

Does the strength of evidence support recommending acupuncture to relieve cancer-related fatigue?

Ann M. Berger

University of Nebraska Medical Center, 985330 Nebraska Medical Center, Omaha, NE 68198-5330, USA

Corresponding to: Ann M. Berger, PhD, APRN, AOCNS, FAAN, Professor and Dorothy Hodges Olson Endowed Chair in Nursing, Director, PhD program in Nursing and Advanced Oncology Clinical Nurse Specialist. University of Nebraska Medical Center, 985330 Nebraska Medical Center, Omaha, NE 68198-5330, USA. Email: aberger@unmc.edu.



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Cancer-related fatigue (fatigue) is reported as the most distressing and persistent symptom experienced by breast cancer patients during and after adjuvant treatment (1,2) and by patients with mixed diagnoses at the end of life (3). Steady progress has been made in defining and measuring fatigue (4), but identifying its' causal mechanisms remains challenging (5,6). Inflammatory processes, dysfunctional hypothalamic-pituitary-adrenal (HPA) axis, and disrupted circadian rhythms have been identified in small samples as etiologies for fatigue (7,8). Interventions that are designed to modify these biological causal mechanisms are most likely to demonstrate positive effects. Because fatigue is a multi-dimensional phenomenon, interventions that modify psycho-social factors also may be effective. The current state of the science in fatigue challenges researchers to test innovative interventions that are rooted in modifying both behavior and biology (9).

The NCCN Guidelines for Cancer-Related Fatigue (Version 1.2013) provide oncology clinicians with three lists of non-pharmacologic interventions; including one for patients on active treatment, at post-treatment, and at the End of Life (10). There are no interventions with Category 1 evidence (based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate) for modifying fatigue in patients at the End of Life. Those interventions with Category 1 evidence for reducing fatigue at the first two stages of the cancer trajectory include activity enhancement, psychosocial interventions [cognitive behavioral therapy (CBT) for fatigue, psycho-educational, and supportive-expressive therapies], and CBT for sleep. All these interventions can be classified as of "Western" origin.

There are no traditional "East Asia" interventions that have adequate strength of evidence to warrant they be rated as Category 1 in the fatigue guidelines and recommended for practice.

The study conducted by Molassiotis *et al.* (11) concluded that acupuncture is an effective intervention for managing fatigue and improving quality of life of patients with breast cancer. The pragmatic, randomized controlled trial (RCT) aimed to assess the effectiveness of a 6-week course of acupuncture for cancer-related fatigue. An experimental group (n=227) was compared to an enhanced usual care group (n=75) of breast cancer patients with moderate to severe fatigue who were post-treatment (mean =20.5 months). Significant differences between group scores were reported on mean General Fatigue (P<0.001) and physical fatigue and mental fatigue (both P<0.001) on the Multidimensional Fatigue Inventory. Furthermore, significant effects of the intervention were found on anxiety and depression (P<0.001) and four components of QOL [physical-, functional-, and emotional- well-being, (all P<0.001); and social functioning well-being (P<0.05)].

These results are promising, but oncology clinicians must be asking: does the strength of evidence support recommending acupuncture to relieve cancer-related fatigue? That question can be answered by performing a critique of how the findings compare to other evidence, as well as the strengths and limitations of the study. Only one other small study (12), in addition to the pilot work on this intervention (13), has reported effects of an acupuncture protocol for fatigue. Usually two large and positive RCTs are expected before evidence is considered strong enough to recommend the intervention for

dissemination in practice (14).

Weighing the strengths and limitations of the large RCT by Molassiotis (11) is needed to determine whether acupuncture is ready to be recommended for fatigue in clinical practice. Strengths of the large study include the use of a pragmatic trial design, a cut-off score for fatigue, a large sample (n=302), a standardized intervention that used registered and experienced acupuncture therapists, and an enhanced usual care group. However, several weaknesses are identified that have implications for research and for practice.

A major limitation of the study was the absence of testing of biological mechanisms that might help explain how acupuncture acts to reduce fatigue. Acupuncture's actions have been shown to decrease inflammation, which has been associated with several symptoms in patients who are post-treatment (8,15). If the primary action of acupuncture is anti-inflammatory, perhaps its' effect will most likely occur in the post-treatment stage? Fatigue may be more amenable to the effects of acupuncture in the early post-treatment phase after the end of adjuvant therapies than in patients with advanced-stage disease receiving palliative care therapies. Thus far, data on acupuncture's effects have been collected from disease-free, not advanced breast cancer patients.

Another major limitation was the lack of a sham acupuncture needling method or another active control group. This was particularly important because this design did not allow the groups to be blinded and may have biased the results. The universally positive findings may be indicative of nonspecific placebo effects in the acupuncture group; especially since no objective physiological data were collected. Perhaps receiving the needle treatment alone resulted in subjective reports of more improvement in those with higher outcome expectations, as has been found in a previous pain study (16).

This first, large, multisite trial to test acupuncture to relieve fatigue provides several implications for future research. As identified by the authors, acupuncture could be an approach to managing symptom clusters rather than only a single symptom and future studies need to be designed and powered to answer that question. Future studies also need to include biological markers to enhance our understanding of the etiology of fatigue in samples that are homogenous in regard to type of cancer, stage of disease, and treatments received. The issue of whether or not to use a sham acupuncture needling method is complex and needs to be carefully considered when designing future,

large trials (17). There is more uniform agreement that acupuncture and other behavioral complementary medicine trials need to include an active control arm as well as a no-treatment arm that serve to reduce nonspecific and placebo effects of the intervention (18,19). Careful consideration of issues regarding study design and methods will increase our understanding of what works, for whom, and under what circumstances to relieve cancer-related fatigue.

Molassiotis and colleagues have introduced an East Asian-based therapy that shows promise as a method to reduce cancer-related fatigue in breast cancer patients who report persistent fatigue in the post-treatment phase. The cascade of positive effects of acupuncture on fatigue, other symptoms, and QOL inspires cancer symptom management researchers to include inflammatory markers when testing acupuncture in future studies that include other types and stages of cancer patients. However, the authors acknowledge that the design of the trial had several limitations that affect the generalizability of the results. Acupuncture will remain in the "Effectiveness Not Established" category on the Oncology Nursing Society's Putting Evidence into Practice (ONS-PEP) fatigue resources until the evidence merits a change (14,20). Well-designed and controlled effectiveness trials are needed before acupuncture can be recommended for practice in fatigued, post-treatment breast cancer patients. Clinicians can encourage patients to select from and use evidence-based interventions for fatigue including activity enhancement, psychosocial (CBT for fatigue, psycho-educational, and supportive-expressive therapies), and CBT for sleep. Researchers need to design and test acupuncture and other interventions for cancer-related fatigue in the overlooked, understudied, and complex population of patients with advanced cancer receiving palliative care.

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