Clinical Trials in Integrative Therapies

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Objectives: *To review clinical trials in natural products and mind-body therapies for oncology symptom management, to discuss issues related to developing clinical trials in this area, and outline examples of rigorous and innovative study design.*

Data Sources: *Peer reviewed literature.*

Conclusion: *Most of the evidence for the integrative therapies reviewed is derived from phase II trials, and is considered preliminary. More research is needed in these therapies to clearly articulate their role in the management of oncology symptoms. Innovative strategies and methodologies for studying integrative therapies have been demonstrated.*

Implications for Nursing Practice: *It is necessary to critically evaluate the literature to be able to educate patients about integrative therapies. Investigators should expand on well-designed studies that demonstrate clinically important effects. Dissemination trials may be a good strategy, once data exists, to move integrative therapies into the care of patients.*

Key Words: *Integrative therapies, clinical trials, mind-body therapies, natural products*

Surveys about the use of complementary and alternative medicine (CAM) in various populations consistently demonstrate that more patients with chronic illnesses, including cancer, use these therapies over people without chronic illness.[1,2] The most prevalent interventions used are herbal/dietary supplements (including mega-vitamins and minerals), spiritual, psychosocial (counseling/support groups), and stress reduction therapies.[3-5] This is somewhat of a contrast to the types of therapies being offered in integrative oncology clinics throughout the United States.

According to an article published by Brauer et al,[6] 71% of the 40 comprehensive cancer centers had some web site related to CAM, and the most common therapies showcased were not biologically based therapies, known now as natural products, but rather acupuncture, meditation, spiritual support, nutrition, yoga, massage, and music therapy. A review of the comprehensive cancer center web sites by the authors of the current article confirmed that mind-body therapies,

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broadly defined, are predominant. With respect to natural products, some web site text refers to "nutritional counseling"; one institution newly offers naturopathic services, and several discussed consultative services related to drug interactions and supplements. The implications of this "mismatch" in use and services indicate a couple of important points: 1) evidence to guide provider recommendations is lacking for most of the natural products with respect to cancer care issues; and 2) patients are likely using natural products "off the shelf" without the needed information about the potential for benefit or harm. Hence, efforts toward patient education about the evidence of integrative therapies are critical, while continued building of the evidence base ensues.

This article will provide a broad overview of the clinical trials published on integrative therapies that have been evaluated for oncology symptom management, focusing examples on popular natural products and mind-body therapies used for stress reduction. Finally, considerations in developing clinical trials in the area of natural products and mind-body therapies will be discussed, concluding with recommendations for moving the science forward. Several other modalities and much more data are available to review, but space constraints demanded limitations.

Overview of Clinical Trials

Clinical trials are a set of procedures or processes in research performed to collect safety and efficacy data about an intervention.[7,8] Clinical trials are the cornerstone of evidence-based medicine and, despite some limitations,[8] are the best accepted evidence of efficacy. There are three phases of human clinical trials (phase IV trials will not be addressed). Phase I trials are often first in human trials, designed to test the safety and maximum tolerated dose of a therapy. They are most often used in trials of pharmaceutical agents to treat disease and generally involve small cohorts of patients assigned to escalating doses of an open-label drug. In pharmaceutical development, phase I trials occur after preclinical trials (in vitro and animal model experiments) have been conducted. Phase II trials are performed with a defined population and are designed to assess efficacy (ie, Does this intervention have an effect on this population with respect to this outcome?). Phase II trials can be single-arm trials or randomized trials that utilize a control or placebo. Phase II trials can also compare interventions against each other to choose the best arms for a phase III trial. There can be confusion and overlap between the terms "pilot trial" and "phase II trials," and often these two types of trials are not well differentiated in the published literature. Generally, a pilot study is a small study with the aim of assessing feasibility and study design.[9] However, pilot studies can also be used to estimate effect size to inform further trials. Phase III studies are randomized controlled trials (RCT) involving sufficiently large numbers of patients in each comparison group to definitively evaluate the effectiveness of an intervention on a population. Effectiveness, as opposed to efficacy, incorporates the evaluation of a clinically meaningful effect and whether the risks are outweighed by the benefit. A phase III trial should have an adequate control group and power to assess the specified primary outcome. Depending on the design, the larger the trial, the more power it will have, and therefore, more able to detect small differences between groups that may not be clinically important.

When reviewing clinical trials in integrative therapies in this article, trials designed to assess dose and safety will be categorized as phase I. These trials are more common in research on natural products than mind-body modalities. Those designed to assess efficacy, without meeting appropriate criteria for a phase III trial, will be classified as phase II. The RCTs, with known dose, adequate control, appropriate power, and a specified apriori primary endpoint, will be classified as phase III.

It is difficult to think about clinical trials without thinking of the cooperative group system because they are the "machines" for generating clinical trial data. With respect to symptom management, the Community Clinical Oncology Program research bases and members generate much of the data from larger phase II and phase III trials. Trials more recently completed or activated in the cooperative groups related to integrative therapies are outlined in Table 1.[10-30]

The fact that clinical trials with natural products are similar to pharmaceutical trials performed for disease management may well be the reason that most of the clinical trials evaluating CAM in the cooperative group system have been with natural products. Benefits of cooperative group research include multiple sites, involvement of community