

Integrative Oncology in North America

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ABSTRACT

Integrative oncology is an evolving evidence-based specialty that uses complementary therapies in concert with medical treatment to enhance its efficacy, improve symptom control, alleviate patient distress and reduce suffering. In North America the evolution of research into complementary therapies was delayed by the narrow focus of the Flexner Report. A government-funded research agenda and incorporation of complementary therapies into medical school curricula have been driven by early evidence of efficacy and patient demand. Integrative oncology focuses on the role of natural health products (botanicals, vitamins, and minerals), nutrition, acupuncture, meditation and other mind-body approaches, music therapy, touch therapies, fitness therapies, and more. Some natural health products, such as herbs and their constituent phytochemicals, may be biologic response modifiers that could increase cancer control. Current research stretches from the laboratory to health services. Institutions are exploring the effectiveness gap in their clinical services and are determining efficacy of complementary therapies through randomized controlled trials. Eventually, the goal is to establish practice guidelines through determining relative effectiveness and value through cost-utility studies. The aim of integrative oncology should be one medicine, not alternative; it should be patient-focused; it should be evidence-based; and it should provide the best care for cancer cure, prevention, symptom control, and quality of life.

KEY WORDS: cancer, complementary therapies, education, integrative, quality of life, research, standards, symptom control

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INTEGRATIVE ONCOLOGY DEFINED

Integrative oncology combines the discipline of modern science with the wisdom of traditional healing. It is an evolving evidence-based specialty that uses complementary therapies in concert with medical treatment to enhance its efficacy, improve symptom control, alleviate patient distress, and reduce suffering. Many of these therapies are used to improve coping and to help patients adhere to their medical treatment program. Integrative oncology focuses on the role of natural health products (botanicals, vitamins and minerals), nutrition, acupuncture, meditation and other mind-body approaches, music therapy, touch therapies (such as massage), fitness therapies, and more. Some natural health

products, such as herbs and their constituent phytochemicals, may be biologic response modifiers that could increase cancer control. The goal of integrative oncology is to increase the efficacy of conventional cancer treatment programs, reduce symptoms, and improve quality of life for cancer patients. When used wisely in a regulated cancer care program, integrative therapies can transform the physical, emotional, and spiritual dimensions of patients' lives and contribute to their rehabilitation following cancer treatment.

Integrative oncology is part of a wider definition of integrative health care. It seeks, through a partnership of patient and practitioner, to treat the whole person, to assist the innate healing properties of each person, and to promote health and wellness as well as the prevention of disease. It is an interdisciplinary blending of both conventional medicine and complementary health care that should provide a seamless continuum of decision making and patient-centered care. It should employ a collaborative team approach guided by consensus building that permits each practitioner and the patient to contribute their particular knowledge and skills. It avoids medical paternalism but encourages evidence-based advice that is consistent with the patient's values. It aims to provide a more

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effective and cost-efficient care plan by synergistically combining therapies and services in a manner that exceeds the collective effort of the individual practices.^{1,2}

The term *complementary therapy* (or *complementary medicine*) is to be distinguished from alternative medicine. They are historically bundled together under the term *complementary and alternative medicine* (CAM). Alternative therapies typically are promoted as viable treatment options and as alternatives to so-called mainstream therapy such as chemotherapy, radiation, and surgery. Alternative therapies are unproven, rarely based on any credible scientific rationale, and potentially harmful, especially when the patients are led away from effective proven therapies through the lure of false promises and an emphasis on a lack of adverse side effects compared with conventional therapies.³⁻⁶

There is no alternative to scientifically evaluated evidence-based medicine. Most patients who use unconventional therapies (all but 2%) do so to complement rather than to replace mainstream treatment.⁷ However, in desperation or because of fear, and when there is inadequate support and communication, patients may seek alternative therapies. Integrative oncology provides the opportunity to evaluate techniques that fall outside the conventional medical domains of surgery, pharmaceuticals, radiotherapy, and conventional psychological support. If proven to be effective and to provide added value, these additional techniques should be incorporated into comprehensive cancer management programs.

HISTORICAL PERSPECTIVES OF INTEGRATIVE MEDICINE IN NORTH AMERICA

In 1910 Abraham Flexner researched and prepared a report that is the foundation of modern American and Canadian medical education. Abraham Flexner was not a doctor but was a secondary-school teacher and principal for 19 years in Louisville, KY. He undertook graduate work at Harvard and the University of Berlin and joined the research staff of the Carnegie Foundation for the Advancement of Teaching. The "Flexner Report" was actually titled "Medical Education in the United States and Canada."⁸ It triggered much-needed reforms in the standards, organization, and curriculum of North American medical schools. At the time of the report, many medical schools were proprietary schools operated more for profit than for education. Flexner criticized these schools as a loose and lax apprenticeship system that lacked defined standards or goals beyond the generation of financial gain. In their stead, Flexner proposed medical schools in the German tradition of strong biomedical sciences together with hands-on clinical training. This led to the classic teaching hospital-based system with a strong emphasis on the objective

application of science to the management of illness in patients. The Flexner Report caused many medical schools to close down, and most of the remaining schools were reformed to conform to the "Flexnerian" model.

The resulting changes in medical education led to the acceptance of the biologic, disease-oriented models. State licensing boards, influenced by the American Medical Association, limited the practice of medicine to graduates of accredited institutions, and research funding became the domain of the major teaching centers. All these factors put great pressure on smaller schools (and their graduates, many of whom were homeopaths) that could not meet the emerging requirements for medical education and practice. As a result, many schools that taught practices such as homeopathy were closed, and homeopaths were shunned and stigmatized. Health practices that did not conform to the new biomedical criteria became the "alternatives" to the standards that evolved after acceptance of the Flexner Report. The terms *alternative medicine*, *complementary medicine*, and *unconventional medicine* subsequently referred to diagnostic methods, treatments, and therapies that appeared not to conform to standard medical practice and, by definition, were not generally taught at accredited medical schools.

Unfortunately, the scientific positivism of the Flexner Report resulted in the discarding of potentially useful interventions that did not fall into the classic domains of surgery and pharmacology. The teaching hospital model distanced the subjective elements of patient management. The importance of the healing relationship between caregiver and patient was largely ignored. In addition, the model emphasized the Cartesian split between mind and body. This restrictive perspective on a multidimensional framework of health care resulted in "throwing out the baby with the bathwater" and delayed research on the contribution of biophysical therapies, psychosomatic interventions, healing relationships, and the development of useful herbal therapies.

Because of the high prevalence of use of alternative medicine in the United States, Congress passed legislation in 1991 that created the Office of Alternative Medicine (OAM) at the National Institutes of Health (NIH), with a directive to begin a program of research on alternative therapies. Its purpose was to "coordinate and support evaluations and investigations that assess the scientific validity, clinical usefulness, and theoretical implications of health care practices that prevent or alleviate suffering or promote healing." The OAM has since developed into the National Center for Complementary and Alternative Medicine (NCCAM). An initial budget of \$2 million (US) grew to over \$100 million (US) for 2004 and was distributed to various research programs in centers of excellence. Under the inaugural leadership of Dr. Stephen Strauss, the sci-

tific rigor applied to conventional medicine is also being applied to complementary and alternative practices. Efforts are being made to standardize and ensure quality of dietary supplements and herbal derivatives, scientifically determine the actions of CAM interventions, and evaluate CAM interventions in rigorous clinical trials.

Medical schools could no longer ignore the resurgence of alternative medicine. In an editorial published in *Academic Medicine* titled "Is There Wheat among the Chaff?" Arthur Grollman concluded that teaching about alternative medicine is important.⁹ Physicians should help patients distinguish between therapies whose efficacy and safety have been established and those that are unproven or unsafe. In a Canadian survey that assessed first-year medical students' attitudes, knowledge, and experiences of CAM, 52% stated that they had used CAM and 84% wanted further education. The deans of Canadian medical schools suggested that medical school curricula should include evidence-based CAM.^{10,11} Simply teaching a pragmatic approach to the practice of CAM is considered inappropriate since mainstream medicine owes much of its success to a foundation of established scientific principles.¹² In fact, as orthodox medical training proceeds, medical students increase their skepticism about CAM.¹³ Medical students should be effectively taught CAM using the principles of evidence-based medicine.^{14,15}

The Consortium of Academic Health Centers for Integrative Medicine was created to affect the direction, assumptions, and outcomes of health care. Currently it includes 27 highly esteemed academic medical centers. Its mission is to help transform health care through rigorous scientific studies, new models of clinical care, and innovative educational programs that integrate biomedicine, the complexity of human beings, the intrinsic nature of healing, and the rich diversity of therapeutic systems. Its education working group facilitates the incorporation of teaching on integrative medicine into all levels of medical education. Its first project was the development of a set of competencies for undergraduate medical education that can serve as a template for schools across the nation as they move to develop a curriculum in this area.¹⁶

Cancer patients are insisting that their health care providers give guidance on complementary therapies, and they wish to have the opportunity to discuss the topic.¹⁷ There is a need for improved communication between cancer patients and their physicians about the use of CAM.^{18,19} The introduction of integrative oncology into the consultation would enable the patient to receive a synthesis of the best of cancer treatment and evidence-based, supportive complementary modalities that effectively relieve many of the physical and emotional symptoms that cancer patients experience.²⁰

The Society for Integrative Oncology (SIO) was founded in 2003, and its inaugural annual conference was held in New York in December 2004. The conference was sponsored by multiple cancer organizations, including the American Cancer Society, the American Society of Clinical Oncology, and the American Society for Therapeutic Radiology and Oncology. The SIO is a nonprofit, multi-disciplinary organization for health professionals committed to the study and application of complementary therapies and botanicals for cancer patients. Many members are from major international academic cancer centers. Members are professionals dedicated to studying and facilitating the cancer treatment and recovery process through the use of integrated evidence-based complementary therapies. The SIO's mission is to educate oncology professionals, patients, caregivers, and relevant others about state-of-the-art integrative therapies, including their scientific validity, clinical benefits, toxicities, and limitations. The SIO provides a convenient forum for presentation, discussion, and peer review of evidence-based research and treatment modalities in the discipline known as integrative medicine. Because a constantly growing number of cancer patients throughout the world turn to both alternative and complementary therapies as part of their cancer treatment plan, it is essential that oncologists have ready access to information about research, existing treatment programs, and both the benefits and dangers of the wide range of complementary therapies available today. Members of the SIO are individuals and organizations dedicated to optimizing cancer treatment by serving as a scientific forum for complementary therapies in cancer care. The SIO promotes the scientific evaluation of these modalities, shares results, and encourages symptom control with therapies found to be beneficial.

Many oncology programs in the United States conduct research on complementary therapies, herbs, and supplements. Centers such as Memorial Sloan-Kettering, Dana-Farber, University of California, and M. D. Anderson now have programs that clinically integrate conventional and complementary medicine.

USE OF CAM BY CANCER PATIENTS IN NORTH AMERICA

The data vary according to the definition of CAM therapies.²¹⁻²⁸ Spirituality and prayer should not be defined as CAM. Some of the population data on CAM are inflated by having included prayer. Although some studies have concluded that the use of CAM was associated with depression,^{29,30} in general, the use of CAM by cancer patients is not associated with perceived distress or poor compliance with medical treatment but with active coping behavior.^{31,32} On the other hand, some patients suffering psy-

chological distress may turn to CAM in desperation.²⁸ Patients seem to consider CAM as supplementary to standard medical methods and one way of avoiding passivity and coping with feelings of hopelessness.

According to one major study, at some time in their life, 83.3% of the population has used CAM.³³⁻³⁵ Use was greatest for spiritual practices (80.5%), vitamins and herbs (62.6%), and movement and physical therapies (59.2%). However, after excluding spiritual practices and psychotherapy, 68.7% had used CAM. A systematic review of relevant published data located 26 surveys of cancer patients from 13 countries.²⁷ The prevalence of CAM use ranged from 7 to 50% in the United States. Another systematic review found that 33% of the population in the United States had used CAM in the preceding 12 months.³⁶

Recent studies in women with breast cancer and men with prostate cancer reveal overall CAM use to be up to 53% and 25%, respectively.³⁷⁻⁴⁰ Some studies show that herbal remedies were combined with prescription medicine in 16% of the population.^{26,35,41} Overall, up to 77% of cancer patients used CAM, including high-dose vitamins in up to 63%. Up to 72% did not inform their physician.⁴²⁻⁴⁴ A study in Canada determined that 66.7% used CAM (vitamins/minerals, green tea, herbal medicines, and dietary supplements).⁴⁵ Alternative practitioners (Chinese medicine and acupuncture, naturopathy, chiropractic, or herbal) were visited by 39.4%. Only 50% of patients informed their physicians. In view of the published statistic that more than 100,000 deaths per year in North America are due to drug interactions, the potential for concealed toxicity between administered products gives cause for concern.⁴⁶

Given the number of patients using CAM, especially combining vitamins and herbs with conventional therapies, the oncology community must improve communication, offer reliable information and education, and initiate research to determine efficacy and potential adverse effects. No longer can we leave patients to the peril of dubious Web sites and publications that are sponsored by some irresponsible commercial enterprises that promote and sell the products they report, often using irrelevant testimonials.⁴⁷ After a critical mass of evidence-based data is accumulated, practice guidelines for CAM and cancer need to be developed.

COMPLEMENTARY THERAPIES USED IN NORTH AMERICA FOR CANCER PATIENTS

Natural Health Products (Botanicals, Vitamins, and Minerals)

The role of botanicals for enhancing the effectiveness of conventional cancer therapies and for reducing adverse effects remains to be defined. In North America natural health products have been poorly standardized and are

often contaminated, usually not evidence based, and unregulated. In the United States herbs and other supplements are not required to meet standards of safety, efficacy, and consistency. The continuing availability of such products in the United States partly results from the 1994 Dietary Supplement and Health Education Act, which created a protective new category for the approximately 20,000 vitamins, minerals, herbs, and other agents sold as supplements prior to October 1994. Spurred by supplement industry lobbying, the act protects supplements from government scrutiny and mandates that the US Food and Drug Administration prove harm before distribution of a product can be regulated.²⁰

There have been major problems with quality assurance. For example, PC-SPES (Botanic Lab, Brea, California) is a mixture of herbs (*Serenoa repens* [saw palmetto], *Panax pseudo-ginseng* [ginseng], *Chrysanthemum morifolium* [chrysanthemum], *Ganoderma lucidum* [reishi mushroom], *Glycyrrhiza glabra* [licorice], *Isatis indigotica* [dyer's woad], *Rabdosia rubescens* [rubescens], and *Scutellaria baicalensis* [skullcap]) that preliminary trials showed to be effective for prostate cancer.⁴⁸⁻⁵¹ Unfortunately, one batch was adulterated at the factory of origin with pharmaceuticals just prior to introduction into a national phase III randomized controlled trial.⁵² This is a shame since current evidence suggests that the herbs alone do have anticancer activity.⁵³

However, with new regulations to establish quality and proof of efficacy, the phytochemical constituents of botanicals may have an expanding role to play in cancer treatment. The federal government in Canada now regulates all botanical medicines.⁵⁴ This is to ensure that all Canadians have ready access to natural health products (NHPs) that are safe, effective, and of high quality, while respecting freedom of choice and philosophical and cultural diversity. The regulations for NHPs have recently undergone extensive modification, with the new regulations taking effect in January 2004 under the authority of the Natural Health Products Directorate. Under the new regulations, all NHPs sold in Canada require product licenses. The regulations set out the requirements for submitting an application for a product license, which includes the quantity of the medical ingredients, the purpose for which the NHP is intended to be sold, and supporting safety and efficacy data. A standards of evidence framework is being developed to ensure that the product claims are supported by appropriate evidence that can be both scientific and traditional, depending on the type of claim being made.

There are many potential roles for Chinese herbs for the support of cancer patients. Different components in a botanical product may have synergistic activities. Clinical studies from China are not usually methodologically sound, and quality control poses significant challenges.^{55,56} However, these studies indicate that specific herbs can increase immu-

nity, reduce fatigue, improve mental alertness, and increase appetite.⁵⁷⁻⁶⁰ The Radiotherapy Oncology Group is developing a randomized controlled trial to determine the effect of American ginseng (*Panax quinquefolius*) derivatives to prevent radiotherapy-induced fatigue. There is preliminary evidence that the ginsenosides (saponins) and polysaccharides found in the various varieties of ginseng decrease fatigue and increase immunity.⁶¹⁻⁶³ A quality-assured derivative of North American ginseng, CVT-E002 (Cold-FX, CV Technologies, Edmonton, Alberta), that mainly contains the polysaccharide component has been shown in a randomized controlled trial to reduce colds and influenza.⁶⁴ Another Chinese herb that has potential antifatigue activity is *Cordyceps sinensis*.^{65,66} There are many NIH-supported research programs that encourage collaboration between American and Chinese institutions to evaluate traditional Chinese herbs for cancer patients in a methodologically sound context.

Herbal derivatives from other traditions are also being evaluated. A randomized double-blind controlled trial has shown that the homeopathic medication TRAUMEEL S (Heel Inc., Albuquerque, New Mexico) significantly reduces the severity and duration of chemotherapy-induced stomatitis in children undergoing bone marrow transplantation.⁶⁷ The Children's Oncology Group (COG) is currently conducting a larger randomized controlled trial of TRAUMEEL S. *Silybum marianum* (milk thistle) appears to protect the liver from hepatotoxic drugs and radiotherapy.^{68,69} The COG is also evaluating *S. marianum* through a randomized controlled trial.

Other herbs are being evaluated as biologic response modifiers that may improve tumor control. Emerging candidates for clinical trials include turmeric (*Curcuma*),^{70,71} maitake mushroom,^{72,73} and *Ganoderma lucidum*.^{74,75} Botanicals are often found to inhibit cancer cells by multiple pathways, such as inducing apoptosis, inhibiting adhesion, and invasion and antagonism of the cyclooxygenase-2 enzyme. Some classes of botanicals, such as Chinese stagnation herbs, may have beneficial radiosensitizing activity through a multitude of physiologic pathways that include anti-angiogenesis and anticoagulant activity.⁷⁶ A randomized trial of radiotherapy plus or minus destagnation herbs for nasopharyngeal cancer demonstrated a doubling of tumor control and survival for the interventional arm.⁷⁷ Data from controlled clinical trials suggest that medicinal mushrooms may be beneficial.^{78,79} A randomized controlled trial of colorectal cancer patients receiving curative resection compared adjuvant chemotherapy alone with chemotherapy plus an extract from the fungus *Coriolus versicolor* (PSK). Both disease-free and overall survival rates were significantly higher in the PSK group.⁸⁰ Many researchers in the United States are working on these interventions. Medicinal mushroom contains a class of polysac-

charides known as β -glucans that promote antitumor activity. They may act synergistically with some of the new therapeutic antibodies such as trastuzumab or rituximab, as well as protecting normal marrow.⁸¹⁻⁸³

It is important for oncologists to be aware of potential serious toxic effects of some herbal remedies.⁸⁴ Historically, herbal remedies have not been formally evaluated for safety, and few have been tested for side effects, quality control, or efficacy.^{85,86} Some herbal remedies are contaminated by heavy metals that can cause serious long-term toxicity. Ayurvedic medicinal products may deliberately contain high levels of heavy metals such as lead, mercury, and arsenic.⁸⁷ Many botanicals interact with the hepatic cytochrome P-450 (CYP) metabolic pathways involved in drug metabolism.⁸⁴ The levels of some drugs, including chemotherapy agents, are increased by botanicals that inhibit CYP. These herbs, or their constituents, include proanthocyanidin (grape seed extract), ginseng, quercetin, valerian, grapefruit, goldenseal, echinacea, red clover, cat's claw, chamomile, licorice, rosemary, and some Chinese herbs.⁸⁸ Conversely, CYP inducers, such as hypericin (St. John's wort) and kava kava reduce the activity of drugs such as indinavir, irinotecan, oral contraceptives, digoxin, cyclosporin, and warfarin.

There are a variety of natural health products to be cautioned around surgery. The risk of bleeding can be increased by vitamin E, feverfew, garlic, ginger, saw palmetto, destagnation Chinese herbs, dong quai, and ginkgo, at high doses or when used in combination. Ginseng can potentiate insulin and precipitate hypoglycemia. Valerian and kava may potentiate anesthetic and sedative drugs, and licorice may result in hypokalemia and cardiac arrhythmias during anesthesia.

St. John's wort and ginseng are monoamine oxidase inhibitors and may increase the toxicity of serotonin and catecholamine reuptake inhibitors such as phenelzine and various antidepressants.

The activity of chemotherapy may be reduced by free radical scavengers (ginkgo, grape seed extract), CYP induction (echinacea, St. John's wort, kava, grape seed extract), and antiestrogen drug inhibition (soy, ginseng). On the other hand, chemotherapy toxicity may be enhanced by CYP inhibition (ginseng, ginkgo, valerian). Generally, no significant interactions with chemotherapy are expected with saw palmetto, black cohosh, cranberry, *S. marianum*, evening primrose, or bilberry. Antioxidants, such as α -lipoic acid, vitamin E, ginkgo, and grape seed extract, could reduce the efficacy of radiotherapy by scavenging free radicals. However, this is a complex interaction. For example, ginkgo can also increase perfusion and oxygenation, thereby increasing radiosensitivity.⁸⁹ On the other hand, the results of a recent randomized trial confirmed that vitamin E might reduce tumor control.⁹⁰ Generally,

long-term administration of vitamin E and β-carotene do not seem to prevent cancers and may be associated with an increased risk of death.^{91,92}

Selenium shows more promise for cancer prevention. The North American Selenium and Vitamin E Cancer Prevention Trial or SELECT study is a randomized controlled trial that is evaluating whether selenium alone, or in combination with vitamin E, can prevent prostate cancer.⁹³ Reduction of radiation toxicity by antioxidants and vitamins is emerging as a more promising area for research, for example, vitamin E for radiation fibrosis and vitamin A for chronic radiation proctopathy.^{94,95} The ingestion of high doses of antioxidants and vitamins during radiotherapy and chemotherapy remains controversial and currently cannot be recommended.⁹⁶

Herbs and their phytochemical derivatives offer a smorgasbord of potential anticancer therapies and agents for symptom control. Government regulation will eventually encourage quality assurance and clinical trials to determine efficacy. There is a plethora of laboratory studies but a dearth of randomized clinical trials. Pharmaceutical production standards are required, and effectiveness should be based on quality assurance, evidence of efficacy, and explicit representation of adverse reactions.

Acupuncture

The neurophysiologic effects of acupuncture are now well documented. Acupuncture points correspond with junctions of intermuscular fascia.^{97–101} Changes in electrical polarity are associated with the release of cytokines that can influence the gene expression of local cells and modulate central nervous system activity through afferent nerve fibers. Functional imaging studies clearly demonstrate a modulation of brainstem nuclei and an interaction with the autonomic nervous system.^{102–106}

Clinical trials are proving that acupuncture can improve some of the more common side effects of cancer and its treatment, such as nausea and vomiting, anxiety, pain, fatigue, depression, xerostomia, and hot flashes. The efficacy of acupuncture for anesthetic- and chemotherapy-induced nausea and vomiting was proven by a series of randomized controlled trials prior to 1996 and systematically reviewed by Vickers.¹⁰⁷ With few exceptions, further randomized controlled trials have generally confirmed the effectiveness of acupuncture for nausea and vomiting, especially when added to antiemetic drugs.^{108–122} In a Cochrane Database systematic review, Lee and Done conclude that stimulation of the pericardium 6 acupoint is effective for postoperative nausea but not vomiting.¹²³ The NIH issued a consensus statement in 1997 supporting the efficacy of acupuncture for adult postoperative and chemotherapy-associated nausea and vomiting.¹²⁴ Some patients still suf-

fer chemotherapy-related nausea and vomiting, despite modern pharmacologic interventions.¹²⁵

Although there are some negative studies, which could be related to technique or inappropriate patient selection, acupuncture is a viable adjunct to drugs to control postoperative or chemotherapy- and radiotherapy-induced nausea or vomiting.^{126,127} It can be administered conveniently using transcutaneous electrical stimulation at specific acupoints with devices such as Codetron (EHM Rehabilitation Technologies, Toronto, Ontario) or ReliefBand (Abbott Laboratories, Abbott Park, Illinois).^{120,128} However, a more recent study did not support the hypothesis that acustimulation bands are efficacious as an adjunct to pharmacologic antiemetics for control of chemotherapy-related nausea in female breast cancer patients.¹²²

Acupuncture may also be used to reduce anxiety prior to procedures.^{129–132} Randomized controlled trials have confirmed that acupuncture is effective for some types of cancer-related pain.^{133–138} A phase II study of acupuncture for patients suffering postchemotherapy fatigue at Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY, USA) showed a clinically important degree of improvement.¹³⁹ Acupuncture may also alleviate depression.^{140,141} Three phase II studies have indicated a partial reversal of xerostomia or dry mouth secondary to radiotherapy.^{142–144} Studies of acupuncture for hot flashes secondary to hormone therapies and menopause are promising.^{145–148} Phase III trials of acupuncture for fatigue and hot flashes are in progress at MSKCC and for xerostomia at the Juravinski Cancer Centre (Hamilton, ON, Canada).

Mind-Body Therapies

The psychosomatic connection between distress and physical illness, as well as the effects of physical illness on mental suffering, is being increasingly recognized. However, the proposal that mental distress may cause cancer or its relapse has not been proven.^{149–152} Currently, there is no level III evidence that psychological interventions can increase survival, apart from indirect effects such as increased adherence to conventional therapies.¹⁵³ The mind-body therapies certainly can help with coping and the reduction of symptoms, smoothing the patient's pathway through conventional therapies, reducing pain, and increasing quality of life.¹⁵⁴

Mind-body interventions aim to use the reciprocal relationship between body and mind to help patients relax, reduce stress, and relieve symptoms associated with cancer and cancer treatments. Several randomized trials have shown effects of hypnosis on pain as well as anxiety and depression in newly diagnosed cancer patients.^{155–159} On the other hand, a recent randomized trial on nonselected patients undergoing radiotherapy did not show any influ-

ence on anxiety or quality of life, although this may be explained by some weaknesses in the trial methodology.^{160,161} Trials have generally found hypnosis and relaxation training to be beneficial against chemotherapy-induced nausea,^{162,163} although some studies showed no differences.¹⁶⁴ Mindfulness meditation improves mood and reduces stress during cancer treatment.¹⁶⁵ Tibetan yoga improves sleep.¹⁶⁶ Chanting the rosary prayer or yoga mantras may induce relaxation.¹⁶⁷ Expressive art therapy may improve coping skills.¹⁶⁸

Professional musicians, who are also music therapists, are trained to deal with the psychosocial as well as clinical issues faced by patients and family members. Music therapy is particularly effective in the supportive care setting, with randomized trials indicating benefit for reducing anxiety,^{169–173} depression,^{174–176} and pain.^{177,178} It may also increase immunity.¹⁷⁹ A randomized controlled trial at the MSKCC concluded that music therapy is a noninvasive and inexpensive intervention that appears to reduce mood disturbance in patients undergoing high-dose therapy with autologous stem cell transplantation.¹⁸⁰

Several randomized trials have suggested that massage reduces anxiety.^{181–183} In a high-quality trial, massage was found to be superior to the control treatment in reducing anxiety, nausea, and fatigue, and improving general well-being.¹⁸³ In another randomized study, pain and anxiety scores were lower with massage, with differences between groups achieving both statistical and clinical significance.¹⁸⁴ The largest report to date is from the MSKCC.¹⁸⁵ The study analyzed before-and-after data from the initial massage session of 1,290 cancer patients during a 3-year period. Swedish and foot massage were the most common interventions. Anxiety, pain, and fatigue were significantly reduced.

In the United Kingdom, aromatherapy is often used for relaxation and coping with medical procedures. The smell of lavender seems to reduce anxiety through the olfactory nerves.^{186–188} A systematic review from the Cochrane Database concludes that massage and aromatherapy confer short-term benefits on psychological well-being.¹⁸⁹

“Energy” Therapies (“Biofield” Medicine)

Many North American health care institutions use so-called energy therapies for supportive care. The practitioners’ theory is that they manipulate an energy field around the patient. However, this energy field has never been detected by objective scientific methodology. The efficacy of these energy therapies is controversial.^{190,191} Studies are complicated by various confounding factors, so the underlying process by which the therapist entrains the patient into a relaxed state is unclear. Nevertheless, there are published reports that therapies such as therapeutic touch

(which, unlike massage, does not actually use touch), Reiki, and polarity therapy influence the autonomic nervous system,¹⁹² affect biologic markers while inducing relaxation,^{193–195} reduce pain,¹⁹⁶ and have a positive influence on cancer-related fatigue and health-related quality of life.¹⁹⁷ Confounding variables include awareness of the practitioner, the patient’s belief system, actual touching (which does occur in Reiki and polarity therapy), and subtle environmental influences such as background music. The NCCAM is sponsoring a randomized controlled trial to determine whether Reiki energy healing affects disease progression and anxiety in patients with localized prostate cancer who are candidates for radical treatment with surgery or radiotherapy.¹⁹⁸

FUTURE RESEARCH

There are huge opportunities for research in integrative oncology, stretching from the laboratory to health services. The definition of health care has expanded since the Flexner Report of 1910.⁸ However, research in the field of integrative health care has only really developed over the past 10 years. Patients rightly expect a multidimensional approach to their health. Nevertheless, we have limited knowledge as to how they select appropriate complementary interventions. In addition, we do not know how individual clinicians select specific complementary interventions for their patients.

We have limited knowledge as to what magnitudes of response are necessary to pursue particular interventions. The potential for adverse events and for financial and missed-opportunity costs are important factors on top of whether there is evidence of efficacy. Pragmatic issues are important. For example, Vickers and colleagues determined the potential utility of acupuncture for treating postchemotherapy fatigue prior to implementing a phase III randomized controlled trial to prove its efficacy.¹³⁹ Wong and colleagues determined the optimal electroacupuncture points and practical issues of implementing acupuncture-like therapy for patients with xerostomia prior to designing a phase III randomized controlled trial.¹⁴² Prior to embarking upon resource-intensive randomized controlled trials of efficacy, it is important to determine the clinical importance of a positive outcome.

Effectiveness gaps are deficiencies in health services not currently covered by conventional interventions. Examples include the predominance of fatigue in cancer patients as well as the continuing high incidence of nausea and vomiting despite antiemetic drugs.^{125,139} Economic considerations will be fundamental for integrating new methodologies into health care systems that are already stretched financially. Adding complementary

therapies could be perceived as increasing expenses. However, a positive impact on quality of life is important since it encourages improved coping and rehabilitation, allowing individuals to restore their productivity. Cost-utility estimates can be made in terms of cost per quality adjusted life year.¹⁹⁹ To perform economic evaluations of therapies, one must first determine their value regarding improvement in patient health status, judged in terms of efficacy and effectiveness. Efficacy uses a reductionist scientific method to examine defined effects of a specific intervention on a defined health outcome. This is a protocol-driven approach in which everything other than the intervention is controlled. Effectiveness research studies the intervention's effect in the real-world clinical setting and is measured by examining all aspects of the treatment's effect on a patient. In view of the multidimensional interactions that contribute to health outcome, effectiveness research is important. For example, for many therapies (drugs and acupuncture alike), the contribution of belief and expectation can synergistically influence outcome (through the placebo or nocebo effects). This interaction can even be documented through functional imaging of the brain.^{200,201}

There is no consensus on what constitutes the definitive set of research methods. The gold standard for conventional medicine is the randomized controlled trial. Many contend that unless complementary therapies are analyzed in this rigorous manner, any claims of efficacy or effectiveness must be treated with skepticism. However, even conventional therapies cannot always meet this standard. It is quite unusual for surgical procedures to be evaluated by this rigorous methodology. Finding appropriate placebos, controls, or sham treatments may be challenging for biophysical therapies such as acupuncture.²⁰² Single-blind methodology is usually possible, although double-blind interventions are not possible when the practitioner is part of the procedure. Another issue is that extrapolation from a single trial to an entire therapy requires that therapy to be characterized by a uniform set of practices. However, complementary therapies may be individualized for pragmatic reasons or to respect a patient's values. Most cancer care programs require proof of general efficacy through randomized controlled trials, but effectiveness may be individualized and reviewed by clinical audit.

Defining effectiveness gaps within our current oncology services is an initial step toward establishing roles for complementary therapies. Allowing our patients to define their needs for clinical services is essential in developing value-based guidelines. However, until we have more resources put into clinical studies of complementary therapies, the development of credible practice guidelines for integrative oncology will be constrained.

CONCLUSIONS

Patients often feel that problems they perceive as important fail to receive sufficient attention. When integrated into an evidence-based program of supportive care, complementary therapies may improve patients' quality of life, increase satisfaction, and strengthen physician-patient relationships. Anticancer technology is extremely important but needs to be softened. Integrative oncology is humanistic and empathetic, but it is also scientific.²⁰³ In North America integrative oncology is already having an important impact on cancer care. It provides added value to standard cancer treatment. The aim of integrative oncology should be one medicine, not alternative; it should be patient focused; it should be evidence based; and it should provide the best care for cancer cure, prevention, symptom control, and quality of life.

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