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Article

ARTICLE

The National Cancer Institute's Conference on Acupuncture for Symptom Management in Oncology: State of the Science, Evidence, and Research Gaps

Farah Z. Zia, Oluwadamilola Olaku, Ting Bao, Ann Berger, Gary Deng, Arthur Yin Fan, Mary K. Garcia, Patricia M. Herman, Ted J. Kaptchuk, Elena J. Ladas, Helene M. Langevin, Lixing Lao, Weidong Lu, Vitaly Napadow, Richard C. Niemtzow, Andrew J. Vickers, Xin Shelley Wang, Claudia M. Witt, Jun J. Mao

Affiliations of authors: Division of Cancer Treatment and Diagnosis, Office of Cancer Complementary and Alternative Medicine, National Cancer Institute, National Institutes of Health, Rockville, MD (FZZ); Kelly Services, Incorporated, Rockville, MD, and Division of Cancer Treatment and Diagnosis, Office of Cancer Complementary and Alternative Medicine, National Cancer Institute, National Institutes of Health, Rockville, MD (OO); Integrative Medicine Service, Memorial Sloan Kettering Cancer Center, New York, NY (TB, GD, AJV, JJM); Pain and Palliative Care Service, National Institutes of Health Clinical Center, Rockville, MD (AB); McLean Center for Complementary and Alternative Medicine, PLC, Vienna, VA (AYF); Department of General Oncology/Integrative Medicine Program, MD Anderson Cancer Center, Houston, TX (MKG); Health Division, RAND Corporation, Santa Monica, CA (PMH); Program in Placebo Studies, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA (TJK); Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Columbia University, New York, NY (EJL); Osher Center for Integrative Medicine, Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (HML); School of Chinese Medicine, University of Hong Kong, Hong Kong, China (LL); Leonard P. Zakim Center for Integrative Therapies, Dana-Farber Cancer Institute, Boston, MA (WL); Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston MA (VN); United States Air Force Acupuncture and Integrative Medical Center, Joint Base Andrews, MD (RCN); Department of Symptom Research, MD Anderson Cancer Center, Houston, TX (XSW); Institute for Complementary and Integrative Medicine, University of Zurich and University Hospital Zurich, Zurich, Switzerland (CMW); Institute for Social Medicine, Epidemiology and Health Economics, Charité, Universitätsmedizin Berlin, Germany (CMW); Center for Integrative Medicine, University of Maryland School of Medicine, Baltimore, MD (CMW).

Correspondence to: Farah Z. Zia, MD, National Cancer Institute, 9609 Medical Center Drive, Suite 5W-610, Rockville, MD 20850 (e-mail: ziaf@mail.nih.gov).

Abstract

The Division of Cancer Treatment and Diagnosis, Office of Cancer Complementary and Alternative Medicine, at the National Cancer Institute (NCI) held a symposium on "Acupuncture for Cancer Symptom Management" on June 16 and 17, 2016. Invited speakers included 19 scientists and scholars with expertise in acupuncture and cancer research from the United States, Europe, and China. The conference reviewed the NCI's grant funding on acupuncture, analyzed the needs of cancer patients, reviewed safety issues, and assessed both the current scientific evidence and research gaps of acupuncture in oncology care. Researchers and stakeholders presented and discussed basic mechanisms of acupuncture; clinical evidence for specific symptoms; and methodological challenges such as placebo effects, novel biostatistical methods, patient-reported outcomes, and comparative effectiveness research. This paper, resulting from the conference, summarizes both the current state of the science and clinical evidence of oncology acupuncture, identifies key scientific gaps, and makes recommendations for future research to increase understanding of both the mechanisms and effects of acupuncture for cancer symptom management.

Acupuncture, a therapy originating from the system of Traditional Chinese Medicine, has been in use in some form for at least 2500 years. Fine needles are inserted and stimulated, either manually or electrically, in order to treat specific symptoms or health conditions. Since the 1970s, this technique has gained popularity around the globe. According to the World Health Organization (WHO), acupuncture is used in at least 103 countries, 29 of which have established regulations for

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providers, and 18 of which have allowed provisions for third-party coverage (1). In the United States alone, about 3.5 million adults or 1.5% of the population receive acupuncture each year (1, 2). Approximately one in 10 cancer survivors in the United States have used acupuncture, with the rate of use noted to be higher among those with cancer as compared with those without (3). Notably, more than 60% of National Cancer Institute (NCI)–designated comprehensive cancer centers incorporate acupuncture for cancer symptom management (4).

Mechanisms of Acupuncture

The mechanisms underlying the effects of acupuncture are complex and involve multiple systems. Stimulation of deep tissue sensory afferent nerves is the initial event that leads to activation of the central nervous system pathways involved in sensory modulation and autonomic regulation. When manual or pulsed electrical stimulation is prolonged for several minutes, activation of descending diffuse noxious inhibitory pathways from the brainstem leads to generalized analgesia that can last several hours (5,6). In various animal models, prolonged acupuncture needle stimulation also leads to modulation of sympathetic and parasympathetic nervous system outflow from the brainstem that has produced a variety of physiological responses including regulation of blood pressure (7), gut motility (8), immune responses (9), glucose metabolism, glucocorticoids, and sex hormones (10,11).

In recent years, through the use of functional brain imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography scans, it has been found that both manual and electrical stimulation of acupuncture needles can alter the activity and connectivity of higher brain structures in humans, particularly the insula and limbic areas involved in affective responses and pain modulation, as well as somatosensory areas such as S1 and S2 (12,13). Long-term effects resulting from acupuncture stimulation have included cortical plasticity (14) and changes in opioid binding (15). Further, mechanical stimulation of connective tissues during needle manipulation can contribute to the transmission of signals to surrounding local tissues (16) as well as sensory nerves, and can also elicit cellular responses in the tissues at the specific site of needle insertion (17). These local effects have been shown to influence adenosine-mediated peripheral sensory modulation (18).

In summary, acupuncture needling and manipulation produce a variety of physiological effects both centrally and peripherally in animal and human experiments. Significant scientific gaps remain in our understanding of the relationships between these mechanisms and the observed responses to acupuncture in clinical trials. This is particularly true in oncology, where few acupuncture mechanistic studies have specifically evaluated oncology-associated outcomes such as pain, where inferences are drawn from studies with populations who had nonmalignant pain. Neuroimaging studies have evaluated brain response to needle stimulation at locations applied for xerostomia and found both increased salivary flow and activation of insula and the human secondary somatosensory cortex (S2), a region of the cortex in the parietal operculum on the ceiling of the lateral sulcus, compared with sham acupuncture (19). Functional MRI studies evaluating acupuncture for neuropathic pain disorders such as carpal tunnel syndrome (14,20,21) may serve as a model for its evaluation in chemotherapy-induced peripheral neuropathy. Recently reported fMRI research on brain circuitry that supports the effects of acupuncture on nausea (22) may also serve as a good initiation point to identify its mechanisms in reducing chemotherapy-induced nausea and vomiting. Therefore, further study is needed to bridge basic mechanistic and clinical research and apply our extensive knowledge of acupuncture physiology to the care of cancer patients.

Safety and Considerations for Practicing Acupuncture in Cancer Care

Acupuncture is considered to be safe for use in the general population when practiced by a licensed practitioner; however, minor side effects have been noted. For example, a large population-based study of acupuncture practice (n = 97 733 patients) revealed the most common toxicities resulting from needling to be local pain (3.3%), bruising (3.2%), minor bleeding (1.4%), and orthostatic problems (0.5%) (23). Rare side effects have also been reported and include infection as well as pneumothorax associated with needling in the chest region (24). Notably, acupuncturists in the oncology setting may encounter patients with a wide range of comorbidities resulting from either cancer treatment or the disease itself. Therefore, “oncology acupuncture” is a specialty area of practice that requires providers to attend to the unique safety issues and psychosocial needs of their patients. Specific areas of concern in this setting from the process of needling include neutropenia and thrombocytopenia, resulting in higher risks of infection and bleeding. Other areas of concern may include dehydration and malnutrition, increasing the possibility for hemodynamic instability. Therefore, based on the increased risks due to disease and treatment-related comorbidities, it is proposed that oncology acupuncturists follow clinical practice guidelines that take into account lab values such as absolute neutrophil and platelet counts. It is also imperative that providers be adequately trained to not only recognize, but also to understand the unique risks that are not necessarily encountered in a general acupuncture environment (25). Lastly, due to the unique nature of this setting, oncology acupuncture providers will benefit from training in psycho-oncology, as well as supportive, palliative, and survivorship care, in order to become an integral part of the professional network that provides comprehensive support for cancer patients.

Clinical Evidence for Acupuncture in Cancer Care

Although oncology acupuncture is still a relatively new field, emerging research has found promising evidence for its role in the management of several symptoms where existing standard options remain a challenge. Garcia et al. (26) synthesized data across randomized controlled trials for effects on symptoms such as pain, fatigue, hot flashes, nausea/vomiting, and xerostomia. Here, we synthesize the data that was presented and discussed at the NCI conference on cancer symptom management.

Pain

Pain is one of the most challenging clinical problems in oncology care, affecting patients with advanced cancers, as well as some survivors. The role of acupuncture in treating nonmalignant chronic pain such as osteoarthritis of the knee or low back

pain has been well characterized in a large, individual patient data meta-analysis involving nearly 18 000 patients (27). Acupuncture was found to be more effective than usual or standard care, and slightly better than sham acupuncture. However, research in cancer pain is highly limited, with major methodological shortcomings. In a recent meta-analysis of 20 randomized clinical trials (n = 892), acupuncture alone was not found to be better than pharmacotherapy for cancer-related pain. However, notably, combination therapy may be more effective than pharmacotherapy alone, resulting in quicker pain relief, longer pain remission, and improved quality of life (28).

Aromatase inhibitor–associated arthralgia, a specific type of pain common in breast cancer survivors, is challenging to manage, often resulting in substantial treatment discontinuation. In a blinded randomized clinical trial evaluating manual vs sham acupuncture for aromatase inhibitor–associated arthralgia, breast cancer patients receiving manual acupuncture experienced significant improvements in joint pain and stiffness that were not observed in those receiving sham acupuncture (29). In another randomized clinical trial of electroacupuncture vs sham acupuncture and waitlist control, electroacupuncture met the primary end point of producing clinically important effects after eight weeks of treatment, along with continued, durable improvement four weeks post-therapy (30). Further, electroacupuncture produced consistent clinical effects, whereas sham acupuncture only reduced pain for patients with very high treatment expectations (31). In addition, any similar benefits achieved with sham acupuncture were not durable.

Chemotherapy-induced peripheral neuropathy is another common pain symptom that presents a management challenge, with few effective available therapies. Bao et al. found that up to 50% of breast cancer survivors experience persistent chemotherapy-induced peripheral neuropathy and, therefore, are at an increased risk for falls (32). A number of small studies examined the efficacy of acupuncture in chemotherapy-induced peripheral neuropathy (33–35). In one pilot study of 27 multiple myeloma patients with moderate to severe bortezomib-induced peripheral neuropathy, neuropathic pain was significantly reduced while functioning improved after 10 weeks of acupuncture treatment (33). Another single-arm study of 19 patients showed that electroacupuncture was safe and may be effective in treating thalidomide/bortezomib-induced peripheral neuropathy in multiple myeloma patients, with significant improvement in the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity questionnaire score after nine weeks of treatment (34). Although both studies are promising, further investigations with additional objective end points and long-term follow-up are necessary, as evidenced by contrasting data observed in similar trials. A randomized clinical trial conducted by Greenlee et al. is noteworthy despite its design as a chemotherapy-induced peripheral neuropathy prevention trial. Women with early-stage breast cancer experiencing taxane-induced peripheral neuropathy received either electroacupuncture or sham acupuncture during chemotherapy. Results indicated that there were no differences in chemotherapy-induced peripheral neuropathy symptoms in either group, but those receiving electroacupuncture experienced a longer pain-recovery time (35). Thus, with inconsistent results from existing studies, clearly further research is needed to understand the subtleties of timing, dosing, and best mode of acupuncture stimulation in order to evaluate its potential to either treat or prevent chemotherapy-induced peripheral neuropathy.

Fatigue

Fatigue due to both disease and chemotherapy is the most common side effect among cancer patients. In a systematic review of seven trials, four showed that acupuncture was superior to usual or standard care, and three showed no improvement (36). In the largest randomized clinical trial to date (n = 246) (37), six sessions of acupuncture were compared with enhanced usual care in patients with breast cancer. The primary outcome was general fatigue at six weeks, measured with the Multidimensional Fatigue Inventory. Adding acupuncture to usual care improved scores significantly. Among those who received acupuncture (n = 197) (38), participants were then further randomized to receive acupuncture, self-needling acupuncture, or no therapy as maintenance. Neither acupuncture method showed enhanced improvement over observation during the maintenance phase, which suggests that a short treatment course may be sufficient for most patients and that additional acupuncture would not lead to further declines in fatigue.

Hot Flashes

Hot flashes are a common and debilitating symptom for some women with breast cancer, particularly those who have undergone chemotherapy-induced ovarian failure, have experienced surgical menopause, or are taking estrogen-blocking hormonal treatments (39). Non–hormonally based drugs such as venlafaxine, gabapentin, citalopram, and clonidine have shown benefit, but have also shown considerable side effects (40). In a systematic review of eight randomized clinical trials (n = 474), Garcia et al. found some promising effects of acupuncture compared with various controls for hot flashes. Unfortunately, numerous methodological limitations made the evidence insufficient to recommend either for or against acupuncture (41). Notably, however, a recent randomized clinical trial (n = 124) among women with breast cancer found that electroacupuncture effects are similar to, but more durable than, gabapentin, with fewer side effects (42). In addition, a recent large randomized clinical trial (n = 190) found that compared with enhanced usual care, manual acupuncture reduced hot flashes and improved quality of life in vasomotor, physical, and psychosocial domains (43). Furthermore, a brief course of 10 acupuncture treatments was associated with therapeutic effects that persisted for six months or longer and did not appear to require continued treatment (42,43).

Nausea/Vomiting

Although there is general consensus that acupuncture is helpful for chemotherapy-induced nausea and vomiting as well as postoperative nausea and vomiting (44), this is primarily based on a number of studies that predate current antiemetic guidelines (25,45–52). Therefore, whether acupuncture has benefits above current standard treatments is unknown. The type of acupuncture point stimulation (manual vs electrical, with or without needles) is also an issue. Findings from a 2006 Cochrane Review (47) indicate that electrical stimulation with needle insertion at Pericardium 6 (palmar aspect of the forearm between the tendons of the palmaris longus and flexor carpi radialis) reduces acute vomiting but not nausea, and electrical stimulation without needles may be generally more effective for nausea but not vomiting. Given such mixed signals, as well as new antiemetic guidelines, future research should evaluate

acupuncture for different specific types of nausea/vomiting, including anticipatory, delayed, and radiation-induced conditions, and evaluate synergy and clinical relevance along with current antiemetic therapy.

Xerostomia

For patients with head and neck cancer undergoing combined chemoradiation treatment, xerostomia is one of the most common and debilitating side effects. Manual acupuncture is the most frequently used delivery method in studies of xerostomia, but evidence of benefit is limited (53,54). Pfister et al. reported a study investigating post–neck dissection pain and dysfunction, comparing manual acupuncture with usual care, and found significant reductions in pain, dysfunction, and xerostomia with manual acupuncture (55). Furthermore, in a trial of 86 patients with nasopharyngeal cancer undergoing radiotherapy, acupuncture significantly prevented increases in xerostomia symptoms and improved quality of life compared with standard care (56). Large NCI-funded clinical trials are currently underway to evaluate the role of acupuncture in both realms of prevention and treatment of radiation-induced xerostomia.

Pediatric Oncology Patients

There is a paucity of studies on the use of acupuncture in children with cancer. Most trials evaluate its utility for chemotherapy-induced nausea/vomiting but are limited in size and use a variety of acupuncture techniques, making comparisons between the studies difficult (57,58). Several studies found acupuncture to be safe and feasible in children, even those as young as one year of age (59–62). A single prospective cohort study (63) reports that children request acupuncture for a variety of symptoms including pain, fatigue, insomnia, and anxiety. It is evident that more research is needed in pediatric oncology, particularly studies that contain a strong translational or biologic component, so as to elucidate the mechanisms by which acupuncture may confer a beneficial effect.

Chokshi et al. (63) recently evaluated demographic predictors and variables in pediatric inpatients and outpatients who received acupuncture. A total of 90 patients were followed for six months, completing a questionnaire before and after treatment. Older children were found to be more accepting of acupuncture and, in general, frequently requested it to control pain. Children and adolescents often report symptom clusters such as pain, nausea/eating problems, sleep-wake disturbances, fatigue, mood disturbances, and appearance changes (64), and the use of individualized acupuncture to address the range of symptoms is an important area for future study. Factors influencing the appropriate administration of acupuncture therapy such as needle size, treatment duration, and frequency, as well as individualized protocols, need to be considered in future studies.

Methodological Challenges in Clinical Research

Despite recent advances in clinical research, significant methodological challenges have been identified by previous systematic reviews (26,28,36,41) and were discussed among panelists during the NCI conference. Participants suggested that future research needs to decrease the risk of bias caused by lack of appropriate random assignment, include larger samples, and use validated patient-reported outcomes to measure symptoms and outcomes of relevance. The involvement of biostatisticians in sample size planning, data analysis, and deciding on appropriate analytical models will improve the rigor of future studies. When appropriate, using mixed-methods research that combines quantitative and qualitative methods can help to better elucidate the patient experience that is difficult to capture using quantitative measures alone. Panelists also discussed the need for development of standardized or individualized acupuncture protocols that are based on the current literature and classic texts, clinical input, and consensus from experienced acupuncturists. Ideally, pilot studies need to be conducted to refine interventions in terms of feasibility, timing, dosing, and mode of needle stimulation before launching into a randomized clinical trial setting. Lastly, longer-term follow-up is needed to evaluate the durability of treatment effects for acupuncture.

An area of substantial discussion and debate is the use of sham acupuncture and placebo effects in clinical research. In practice, acupuncture is a complex intervention that involves needling, patient-provider interactions, and the engagement of patients during the therapeutic process. Research has found that sham acupuncture produced greater pain symptom relief than placebo pills (31,65). Opponents to the use of sham acupuncture in research argue that the sensory input provided may stimulate the same neuropathways as acupuncture and that sham acupuncture is therefore not entirely physiologically inert, as is the case with a traditional placebo pill. Proponents for the use of sham acupuncture argue for its utility in partial blinding, at least to the research subject, and its ability to help quantify the efficacy of specific needling protocols, including insertion technique and needling depth.

There are also different types of sham acupuncture devices: those that penetrate the skin and others that employ nonpenetrating retracting needles. Ideally, the choice to use sham as well as the appropriate delivery device should be guided by the research question. For example, if the investigator strives to better understand the need for specific acupuncture points or the efficacy of a particular type of acupuncture needle stimulation technique, then use of a sham control is appropriate. However, if the investigator's goal is to better understand acupuncture's effectiveness for a specific symptom, then comparing it with usual care or active controls (drugs or other nonpharmacological interventions) may be more appropriate.

Future Research Directions

Based on the current state of the science and evidence of acupuncture in oncology, the panelists participating in the NCI conference on acupuncture discussed the following key areas to accelerate the pace of scientific discovery and translation in order to inform evidence-based integration of acupuncture into conventional cancer care settings to improve symptom management:

- basic and translational research to increase the understanding of mechanisms underlying the effect of acupuncture on specific symptoms (eg, chemotherapy-induced peripheral neuropathy, xerostomia);
- mechanistic studies to inform the type of needle stimulation required (ie, manual, electric, or thermal) and/or dosage that may improve effects on specific symptoms;
- translational research incorporating biological markers (eg, genetic polymorphisms) or behavioral measures (eg,

expectancy) to identify who may respond best to acupuncture intervention;
- large and adequately powered trials with long-term follow-up to determine the definitive effects of acupuncture for common symptoms such as pain, fatigue, and hot flashes, where there are promising signals from small trials;
- acupuncture to target common symptom clusters such as pain, sleep disturbance, fatigue, and psychological distress;
- test models of acupuncture integration into conventional care to assess effects on adherence to cancer therapies such as chemotherapy and hormone therapy;
- evaluate the effect of acupuncture on other outcomes such as pain medications including opioid usage in cancer survivors;
- use big data in electronic medical records and/or perform large pragmatic trials to evaluate the effectiveness or cost-effectiveness of acupuncture in usual care to improve patient experience and outcomes;
- conduct research in underserved populations including racial/ethnic minorities, pediatric populations, and patients with rare cancers to evaluate the potential role of acupuncture to ameliorate health disparities in symptom management; and
- develop validated patient-reported outcomes to measure outcomes of relevance in oncology acupuncture practice.

Health Service and Policy Implications

Given the emerging clinical evidence and substantial unmet symptom management needs, five of the 11 National Comprehensive Cancer Network guidelines for supportive care recommend the use of acupuncture for adult cancer pain, cancer-related fatigue, chemotherapy-induced nausea, palliative care, and cancer survivorship (66). As research evidence accumulates, effort should be directed toward translating knowledge into action. Specific and clear clinical pathways need to be developed to guide the integration of acupuncture into conventional treatments along the cancer care continuum. High-quality educational programs are needed to train community acupuncturists in the knowledge, skills, and competencies required to deliver acupuncture safely and effectively in oncology settings; furthermore, primary care providers and oncologists, as well as patients themselves, require education about the evidence for acupuncture to manage cancer symptoms in order to direct appropriate referrals. Lastly, third-party coverage for acupuncture needs to be made available to allow patients from diverse socioeconomic backgrounds better access to acupuncture for cancer symptom management.

Notes

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