture, administration of botanicals, and physical therapy, largely for acute or chronic musculoskeletal disorders.

The efficacy of chiropractic remains uncertain. Most controlled prospective studies of chiropractic involve manipulation for acute or subacute low-back pain. When chiropractic manipulation was compared to receiving an educational booklet on low-back pain, the group receiving manipulation had significantly less severe symptoms at 4 weeks ( $p = 0.02$ ) but not at 12 weeks ( $p = 0.06$ ) with respect to “bothersome” complaints, and only an insignificant improvement ( $p = 0.32-0.45$ ) on the more definitive Roland Disability Scale at both time points (16). Previous clinical opinion was more encouraging as to the short-term benefit of chiropractic manipulation, with high rates of patient satisfaction. Yet, in the aggregate, the repeated manipulations are at least as expensive as any other interventions for low-back pain except surgical ones.

Osteopathy is also rooted in physical manipulation, but over the past half century, osteopathic practice has become increasingly mainstream and is now largely indistinguishable from allopathic (medical) practice.

## Mind-Body Techniques

The mind and the body engage in a constant interplay that is mediated physically through neural pathways and chemically through the endocrine system and other systems of circulating mediators. Bodily functions are influenced by emotions, and emotions contribute to symptoms. Given the universal prevalence of superstition, ritual, and religious practice throughout human experience, one can assume safely that psychic interventions such as meditation and prayer have essentially always been used in efforts to forestall or ameliorate physical and mental suffering.

Over the past century, a range of psychotherapeutic and psychopharmacological tools were developed to soothe the mind and ameliorate somatic complaints.

Numerous techniques rooted in far more ancient healing methods coexisted with these newer techniques and have emerged as elements of CAM. The boundary between these CAM and more conventional mind-body techniques is not well-defined but is largely decided according to each technique's acceptance by mainstream medical communities. Meditation, dance, music therapy, art therapy, and intercessory prayer are considered complementary or alternative approaches; most uses of hypnosis, cognitive therapies, and biofeedback, however, are well integrated with conventional medicine.

## Energy Therapies

A variety of approaches invoke energy systems as vehicles for healing. Some are understood through contemporary physics, such as magnets, whereas others engage putative energies that remain to be demonstrated objectively. For example, certain Asian traditions attribute health to the proper flow of vital energies through the body. Efforts to restore or strengthen this flow are goals of modalities such as qi gong (pronounced "chee gun"), a traditional Chinese form of health maintenance based on the concepts of *qi*, meaning the vital energy of the body, and *gong*, cultivation of the *qi* (17). Qi gong exercises involve meditation, rhythmical movements, and breathing. The exercises are intended to regulate the mind and to increase circulation of the blood (18), and also to increase respiratory capacity. Qi gong has been specifically used for hypertension and respiratory diseases, among other diseases (17). As concluded by one review of the extant data, "The reported studies do not necessarily measure up to the strict protocols required for randomized controlled trials" (17).

Distant healing refers to "the intentional influence of one or more persons upon another living system without utilizing known physical means of intervention" (19). This can take the form of intercessory prayer, in which a person extends mental energies on behalf of another, even at great distances, and "Therapeutic Touch," in which the healing energies are believed to extend from the healer's hands as they pass close to a patient's body (20).

The lack of plausible biophysical mechanisms for many of these energy healing approaches makes them exceedingly controversial. Yet, one energy approach is gaining traction both in the American marketplace and in academic medical centers.

Acupuncture was originally conceived to restore the flow of *qi*. Acupuncture was already in use in East Asia by the first century BC, with the intention to "harmonize" a patient's state of being (21). Two important states of being identified by the ancient Chinese were termed yin and yang. Yin is associated with cold, darkness, passivity, receptivity, tranquility, and quiescence. Yang is associated with heat, stimulation, excess, assertiveness, and dynamism. Another recognized state of being is "dampness," which has the yin qualities of coldness and softness, and the yang quality of excess. To harmonize imbalances in yin-yang and other states of being, fine needles were inserted into specific points on the body along "meridians" connected to vital centers.

There have been numerous studies of acupuncture's clinical effects, and with evolving explanations of how they may be mediated, there is growing acceptance of their potential benefits. One recent review listed 235 randomized clinical trials of acupuncture for pain, as well as 200 randomized clinical trials for other conditions such as asthma and pulmonary disease, emesis, and various addictions (21). In 1997, a National Institutes of Health Consensus Development Panel concluded that needle acupuncture is probably efficacious for adult postoperative and chemotherapy-associated nausea and vomiting, and for postoperative dental pain (22). Shen et al. subsequently confirmed the effectiveness of acupuncture for chemotherapy-induced emesis in breast cancer patients. The group receiving electroacupuncture (in which mild electrical stimulation is delivered through the acupuncture needles) experienced a mean of 6.3 episodes of vomiting, compared to 10.7 episodes for a minimal needling negative-control group and 13.4 episodes for a positive-control group receiving conventional antiemetic drugs (23).

Recent research has not established the basis for the traditional acupuncture points or meridians, but the stimulation by needling of small-diameter nerves within the musculature appears to have physiological effects. Such stimulation activates the spinal cord, brain stem, and hypothalamus, which in turn can trigger release of endogenous opioids. Functional magnetic resonance imaging and positron-emission tomography scanning have shown that needling affects specific areas of the brain. Some of the neuronal pathways that must be engaged in these activities would not have been predicted by conventional medicine. For example, part of the occipital lobe normally activated by a visual cue was also activated by acupuncture to the medial aspect of the big toe, the site traditionally needed by acupuncturists aiming to address certain visual disorders (24).

## Alternative Medical Systems

Alternative medical systems comprise interventions that do not rely on any elements of conventional medicine. Examples of alternative medical systems include traditional Chinese medicine, Ayurveda (meaning "science of life") of India, and various Native American healing approaches. Each is a complex system that incorporates natural products, diet, spiritual elements, and other modalities.

Newer alternative systems include homeopathic medicine and naturopathic medicine, both founded in Germany in the nineteenth century. Homeopathy began as a reaction to the unsafe interventions of that time, such as purging and leeching. Homeopathic medicine is based on the concepts of "similars" and "potencies." These concepts signify that symptoms of an illness will respond to administration of infinitesimal amounts of an agent that in higher concentrations would produce similar symptoms in healthy subjects (25). The notion that small amounts of a substance can be healthful was reinforced by the success of vaccines and allergy desensitization. Frequently, however, homeopathic medications are so dilute as to invite serious skepticism. For example, Jacobs et al. treated infantile diarrhea in developing countries with a homeopathic agent "diluted 1:100 in a water/alcohol

solution 30 times for a final concentration of  $1 \times 10^{-60}$ ," well beyond Avogadro's number of molecules in a mole (26).

Naturopathic medicine derives from nineteenth-century German practices that aimed to promote self-healing with such nontoxic measures as a proper diet. Today the practice involves lifestyle recommendations, conventional drugs in tolerated doses, herbs, acupuncture, and more.

## Prevalence and Appeal of CAM Interventions

Despite remarkable gains in lifespan and life quality over the past century, and the spotty evidence supporting CAM approaches, CAM interventions are widely practiced. In 1997, Americans made ~600 million visits to CAM practitioners with ~\$25 billion out-of-pocket costs for alternative therapies. Among US adults in 1999, 33% of women and 24% of men used CAM, as did 31%–33% of 35–54-year-olds. The most commonly used modalities were prayer (used by 14% of adults), herbal medicine (10%), and chiropractic therapies (8%) (27). For some chronic, debilitating diseases, use of CAM interventions is even more prevalent; as many as 84% of AIDS patients use CAM (28).

These large expenditures of time and money signify that CAM has fundamental appeal for patients. At the least, CAM interventions offer hope as a defense against diseases for which there are few conventional medicines, and warm personal relationships as a defense against medical procedures that can be cold and isolating. (29).

## Disadvantages of CAM Interventions

The resources expended on CAM interventions are substantial and could be unwise. Reliance on an ineffective CAM agent may dissuade a patient from pursuing or adhering to more conventional approaches that are proven effective. Some who use complementary modalities may be merely "hedging their bets," doing something extra, hoping it will make up for any inherent deficiencies in the conventional approaches. This strategy rests on the assumption that the complementary approach is natural and, even if proven ineffective, is at least safe—an assumption that may not be valid. As De Smet observed, "Since the drug receptors in our body cannot distinguish whether a molecule comes from the plant kingdom or from the chemical laboratory, naturalness does not, by definition, guarantee harmlessness" (30).

Herbal medicines are plagued by contamination with heavy metals and filth, by adulteration with prescription drugs, wide divergence from labeled content, interference with the pharmacokinetics of life-saving drugs, and even some inherent toxicities. Between 1990 and 1999, the FDA recalled more than 100 dietary supplements because they caused eosinophilia-myalgia syndrome, digitalis intoxication, hypervitaminosis D, and *Salmonella* infection (31).

There are several prominent recent examples of unexpected clinical problems related to herbal medicines. The product PC-SPES was used by thousands of men with advanced prostate cancer. It was removed from the market in mid-2002 when

found to be contaminated with the synthetic drugs warfarin and diethylstilbesterol (32, 33). “Chinese herb nephropathy” refers to nephropathy and/or cancer caused by weight-reducing pills supposed to contain the Chinese herb *Sephania tetrandara* for which the nephrotoxic herb, *Aristolochia fangchi*, was inadvertently substituted (34). Dietary supplements containing ephedra may not provide much benefit with respect to weight loss or athletic performance (35) but may result in cardiovascular and central nervous system toxicity (36). Kava (*Piper methysticum*), used for its central nervous system effects, may result in liver toxicity (reviewed in 37). Furthermore, botanicals can modify host metabolic enzymes to such an extent that the concentrations of conventional agents are materially altered. St John’s wort decreased the area-under-the-curve concentration of the anti-HIV drug indinavir by a mean of 57% in normal volunteers (38), and garlic decreased the area-under-the-curve concentration of another anti-HIV drug, saquinavir, by 51% (39).

## RESEARCH AGENDA FOR COMPLEMENTARY AND ALTERNATIVE MEDICINES

The above summary of the domains and present clinical status of CAM interventions indicates that although a vast number are in use, few have been shown to be safe or beneficial. The costs of CAM approaches and their potential risks and benefits provide the public-health rationale for subjecting them to critical appraisal. In pursuit of this vision, the US Congress authorized in 1998 the establishment of a new component of the National Institutes of Health—the National Center for Complementary and Alternative Medicine (NCCAM)—with a mandate to conduct CAM research, train CAM investigators, and disseminate authoritative information to practitioners and the public.

At NCCAM, our own evolving experience with studies of CAM modalities is that too many are weakened by bad assumptions: that the product is well defined; that the optimal dose is known; that the right target population for study has been selected; that practitioners administer the product similarly; that any honest investigator could verify the received wisdom that the treatment is safe and effective. In challenging these assumptions, we are forced to reflect on lessons learned from the more orderly sequence by which conventional treatments are developed and to exploit those strategies that would best suit the particular characteristics of CAM agents. In the end, our goal is to give CAM modalities the best possible chance of proving beneficial.

The fundamental requirements for conventional clinical agents are that they be reproducibly manufactured and administered, be safe, and be effective. In regulatory parlance, the term “manufacturing” refers to the totality of chemistry-manufacturing-control: synthesis of a drug, manufacturing of the product to be administered to the patient, and control of these processes so that the drug and product are made reproducibly. This is certainly relevant to dietary supplements, given their distressing variability. First, nonclinical (in vitro or animal) studies attempt to predict the efficacy and safety likely to be seen in clinical trials, and

they attempt to determine the pharmacokinetic and biochemical mechanisms for efficacy and safety. Next, clinical trials provide the actual clinical data on safety, efficacy, and mechanisms.

The tools and techniques required to conduct CAM research are essentially the same as those for conventional research. Yet, because CAM approaches are already in practice, some confidence in their safety pre-exists formal investigation, and some of the regulatory mandates designed for new chemical entities can be modified.

## Chemistry-Manufacturing-Control Considerations for Botanical Dietary Supplements

Unlike synthetic drugs, botanical drugs are complex mixtures. The active ingredient can be hypothesized but is rarely known for certain. For example, St. John's wort extracts contain naphodianthrones such as hypericin and pseudohypericin; flavones such as hyperoside, quercitrin, and rutin; aglycones such as quercetin, kampferol, luteolin, and myricetin; and phloroglucinaols such as hyperforin, in addition to probably hundreds of unnamed components. The presumed value of St. John's wort for affective disorders has been tied to a number of its constituents, but ultimately, its psychoactive compound(s) are unproven. For this and other botanicals, reproducible manufacturing requires consistent generation of unknown and therefore unanalyzable constituents. To do this, the process by which the final product is generated—botanical growth, harvest, and extraction; the manufacturing processes leading to the final clinical product—must be rigorously controlled.

It has long been known that differences in plant species, growth conditions, time of harvest, and extraction conditions materially affect the composition of the final product. A good historical example is that of digitalis. The publication of a new Pharmacopoeia circa 1907 stimulated the following comments in *JAMA*: "One of the first essentials. . . , satisfactory to both patient and physician, is that the remedy used shall not only possess the qualities usually ascribed to it, but also that different preparations of the same drug shall possess these qualities to a uniform degree, or in other words, shall be of uniform strength. . . ." and further, "it is impossible to fix any chemical standard to which preparations of digitalis and its allies shall conform, on account of the difficulty connected with the isolation of the glucosides. . . the crude drug itself varies notoriously in its content of active principle. This variation depends on the time when the leaves are gathered, and the country from which the plant is obtained. . . . The US Pharmacopoeia directs that the leaves of the second year's growth shall be gathered at the commencement of flowering. Experience has shown that these are best dried in a current of warm air and then should be preserved in tin containers to protect the drug from light, air, and moisture" (40). These admonitions are broadly relevant to the problem of standardizing botanical remedies today.

A more modern, and ultimately highly successful, example is that of the new antimalarial agent artemisinin. Pure artemisinin is purified from *A. annua* leaves. *A. annua* grows on the banks of the Potomac river in Maryland, USA, but the yield

is ~0.05%. Artemisinin yields from China range from 0.01% to 0.5%, with the highest from varieties grown in Sichuan Province (41). Because the yield varies with local varieties and growth conditions, all artemisinin is currently derived from high-yielding regions of Southeast Asia.

As a result of its recalls of contaminated and adulterated dietary supplements, in 2003 the FDA proposed new chemistry-manufacturing-control (CMC) standards for marketed dietary supplements. These standards will make manufacturing controls more like those for conventional drugs. A key feature of the new standards is the introduction of process controls to supplement analysis of the final product.

With respect to botanicals used as drugs in clinical trials, the FDA has issued draft requirements for phase 1/2 studies and phase 3 studies (42). NCCAM promulgated its adaptation of these requirements for all studies it supports, as summarized in Table 1, columns 4 and 5 (43).

Proposals for phase 1/2 studies are to include a description of the plant and the extraction procedure; analysis of the clinical formulation for putative active ingredient(s), for a chemical fingerprint representing the unidentified ingredients, and for lack of contamination by pesticides, heavy metals, and synthetic drug

**TABLE 1** Chemistry-manufacturing-control considerations for clinical trials

Study subject	Study parameter	Study details	Data to support Phase 1/2	Data to support Phase 3	
PLANT SUBSTANCE	Starting material	Botanical description	X	Expanded	
		Extraction procedure	X	Expanded	
		Quantity of active moiety		X	
		Identity: chemical/ biologic assay		X	
		Stability		X	
PLANT PRODUCT	Manufacturing	Reagents/process		X	
		Finished product	X	X	
	Product assay	Methods/specifications		X	
		Identity: chemical/ biologic assay	X	X	
		Purity		X	
	Storage	Describe conditions	X	X	
	Stability	Light/heat/time	X	X	
	Excipients	List		X	
	Impurities	List/analyze	X	X	
	Reference standard	Standard batch		X	
	In process controls	SOPs		X	
	Bioavailability	Disintegration/ dissolution rate		X	X
Microbiology	Contamination			X	
Environmental	Assessment			X	

adulterants; demonstration that the analyzed components dissolve in physiological solutions; and demonstration that the ingredients are stable over the length of the trial. Phase 3 studies involve a larger number of patients and are penultimate to registration, marketing, and the less-monitored use of the agent by the general public. Thus, for phase 3 studies, extra confidence in the information is needed. This is provided by formal process controls demonstrating that the plants were cultivated/harvested according to good agricultural/harvesting practices, and that extraction, analysis, and manufacturing were performed according to good manufacturing practices.

## **Chemistry-Manufacturing-Control Considerations for Nonbotanical Dietary Supplements**

Some nonbotanical dietary supplements, such as glucosamine or melatonin, differ from botanical drugs in being single chemical entities. CMC requirements for these substances can therefore approximate those of a conventional agent.

## **Nonclinical Considerations for All CAM Interventions**

Nonclinical information generally needed to support investigation of a conventional drug consists of *in vitro* and animal data on efficacy, toxicity, and pharmacokinetics/mechanisms. In the case of CAM agents, because of their substantial human use prior to formal investigation, clinical tolerance may be reasonably predicted and animal studies are not required to protect human subjects. Therefore, the FDA draft botanical guidelines and NCCAM policy do not require *in vitro* or animal experimentation prior to clinical experimentation.

The ultimate criterion for clinical use is a favorable clinical therapeutic index, irrespective of a mechanistic understanding of the effects or their correlation with nonclinical data. Nevertheless, nonclinical experimentation has considerable value. Attractive nonclinical and mechanistic data frequently provide the confidence to pursue a clinical program and/or result in a better design of that program. Moreover, some understanding of mechanism helps lead to general acceptance of an approach.

## **Clinical Considerations for All CAM Interventions**

Demonstration of the clinical value of both biological agents and nonbiological approaches can follow similar developmental schemata (Table 2). Whether the interventions have arisen from laboratory investigations or have evolved over the centuries or in modern clinics through empirical trial and observation, clinical value must be demonstrated in the manner that is used for new conventional interventions. A first step in the formal prospective evaluation of CAM interventions is to determine how much to give and how often. Each intervention can be underdosed, and so have little effect, or overdosed so that it is toxic (biological agents), physically painful (manipulative and body-based interventions), or unnecessarily costly (all interventions). Once the apparent optimum dose is determined in

**TABLE 2** Clinical considerations for CAM clinical trials

Study	Study parameter	Study details	Data to support Phase 1/2	Data to support Phase 3
PHASE I	Toxicity	Single dose Multiple dose	X	X (if possible) (if possible)
	Pharmacokinetics (biologics)	Fed vs fasted drug-drug interactions		
PHASE II	Efficacy	Multiple dose		X
PHASE III	Efficacy and Toxicity	Large comparative trials in adults Additional trial in children		

these phase 1/2 trials, large phase 3 trials can compare the optimum dose to a conventional intervention.

## Design of Clinical Studies

Many of the disorders for which CAM modalities are prescribed have variable natural histories and are highly subjective. These features make their study relatively difficult. Consequently, particular attention should be paid to the essential features of study design: control groups, entry criteria, endpoints, sample size, reproducible administration of the interventions, and compliance.

**PLACEBO CONTROL GROUPS** Responses to CAM and conventional approaches can be influenced by patients' expectation that they will benefit from a powerful intervention by a skilled practitioner. Thus, the best efficacy studies are placebo-controlled, unless this exposes patients to unacceptable suffering or morbidity. Studies of certain CAM modalities, particularly the physical interventions such as chiropractic manipulation, can be as difficult to blind as conventional surgical interventions. Nevertheless, the placebo effect can be significant for physical interventions, and randomized placebo controls are useful if they can be instituted. A randomized study of arthroscopic surgery suggested that surgical techniques elicit such strong placebo effects that the long-standing practice had no specific value (44).

The need for placebo controls is particularly important in studies of CAM agents because of their widespread clinical use and social acceptance prior to formal evaluation. Countless patients and their physicians may be correct that a particular CAM therapy produced a major improvement in the patient's condition, without the CAM therapy having any specific value, if there is a large placebo effect for that condition. Perhaps one example of this dilemma is St. John's wort. In one large study of its value for major depression of moderate severity, a partial

response (50% improvement in the standard Hamilton D index of depression) or full response was seen in 38% of patients but in 43% of placebo recipients (45). This study's finding that St. John's wort had no specific efficacy could not have been revealed without a placebo study arm.

**DISEASE SEVERITY CRITERIA** Because the diseases treated with CAM agents are often chronic, have widely variable placebo response rates, and have small effect sizes in response to conventional treatment, the characteristics of the patients enrolled in a study can influence its likelihood of success. Davidson's study of St. John's wort for major depression showed no effect greater than placebo, whereas Lecrubier's study (46) did show a statistically significant effect. The studies involved different formulations of St. John's wort but the same concentration of the putative active ingredient hypericin, and both used the same efficacy criterion. Why did the outcomes differ? One hypothesis is that the patients were differentially seeking care and thus may have differed in severity of depression (46). On the other hand, increased severity of disease may modify drug response rates and placebo response rates equally, so that enrollment of sicker patients may not generally demonstrate the specific efficacy of CAM interventions (47).

**DISEASE ENDPOINTS** It is important to apply objective measures of disease severity where possible, or at least to utilize well-validated instruments for subjective endpoints. For example, the best studies of glucosamine for osteoarthritis use not only the well-accepted WOMAC index of pain, physical function, and stiffness, but also coded flexion X-rays to measure the joint space (48).

**SAMPLE SIZE** Many CAM interventions are used in conditions for which conventional drugs are only modestly effective, yet these small effect sizes are of clinical significance. In the above-mentioned St. John's wort study, only 25% of patients treated with the standard serotonin-specific reuptake inhibitor sertraline demonstrated a full response.

Small effect sizes mean that large numbers of patients must be enrolled to statistically differentiate standard therapy from placebo. Controlled trials of agents with small effect sizes are therefore very expensive. The problem of expending large resources on a study that may fail is an unfortunate challenge of CAM research and reflects the fact that these approaches enter formal clinical experimentation on the basis of anecdotes.

**REPRODUCIBLE ADMINISTRATION OF INTERVENTION** Botanical drugs are difficult to manufacture reproducibly but (like conventional drugs) are simple to administer. In contrast, other CAM modalities, such as manipulative and body-based interventions, mind-body interventions, and energy therapies, have no manufacturing issues but (like conventional interventions such as surgery and psychotherapy) can be difficult to administer reproducibly. In each of these settings, the best study designs

incorporate a “manual of administration” so that the interventions are performed in a standardized manner to which each practitioner agrees.

**COMPLIANCE** Strong preferences of patients towards CAM or conventional interventions can threaten study blinding and randomization. Because dietary supplements are widely marketed, patients enrolled in a blinded placebo-controlled study who are not improving as much as they had anticipated might “cheat” by purchasing and taking the study supplement (49). In a study of an intensive nutritional intervention for pancreatic cancer, it was difficult to enroll subjects. Subjects who strongly desired conventional chemotherapy refused to risk being randomized to the nutritional approach, whereas patients who feared the toxicity of chemotherapy and its modest benefits in pancreatic cancer only wanted to receive the nutritional approach. In the end, the study had to be redesigned to allow self-selection, with the hope that the disease severity of subjects who do enroll into each study arm will, in the end, be comparable.

## CONCLUSIONS

Complementary and alternative medicines are interventions that have entered clinical use without the prior demonstration of safety and efficacy required for conventional interventions. Given the high costs of developing new drugs and the popular appeal of CAM interventions, investigation of their therapeutic index is an attractive means of augmenting our clinical armamentarium. The agenda for CAM research focuses on providing the confidence in manufacturing, administration, safety, and efficacy afforded by conventional agents.

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