

# Acupuncture and fatigue: Current basis for shared communication between breast cancer survivors and providers

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## Abstract

**Introduction** Fatigue is the most common symptom reported by survivors of cancer. At present the medical community lacks evidence-based options for its management.

**Materials and methods** This paper describes the rationale, current evidence, and research in progress as related to the use of acupuncture as a potential option.

**Results** Preliminary evidence suggests that clinicians and cancer survivors may find benefit in considering acupuncture as an option for managing fatigue; this is especially appealing since acupuncture appears to be a safe medical technique. We draw upon our research and clinical experience to generate a description of considerations for patient and provider when thinking about acupuncture as an option for the management of fatigue in non-anemic, disease-free breast cancer survivors.

**Discussion/conclusions** Research examining its relative effectiveness and potential for integration with other approaches is a logical next step if the results from RCTs are positive.

**Implications for cancer survivors** Acupuncture is not routinely considered in mainstream discussions of options for fatigue management. While future research will more clearly determine its relative effectiveness, given the present options available clinicians and breast cancer survivors may find benefit in considering and discussing acupuncture as an approach for managing persistent fatigue.

**Keywords** Acupuncture · Cancer survivors · Fatigue · Health communication · CAM

Fatigue is the most common and distressing symptom reported by patients with cancer during cancer treatment, at end of life, and post primary treatment while the cancer is in remission [1]. We concentrate here on this latter stage and reserve use of the word survivor to describe those people who are post primary treatment and whose cancer is in remission. Fatigue is a chronic form of “tiredness” perceived by the patient as being unusual/abnormal, absolutely disproportionate to the amount of activity carried out, and, worst of all, not alleviated by resting or sleeping [2]. Bower and colleagues estimate prevalence as approximately one-third of disease-free breast cancer survivors based upon data from a large cohort study [3, 4]. In a controlled comparison with a healthy comparison groups, Andrykowsky and colleagues demonstrate that off-treatment fatigue in breast cancer survivors is more intense and more persistent relative to fatigue in age-matched women without a history of breast cancer [5]. Dealing with this symptom burden is vital because fatigue is not only prevalent, it can impact overall function [5] and it is an independent predictor of recurrence-free and overall survival [6].

At present, high-quality scientific evidence is not available to guide standard of care for managing fatigue in breast

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cancer survivors. The single exception is that strong scientific evidence informs the prescription of erythropoiesis-stimulating proteins to address anemia-induced fatigue in cancer patients and survivors. However, only a minority of cancer-related fatigue cases are anemia-related [7]. The United States National Cancer Institute has developed and disseminated treatment “guidelines” for cancer-related fatigue (NCI 2005) [8]. These guidelines include a short post-script on considerations for patients post-primary treatment. For fatigue in cancer patients not attributable to anemia, the primary methods discussed in the 2005 NCI Guidelines are psychostimulants, exercise, cognitive behavior therapy, activity and rest, and patient education. The 2005 NCI Guidelines state “There is no agreed-upon approach for the evaluation and treatment of fatigue...” The National Comprehensive Cancer Network (NCCN), in conjunction with the American Cancer Society (ACS), has also developed a set of treatment guidelines for fatigue in patients with cancer [9]. They explicitly discuss self-care, exercise, psychosocial strategies, and medications as options for survivors. The panel of experts who developed the NCCN 2005 “Guidelines” reached consensus in light of scientific evidence and currently accepted approaches to treatment; they do not discuss the scientific evidence as explicitly as is done in the 2005 NCI guidelines. The lack of evidence to guide standard of care is underscored by a 2003 National Institutes of Health State-of-the-Science Panel who declare “Unfortunately, there is little convincing evidence for effective therapies [10].”

The current paper discusses acupuncture as a potential treatment option by describing the approach, providing an overview of currently available evidence, and providing some considerations that can assist the cancer survivor and her (his) physician in carrying out informed decision-making. This involves a consideration of at least two options in light of evidence and personal preferences [40, 41]. To facilitate this effort, we stake out a middle ground between the positions of speedy rejection and unreasoned acceptance of acupuncture as an option for managing post primary treatment fatigue. Accordingly, we provide a brief review of the option for which there is arguably the best evidence available (exercise) and the option which is perhaps most familiar to clinicians (medications). We distill these thoughts into an aid to facilitate communication and informed decision-making that involves acupuncture in light of the evidence at this point in time.

### Acupuncture for fatigue in breast cancer survivors

As we describe in more detail elsewhere, Traditional Chinese Medicine (TCM) conceptualizes health and disease through a macroscopic and functional understanding of the

human body as well as its energetic interaction with the social and natural environment [11]. TCM emphasizes the centrality of dynamic homeostatic balance, innate self-healing mechanisms, and the inseparable nature of body, mind and spirit. Acupuncture is one of the best-known treatment modalities of TCM. Practitioners diagnose and treat survivors of cancer as they would patients with other diseases, focusing on enhancing the body’s immunity, improving homeostatic reserve and facilitating innate self-regulating and healing mechanisms. From a biomedical perspective, clinicians utilize acupuncture to assist individuals to return to homeostatic balance through neurotransmitter systems such as serotonin and endorphins [45]. Cho and colleagues provide an interesting review of the underlying neuro mechanisms of acupuncture, showing its role in modulation of the hypothalamic-pituitary-adrenal (HPA) axis [46]. This is important because accumulating evidence is indicating that biologically, persistent fatigue in breast cancer survivors may be due to alterations in HPA axis function [43].

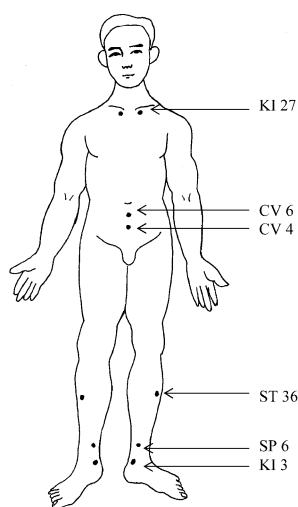
Acupuncture involves insertion of extremely fine needles into precisely-specified anatomical points located in the vicinity of peripheral nerves and their bifurcations, neuromuscular attachments, blood vessels, and ligaments [12]. There are 361 anatomical points known as acupuncture points located on one of 14 energetic meridians [13]. The existence of energetic meridians in humans has been suggested with radioactive tracer research and biophysical studies, as well as nitric oxide studies [14]. Traditional Chinese medical theory specifies that needling of acupuncture points will produce identifiable and reproducible effects. For example, needling the acupuncture point known as stomach 36 is theorized to relieve lack of energy as well as insomnia [13].

There is preliminary scientific evidence that acupuncture may help alleviate fatigue. Vickers and colleagues report on an uncontrolled study employing a standardized acupuncture treatment protocol in cancer patients who had completed chemotherapy [15]. A plurality of patients (32%) had breast cancer. On average, the patients were 24 months beyond treatment. All experienced fatigue which was measured with the Brief Fatigue Inventory administered at the clinic immediately before the first treatment and then at home either 1 or 2 weeks after the final treatment.

Vickers and colleagues clearly describe the procedural details of the treatment administered in their study [15]. Although some patients at the beginning of the study received acupuncture twice weekly for 4 weeks, this was modified to once weekly treatments for 6 weeks for convenience of patients. Six different acupuncturists provided care as part of the study, according to a specific protocol of acupuncture points derived from a Traditional Chinese medicine textbook: ST36, SP6, CV6, CV4, KI3, and KI27

(a slight variation of the point prescription was used at the beginning of the study). Figure 1 shows and describes the location of the acupuncture points in the prescription and lists the fatigue related function of each acupuncture point. After insertion and manipulation, needles were retained in place for 20 min. Patients ages ranged from 43 to 78 years old and it was found that those aged more than 65 benefited less from the treatment. Patients were also administered the Hospital Anxiety and Depression Scale (HADS) at baseline and it was found that those with higher scores at baseline did not respond as well to the acupuncture treatment. The authors report no adverse events attributable to acupuncture in their study.

At present, there are no further published investigations concerning the use of acupuncture to relieve fatigue in breast cancer survivors. However, a PubMed search with the keywords acupuncture and fatigue followed by hand-searches of related bibliographies identified three studies of acupuncture for fatigue in other patient populations. Two concern patients with fibromyalgia for which the primary outcome was pain and a secondary outcome was fatigue. In the first, investigators documented that acupuncture treatments over the course of 9 weeks led to a statistically significant reduction in fatigue, as measured by the Multi-



Points	Locations	Indications
KI 27 (Shu Fu)	In the depression on the lower border of the clavicle, 2 cun lateral to the anterior midline.	Lack of appetite
CV 6 (Qi Hai)	On the anterior midline, 1.5 cun below the umbilicus.	Emaciated, lack of energy on limbs
CV 4 (Guan Yuan)	On the anterior midline, 3 cun below the umbilicus.	Lack of energy, dizziness
ST 36 (Zu San Li)	3 cun below the lower border of the patella, one-finger breadth from the anterior border of the tibia.	Lack of energy, depression, insomnia
SP 6 (San Yin Jiao)	3 cun directly above the tip of the medial malleolus, posterior to the medial border of tibia.	Weak stomach, insomnia
KI 3 (Tai Xi)	In the depression between the tip of the medial malleolus and Achilles' tendon.	Insomnia, dizziness, headache

**Figure 1** Point prescription for post-chemotherapy fatigue. Notes: one cun—when the patient's middle finger is flexed, the distance between the two medial ends of the creases of the interphalangeal joints is taken as one cun; Drawing by Bo Xiao, L.Ac.; point prescription from Vickers and colleagues [15], point locations from Cheng [13], and point indications from Yang [48].

Dimensional Fatigue Inventory questionnaire [16]. In the second, investigators showed that acupuncture treatments administered twice weekly for 12 weeks reduced fatigue as measured by a visual analogue scale, but that this was not significantly different than that in patients receiving sham acupuncture [17]. A third showed that a physician used manual acupuncture, along with patient education, to improve quality of life in a series of consecutive patients visiting an integrative medical clinic at a major university [18]. The instrument used to assess quality of life was the SF-36, which includes a subscale for energy/vitality (fatigue reverse-scored), which was filled out at baseline and then immediately after the sixth visit.

In general, acupuncture is considered to be a safe technique [19]. Acupuncture needles are about 20 times thinner than the needles used for drawing blood [hypodermic needles]. Patients generally complain of little or no discomfort from insertion of acupuncture needles, although there may be a feeling of heaviness or numbness. A meta-analysis of acupuncture studies estimates the risk of a serious adverse event to be on the order of 0.05 per 10,000 treatments [20]. The most well-known adverse event associated with acupuncture is pneumothorax and a few published case studies document that this is a potential problem. Only two cases of pneumothorax have been reported in provider-reported prospective surveys of acupuncture involving 14,340 patients who received in total 139,988 treatments [20]. To address underreporting of adverse events that might occur in meta-analyses of provider-reported events (such as those analyzed in [20]), Macpherson and colleagues surveyed 6,348 individuals who had received acupuncture on adverse events, finding only three that could be classified as a serious adverse event (and their reports on these events make clear that few people would attribute all three adverse events to acupuncture) [19]. In that survey, the most commonly reported direct non-serious adverse events were exhaustion and prolonged or unacceptable pain at the needling site [19].

Due to the promise of the preliminary evidence, there are two randomized controlled trials currently underway to rigorously assess the efficacy of acupuncture in alleviating cancer-related fatigue among cancer survivors post primary treatment. Vickers and collaborators are conducting a randomized controlled trial of acupuncture for post primary treatment fatigue in cancer patients [21]. A study at UCLA led by Hui is conducting a Phase IIB randomized controlled trial in which acupuncture plus patient education will be compared to standard care for disease-free breast cancer survivors with fatigue [22]. These trials will better inform us as to the utility of acupuncture as a viable option for managing fatigue in disease-free breast cancer survivors, although questions will arise as to whether effectiveness varies by number of years out from primary treatment and

diagnosis. However, while these trials are necessary to determine whether structured scientific evidence will justify the use of acupuncture, at present the cancer survivor is left with very few options for persistent or recurrent fatigue.

### Well-known options for managing fatigue in breast cancer survivors

Shared medical-decision making is not possible without a consideration of at least two options. This paper is not a systematic review of all the potential options available for managing fatigue in cancer survivors. However, we will provide a brief discussion of the option which is arguably best supported by scientific evidence—exercise. There are systematic reviews on this topic [27, 33, 47], from which we identified two randomized controlled trials. We also discuss the one medication which is named in both the 2005 NCI Guidelines and the 2005 NCCN Guidelines—methylphenidate (Ritalin). There is also limited evidence for self-care activities such as meditation [23, 24] and psychosocial strategies such as cognitive behavior therapy [23, 25, 26]; however, we are unable to discuss these options within the confines of this paper.

Two randomized controlled trials have been conducted regarding exercise as a therapy for relieving fatigue post-treatment women who are disease-free breast cancer survivors, both of which have positive results [27]. Courneya and colleagues assess a regimen consisting of training three times per week for 15 weeks on cycle ergometers, with a measure of fatigue (the 13-item fatigue scale of the FACT measurement system) at baseline and then at study conclusion [28]. Pinto and colleagues assess a regimen consisting of moderate-intensity level walks for 12 weeks that began with walks of at least 10 min two times a week and gradually increased to 30 min for 5 days a week [29]. Researchers used a visual analogue scale for fatigue which was administered at baseline and then again at study conclusion. In both trials, those in the exercise group experienced a statistically significant reduction in fatigue relative to controls and researchers found the exercise intervention to be safe.

The unlabelled use of methylphenidate (Ritalin) includes fatigue in cancer patients and survivors [30]. A newly published phase II study of methylphenidate for the treatment of fatigue in cancer survivors provides statistical evidence of benefit at study conclusion (6 weeks after baseline). The statistical evidence should be viewed with caution because the conventional bar (two-sided test with a  $P$  of 0.05) was lowered substantially (one-sided test with a  $P$  of 0.20). Of the 37 patients enrolled into the study, six (19%) withdrew due to adverse events. Of those that remained, 6 experienced restlessness/anxiety (16%), three

experienced dizziness (8%), three experienced headaches (8%), one experienced heart palpitations (2%), and one experienced back spasms (2%). This study appeared after the 2005 guidelines were published. There appears to be consensus that methylphenidate produces adverse reactions of a non-serious nature (e.g. stomach, sleep, and blood pressure problems) related to its stimulant effects [31]. There have been a few reports of serious events, of which the most common appears to be toxic psychosis and it has a rare potential for others such as Tourette's syndrome, seizures, and sudden death. Methylphenidate is known to have a variety of adverse interactions with other drugs and negative pharmacologic effects. Of special relevance for cancer survivors is that it has the potential to interact adversely with psychoactive drugs such as tricyclic antidepressants [31]. This potential for interaction, as well as its own antidepressant effect, is one reason why physicians often take their patients off tricyclic antidepressants when prescribing methylphenidate.

As is pointed out in the 2005 NCI Guidelines, the evidence does not clearly support the use of any one method for managing fatigue in cancer survivors [9]. The paradigm of shared medical decision-making has been developed for situations in which there are multiple options to consider, no scientifically-identified “best” option, and it can be expected that patients will vary in how they value trade-offs between risks, benefits and costs [32]. Shared medical decision-making does not inherently involve pitting therapeutic options against each other, but could involve a consideration of integration. If a patient has limited financial or temporal resources, however, he or she may be in the uncomfortable position of only being able to select. A utility of the shared medical decision-making paradigm is that it may be beneficially applied in either situation.

### Facilitating communication and decision-making of fatigue in breast cancer survivors

Shared medical decision-making is a paradigm that advocates physicians share decision-making with their patients in situations where there are multiple options but no consensus about which is best (“preference sensitive decisions”) [33, 34]. Even if physicians were to secure information from the published literature clearly indicating a particular option, that this would be insufficient for themselves, or anyone else, to make a fail-safe decision about their patient's health care, because it is difficult to translate results about probable treatment outcomes garnered from random clinical trials into clinical practice [35]. As is well known by those who attempt to provide scientifically sound practice, the problem is far more subtle than accounting for

**Table 1** Acupuncture: one option for fatigue

Acupuncture for fatigue in cancer survivors
Identifying an acupuncturist
Does the acupuncturist have a valid, up-to-date license?
Can acupuncturist provide evidence of training? (e.g. highest certification available)
Can acupuncturist provide evidence of experience? (e.g. letters of reference from patients/providers)
Does acupuncturist have written forms disclosing risks and benefits of treatment?
Will acupuncturist refrain from herbal prescriptions?
Will acupuncturist only needle standard acupuncture points?
Does acupuncturist have liability insurance and, if so, what are the specified limits?
Visit logistics
How long will it take patient to travel back and forth for the visit?
If patient will drive, is there free parking?
What is the duration of each individual session?
Do patients typically have to wait long in the waiting room?
Will patient need to secure time off from work?
Practice logistics
Does patient have a strong reaction against insertion of thin needles into medically-specified acupuncture points?
How do patients approach spirituality? (Some prefer Buddhist or New Age Spirituality elements and some acupuncturists incorporate these into their practice. Other acupuncturists do not practice spirituality and some are Christian.)
How does patient feel about laying down on a massage table for approximately 30 minutes with dimmed lights and gentle music? (Not all acupuncturists play music)
Costs
Chinese Medicine Schools have student-provided acupuncture for approximately \$25 a session
A customary charge from an independent practitioner ranges from \$30 to 50 a session
Will the acupuncturist handle the insurance claim?
Is patient's insurance likely to reimburse?
Safety
Patients generally complain of little or no discomfort from insertion of acupuncture needles, although there may be a sting or a feeling of numbness
Acupuncture needles are about 20 times thinner than the needles used for drawing blood [hypodermic needles]
Acupuncture is very safe; serious adverse events occurring approximately 0.05 per 10,000 treatments, minor adverse events that may occur are bleeding (a few drops) or development of a small bruise around the needled area
Contraindications for patients with cancer and survivors include bleeding diathesis and anti-thrombotic therapy

exclusion criteria that limit the generalizability of RCT results to everyday practice. Individual patients are more or less bothered by the same symptoms, react differently to the experience of treatment, anticipate different reactions to the benefits and harms of the treatment, and differently evaluate trade-offs between the two [35]. Since there is limited evidence and different options have varying benefits and drawbacks, choosing a treatment for fatigue is preference sensitive.

The Institute of Medicine (IOM) indicates that research on cancer survivors' decision-making about use of health services is an important area of priority [36, 37]. In a separate report, they specifically call for studies on decision-making about CAM treatments such as acupuncture [35]. A PubMed search failed to uncover any studies that attempt to identify the preferences of breast cancer survivors which might inform the selection of treatment options for fatigue

in breast cancer survivors, especially with reference to acupuncture.

On the basis of our experience, we offer "communication points" for physicians and patients concerning acupuncture as an option for managing fatigue in cancer survivors (see Table 1) [38, 39]. We also offer the following "jumping off" points for further discussion with the understanding that physicians and patients will modify in light of local circumstances. We do not see acupuncture burdensome in terms of arranging provider visits. We see it as favorable in terms of the actual experience of receipt of treatment. This would be unfavorable, however, if patients find it difficult to be alone or are very afraid of needles. We see the costs as amounting to a total of \$360 (6 visits at \$60 apiece, assuming no insurance coverage).

Acupuncture is one option for management of fatigue in breast cancer survivors, but there are also other viable

options. This raises the issue—who will choose the method of fatigue management? Patients, especially cancer patients, prefer shared decision-making [40]. Moreover, shared decision-making that involves the use of decision aids is associated with greater knowledge and more realistic expectations about what an option can accomplish [41]. The aid we provide is only a first step towards formally including acupuncture amongst the options to consider with an eye towards facilitating shared decision-making. As more evidence accumulates, decisions will be more concordant with preferences and more detailed aids will be developed.

## Discussion

Cancer survivors seek advice from a physician when they have questions about fatigue [1]. Physicians, especially oncologists, are unlikely to proactively propose acupuncture and other types of complementary and alternative medicine as an option for their patients [42]. But breast cancer survivors have a demonstrated interest in modalities such as acupuncture [49]. One concern that mainstream clinicians have with acupuncturists is that they may prescribe herbs and that these herbs may negatively interact with pharmaceutical agents.

Fatigue in cancer survivors is the most common symptom, the most distressing symptom, and, most notably, associated with mortality [6]. For these reasons, it needs to be addressed. Aside from the minority of instances in which anemia is the underlying cause [7], the etiology of fatigue in cancer survivors is unclear. Multiple factors, including non-specific factors, may contribute to fatigue in breast cancer survivors [43]. Acupuncture is one approach that has the potential to provide relief from stress, anxiety, mild depression, and pain of soft articular origin [11], all of which may contribute to fatigue or are associated with fatigue [44].

At present no methods for persistent or episodic fatigue are definitively supported by scientific evidence. Given this context, it is important for physicians to communicate openly with patients about options, acknowledge limitations of the current evidence, express their own predispositions, and help patients articulate their preferences. It is essential that we develop an evidence base and, during this process, maintain an open communication process.

**Postscript** After submission, the authors learned that Molassiotis, Sylt, and Diggins conducted a well-executed randomized controlled trial demonstrating acupuncture to effectively relieve fatigue in survivors of breast and other cancers [50].

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