Trends and Current Status of Clinical Trials of Herbal Medicine in the United States

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1. Introduction

In this paper, we report on the current scientific studies of herbal products in the United States. We review this from both a historical and economic perspective, which has led to the increased need to conduct quality randomized clinical trials in herbal medicine. We report on several published examples of both positive and negative trials, comment on the limitations of these trials, and make recommendations for future work. In addition, we present the results of a survey of design features of randomized clinical trials in herbal medicine.

2. Background

In the United States, herbal use began in the 17th and 18th centuries when homemade botanical remedies (later, "patent medicines") were provided by women in the home. In the 19th century, due to developments in scientific investigations, the practice of botanical healing was dismissed as "quackery". However, in 1992, recognition of the rising use of herbal medicines and other nontraditional remedies led to the establishment of the Office of Alternative Medicine by the National Institutes of Health with a budget of $2 million. Ten years later, the Office became the National Center for Complementary and Alternative Medicine (NCCAM) with a budget of $73 million in 2000.

In 1990 a survey was conducted regarding the utilization of 16 commonly used complimentary and alternative medicine (CAM) therapies (Eisenberg et al, 1998). Among the representative sample of 1,539 American adults, 34% reported using one of more CAM therapies, including relaxation techniques, chiropractic, massage and imagery. It was estimated that the number of visits (338 million per year) exceeded visits to all primary care physicians. In 1990, the expenditure was $13.7 billion dollars.

Americans spent $533 million in 8,000 health food stores in 1994, and sales of herbal medicines are growing by 20% a year (Winslow and Kroll, 1998). The top selling herbal products in the U.S. are: ginseng (= $78 million in annual sales), garlic (= $67.6 million), ginkgo biloba (= $66 million), Echinacea (= $14 million), and St. John' s Wort (= $13.5 million). Insurance plans and managed care organizations are beginning to offer reimbursements for alternative treatments, including herbal medicines.

In an editorial by Angell and Kasirer (1998), it was concluded, "once a therapy (such as an herbal product) has been tested rigorously, it no longer matters whether it was considered alternative at the outset. If it is found to be reasonably safe and effective, it will be accepted". Thus, the CAM research agenda is to determine the efficacy and safety of widely used and/or promising therapies. However, a primary issue regarding CAM research is that there is no opportunity to patent most CAM therapies, a major limitation for supporting the research necessary to demonstrate effectiveness, efficacy and safety of CAM therapies.

3. Examples of Positive and Negative Randomized Clinical Trials

In 1998, McCrindle et al (1998) conducted a randomized, double blind, placebo-controlled clinical trial to determine whether garlic extract therapy is efficacious and safe in children with hypercholestoremia. Design features included: a) medication formulated by a single independent pharmacist, b) placebo control, c) masking of clinical investigators/staff, d) standardized laboratory procedures, e) prior sample size calculations, and f) pre-planned analytic approaches. Although compliance was ascertained by pill counts, no direct biologic measure of compliance was made. No significant effect of garlic extract therapy on cardiovascular risk factors was found. The authors point out that the mechanisms by which garlic or its active components might have effects on lipid profiles has not been determined.

A randomized, double-blind, cross-over clinical trial in soy was conducted by Quella et al (2000). The objective was to determine whether soy-derived phytoestrogens could alleviate hot flashes for breast cancer survivors. Design features included: a) standardization of medication formulation by a single independent pharmacist, b) placebo control, c) masking of clinical investigators/staff, d) standardized laboratory procedures, e) prior sample size calculations, and f) pre-planned analytic approaches. Although compliance was ascertained by pill counts, again no direct biologic measure of compliance was made. No significant effect of soy on the reduction of hot flashes was found. Although the authors point out that there is no consensus agreement as to the optimal daily dose, or the length of treatment time on soy isoflavones, they did justify their choice of daily dose and length of treatment. They conclude that another soy-based preparation might alleviate hot flashes, but a more definitive claim requires a definitive clinical trial.

On the positive side, Bensoussan et al (2000) conducted a randomized, double blind, placebo-controlled clinical trial to determine whether Chinese herbal medicine is efficacious and safe in the treatment of irritable bowel syndrome. Design features included: a) a pre-randomization run-in to assess measurement reliability and to evaluate the "placebo effect", b) patients saw the same herbalist (out of 3) during the course of treatment, c) three treatment arms = placebo, standard, individualized. No prior data were available to determine effect size/power. Compared to placebo, significant benefit was found due to standard and individualized herbal medicine treatment in both patient an gastroenterologist evaluations. Long-term benefit was found for the individualized Chinese herbal medicine treatment.

4. Other Issues Related to Herbal Clinical Trials

One key issue in planning clinical trials is that some herbs have been shown to be poisonous. For example, Moore and Adler (2000) reported on a case in the United States of lead poisoning from an Indian herbal vitamin. The child, who was developmentally delayed, was given an herbal vitamin (3 times/day for 4 years) to strengthen the brain. A traditional medicine healer told the parents that "the tablets were pure medicinal herbs and plants, free from any harmful or toxic substances." In fact, the tablets contained large amounts of lead and mercury, leading to significant lead burden. The authors concluded that "physicians who treat diverse ethnic populations need to become aware of traditional herbals as an alternative treatment. However, physicians need to inquire about their use, and be knowledgeable about benefits and risks."

Another key issue is that there may be herb-drug interaction. In a review article, Fugh-Berman (2000) points out that there is a dearth of reports about herbal medicine adverse events and herbal x drug interactions. In addition, experimental data, case reports and case series regarding herb-drug interactions are limited. Based on a large survey of the literature, a series of herb-drug interactions are given, including: a) bleeding when warfarin is combined with Ginkgo biloba, garlic, dong quai or danshen; b) serotonin syndrome when St. Johns' wort is combined with serotonin-reuptake inhibitors; and c) induction of mania in depressed patients when antidepressants are mixed with Panax ginseng.

Another key issue is the quality control of any particular herb or mixture of herbs. As with drugs, an herb that is not toxic or therapeutic in one form or strength may be helpful or harmful in a different preparation (Angell and Kassirer, 1998). The potency of various compounds is affected by

growing conditions, storage, handling, and preparation such that the potency of various products from the same plant can vary 10,000-fold (Angell and Kassirer, 1998).

5. Goals for the Future

Because the use of herbal medicine in the United States is increasing, knowledge of the nature of the preparations, and potential benefits and risks, as well as drug-herb interactions is necessary. It is recommended that clinical studies are conducted which parallel the strategies, designs and reporting procedures that are expected for drug trials (Table 1). However, these strategies and challenges may differ depending on whether the use of the herbal product is for a dietary supplement or treatment, and whether single or compound herbal products are used (Table 2).

Table 1: Recommended Strategies for Future Herbal Trials

Phasing of Clinical Trials
Phase I: Establish Maximum Dosage
Phase II: Demonstrate Effectiveness
Phase III: Compare Against Standard: determine risks and benefits
Phase IV: Assess New, Long-term Effects
Design Issues for Phase III and IV Clinical Trials
State objective and define study population. Frame research question, rationale and translate into study hypotheses.
Select the appropriate study design
Define the study variables
Select the study sample and determine the sample size
Identify bias and masking methods
Describe the analytic plan
Reporting Guidelines
Study population
Therapy
Study design
Patient accounting
Follow-up
Data quality control
End point documentation

Table 2: Challenges for Herbal Trials

Category	Phase	Challenges
Food supplement	I	• Not necessary
	II	• Not necessary
	III	• Long term follow-up of safety • Large sample sizes are needed
Single herb as medication	I	• Follow same guidelines as for drug trials
	II	• Follow same guidelines as for drug trials
	III	• Follow same guidelines as for drug trials

Category	Phase	Challenges
Compound herbs as medication	I	• Recommended dose from herbal practitioner vs. dose from Phase I trial? • If high toxicity rate, change dose or the format of the compound? • How to identify unexpected side effects
	II	• Drug herb interaction
	III	• Drug herb interaction

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RESUME. In this paper, we report on the current scientific studies of herbal products in the United States. We review this from both a historical and economic perspective, which has led to the increased need to conduct quality randomized clinical trials in herbal medicine.