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How Effective is Acupuncture in Treating Cancer-Related Fatigue in Adult Cancer Patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences- Physician Assistant

Department of Physician Assistant Studies

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not acupuncture is an effective course of treatment for improving cancer-related fatigue in adult cancer patients.

DESIGN: Review of three English language primary randomized controlled studies published from 2006-2012.

DATA SOURCES: Three randomized controlled trials studying the effects of acupuncture therapy on cancer-related fatigue were found using PubMed and Cochrane databases.

OUTCOMES MEASURED: Each of the three trials assessed the efficacy and clinical improvement of cancer-related fatigue after acupuncture therapy. Results were measured on the Functional Assessment of Chronic-Illness Therapy-Fatigue Subscale (FACIT-F) or the Multidimensional Fatigue Inventory (MFI).

RESULTS: In a pilot, randomized, double-blind controlled trial by Balk et al, the acupuncture group showed improvement compared to the sham acupuncture group, but results were statistically insignificant due to a small sample size. Both randomized controlled trials by Molassiotis et al (2006) and Molassiotis et al (2012) had clinically significant improvement in cancer-related fatigue after acupuncture therapy as compared to sham-acupuncture or usual enhanced care.

CONCLUSIONS: All three randomized controlled trials demonstrated in some degree that acupuncture is an effective form of therapy to improve cancer-related fatigue.

KEY WORDS: Acupuncture, cancer-related fatigue

INTRODUCTION

Cancer is defined as a malignant uncontrolled division of abnormal cells which can occur anywhere within the body. There is an innumerable amount of research being done in order to find effective ways of treating different forms of cancer. Some common forms of therapy include surgical resection, chemotherapy, radiation therapy, and other pharmacological interventions. Unfortunately, there has not been one ideal treatment course to combat cancer and like most therapeutic regimens, there are expected adverse effects. Cancer-related fatigue (CRF) is characterized by feelings of tiredness, weakness and lack of energy that is not relieved by rest or sleep¹. Cancer-related fatigue can be due to the disease state itself or as a side effect of its treatment. Although the pathophysiology is largely unknown, up to 78% of cancer patients experience fatigue as a result of treatment and often persists after discontinuation of therapeutic treatment¹. Many patients report that cancer-related fatigue has a bigger impact on quality of life as compared to other common cancer side effects such as pain, nausea, or vomiting². This paper evaluates three randomized trials comparing the efficacy of acupuncture for improvement of cancer-related fatigue in adult patients.

According to the American Cancer Society³, there is an estimation of 1,658,370 new cancer cases in 2015. Despite rigorous cancer research, this number continues to rise each year. Because cancer is such a broad category of disease, cancer patients are seen in all fields of medicine. Uncontrolled, abnormal cell growth has no limitation of age, sex, or body system. Cancer is specialized into the field of oncology, but a cancer patient can be found in any scope of practice. The impact of cancer-related fatigue on healthcare is difficult to measure because it is often considered as an inevitability of cancer rather than a medical symptom. In a study published in the *Annals of Oncology*⁴, fatigue was reported to be the most distressing side

effect of cancer treatment as compared to other side effects such as nausea and pain. However, 52% of those patients did not report their fatigue to their physician⁴. There is not enough attention on this symptom that has such a profound impact on the patient's life. If recognition and addressment of cancer-related fatigue improved, there could be greater compliance with cancer treatment and quicker recovery. In order for this to happen, clinicians, such as physician assistants, need to be able recognize the signs of cancer relate fatigue, in any practice or setting. They then must have the resources to offer their patients effective treatment options to reduce their fatigue and ultimately improve the patient's quality of life, and possibly cancer prognosis.

Cancer-related fatigue is known to profoundly affect a patient's ability to perform various tasks associated with daily living. It can limit their personal and social roles they have with their families or communities, leading to an overall decrement of quality of life. The underlying causes of CRF are poorly understood but the combination of disease and treatment puts a great deal of stress on a patient's physical and mental health. According to an article published in *The Oncologist*⁵, "CRF has been reported throughout the course of malignant disease: from diagnosis, during therapy, and for months to years after completion of treatment while patients are in clinical remission." Pharmacologic treatments used to reduce cancer-related fatigue include psychostimulants such as methylphenidate, antidepressants such as nortriptyline, and glucocorticoids. Non-pharmacological recommendations to manage CFR include rest, improving exercise and diet regimens, blood transfusions, yoga, massage, music therapy, cognitive-behavioral and psychosocial interventions. Acupuncture is one of the oldest forms of alternative medicine, recognized to treat a variety of things such as pain, stress, headaches, and nausea. It is now slowly gaining acceptance for treatment of cancer-related fatigue.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not acupuncture is an effective course of treatment for improving cancer-related fatigue in adult cancer patients.

METHODS

The three studies utilized in this review include three randomized control trials which met the following criteria: The population consisted of adult cancer patients who have experienced chemotherapy or some form of radiation therapy. The intervention used was acupuncture over a two to six week period. The treatment group receiving acupuncture versus the experimental group receiving enhanced usual care or sham acupuncture/acupressure.^{1,2,6} The outcome measured in all three studies was the efficacy of acupuncture for the treatment of cancer-related fatigue.

Key words used to locate the literature consisted of acupuncture and cancer-related fatigue. All articles were originally written in English from peer-reviewed journals published within the last ten years. The articles were searched via PubMed and were selected based on their relevance to my clinical question and if the study measured patient oriented outcomes (POEMS). Inclusion criteria consisted of randomized controlled trials with adult cancer patients who previously received some form of chemotherapy or radiation therapy. Exclusion criteria consisted of patients in the process of cancer treatment during the time of the study, patients with any known bleeding disorders, anemia, or taking corticosteroids. Statistics that were reported and utilized were numbers needed to treat (NNT), standard deviation, p-values, baseline tests, and ANOVA, ANCOVA, 95% confidence intervals, and t-tests.

Table 1: Demographics and characteristics of the studies utilized for this review

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/d	Interventions
Balk (2009)	RCT	27	40-69	-Woman with localized ca who had surgery alone or in combination with radiation therapy. -Score of 44 or lower on the FACIT-F	-Hx of acupuncture tx -allergy to stainless steel -a pacemaker - anticoagulant tx or known bleeding d/o -Seizure d/o or if they are receiving combination tx of radiation and chemotherapy	4	Acupuncture x1-2/wk during a 6-week course of radiation therapy
Molassiotis (2012)	RCT	302	25-80	-Diagnosis of I, II, or IIA breast cancer -Had completed chemotherapy at least 1mo and up to 5yrs prev -had not planned to receive chemoradiotherapy during the study -had a score >5 on a 0 to 10 screening scale	- needle phobia -<50,000/microL platelet count -comorbidity with a bleeding disorder or thyroid disorder -pregnancy -Hb <10g/dL - Hct <30% -active tx for anemia with erythropoietin or blood transfusions -corticosteroid use -life expectancy <6mo -if the ipsilateral arm of patients had undergone axillary dissection	59	Acupuncture x 1wk for 6 weeks
Molassiotis (2007)	RCT	47	20-76	-Patients with ca who have completed chemotherapy at least 1month before -Patients with score of five or more on the screening tool for fatigue -anticipated survival more than 3mo -No schedule to receive cancer tx during the study period	-needle phobia -low platelet count -suffered from a bleeding disorder -pregnancy -had lymphedema at the area of the acupuncture for anemia -Hb <9g/dL, hct<30, or active tx for anemia - Karnofsky score <70 or were receiving steroids to combat fatigue	13	6, 20 minute sessions over 2 weeks

OUTCOMES MEASURED

All outcomes measured in the trial were based on patient oriented evidence that assessed the efficacy and clinical improvement of cancer-related fatigue after treatments of acupuncture in post-chemotherapy or post-radiation therapy patients. The Balk et al study¹ measured the participant's fatigue before and after the treatment using the Functional Assessment of Chronic-Illness Therapy-Fatigue Subscale (FACIT-F). It specifically measured the quality of life and fatigue experience of cancer patients. Both Molassiotis et al studies^{2,6} measured general fatigue using the Multidimensional Fatigue Inventory. In the Molassiotis et al study⁶, secondary outcomes of mental fatigue, activity and motivation were measured by the Hospital Anxiety and Depression Scale (HADS) and quality of life was measured by the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) module.

RESULTS

The Balk et al¹ study compared a 6 week program of true acupuncture (n=16) to sham acupuncture (n=11). The participants of the study were women with the mean age of 54.1 years and all but one participant had breast cancer; the one remaining patient had endometrial cancer. All participants scored 44 or worse (the lower the score, the worse the fatigue) on the FACIT-F before the study began. All participants in both groups received treatment twice per week for 6 weeks. Data was collected at baseline, 3 weeks, 6 weeks, and 4 weeks after the last treatment. 23 out of the 27 original subjects completed the study to the 10th week of data collection. Mean FACIT-F difference between baseline and the 10th week follow up appointment was 6, or an 18.81% improvement for real acupuncture and 3.2, or an 8.74% improvement in the control

group. The difference in mean change between the two groups was 2.8 utilizing ANOVA with $p=.457$, making the data statistically insignificant.

Table 2: Mean FACIT-F Scale scores at baseline and follow-up appointments by treatment group

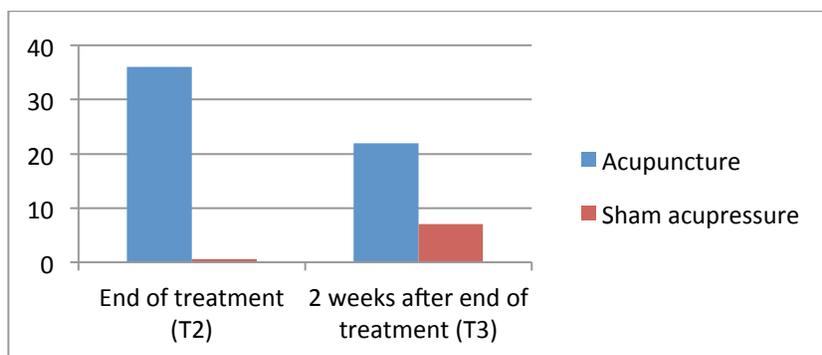
	Baseline	Week 3	Week 6	Week 10
Real Acupuncture	31.9	37.9	39.5	39.8
Sham Acupuncture	36.6	34.8	36.2	37.9

The Molassiotis et al² study consisted of six 20-minute sessions of either acupuncture (n=13) or sham acupuncture (n=13), over the span of two weeks. Patients completed the Multidimensional Fatigue Inventory before treatments began (T1), at the end of the 2-week intervention (T2), and 2 weeks after the completion of treatment (T3).

Table 3: Mean MDI scores over time for the general fatigue subcategory, mean (S.D.)

	T1	T2	T2
Acupuncture	16.4 (2.4)	10.5 (3.0)	12.8 (3.2)
Sham Acupressure	17.8 (2.5)	17.7 (2.6)	16.9 (3.0)

Figure 1: Percent improvement of general fatigue over time in the two groups compared to baseline scores.



General fatigue improved highest in the acupuncture group immediately post-treatment by 36%, whereas the sham acupuncture group did not improve at all. Through the regression analysis (ANCOVA), acupuncture was found to be significantly more effective than sham acupuncture

immediately after treatment, at T2, ($F=7.37$; $d.f.=1,33$; $P=0.01$). The 95% CI for the two groups was -9.19 to -3.89. Treatment was well tolerated in subjects of all three studies, and minimal side effects experienced by participants in the Molassiotis et al² included spot bleeding and bruising.

The Molassiotis et al⁶ study had three hundred and two breast cancer patients participate in their study involving acupuncture and improving cancer-related fatigue. The treatment group had an acupuncture session by a qualified provider, once a week for 6 weeks. The control group did standard care (SC) techniques for cancer-related fatigue which were outlined in a booklet that was given to all subjects of the study. Before treatment began and the end of 6 weeks, patients completed the Multidimensional Fatigue Inventory (MFI) to measure general fatigue (GF). A simple t-test was applied to fatigue change scores (week 6- baseline) and the primary analysis was an analysis of covariance (ANCOVA). Standard care mean score ($GF_{wk6} - GF_{wk0}$) = -0.53 and the acupuncture mean score ($GF_{wk6} - GF_{wk0}$) = -2.96. The difference (acupuncture - SC) in mean change in general fatigue = -2.43. The trial arm effect was highly significant ($p < .001$) with a narrow 95% CI, -3.19 to -1.67.

Figure 2: Change in MFI: General Fatigue scores from baseline to 6 weeks

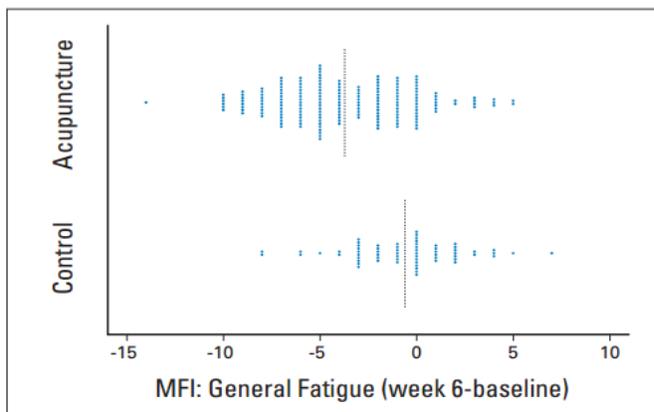


Table 3: Difference in outcomes at week 6 for general fatigue, physical fatigue and mental fatigue

MFI category	Trial Arm <i>P</i>	Acupuncture Effect *	SE	95% CI
General fatigue	<.001	-2.49	0.44	-3.29 to -1.69
Physical fatigue	<.001	-2.36	0.45	-3.25 to -1.47
Mental fatigue	<.001	-1.94	0.44	-2.81 to -1.07
Reduced activity	<.001	-2.29	0.41	-3.10 to -1.48
Reduced motivation	<.001	-2.02	0.40	-2.82 to -1.22

*Estimated difference in week 6 score (acupuncture-control) given equal baseline scores.

DISCUSSION

Acupuncture is one of the oldest forms of medical intervention that began about 2000 years ago and is a signature of traditional Chinese therapy. Over the years, the practice has diversified and broadened its techniques and styles. The basic concept of acupuncture is to restore balance in the “yin and yang” of the physical body by stimulating specific anatomical points⁷. Various research models have indicated multiple physiologic effects as a result of acupuncture. It is known that this form of therapy has an effect on inflammatory cytokines, T lymphocytes, various peptides and newer research is suggesting it has an effect on the tumor necrosis factor⁷. Clinical indications for acupuncture include headaches, chronic pain, nausea, and allergic rhinitis⁷. With research studies like the three included in this review, acupuncture is becoming an accepted form of therapy to treat cancer-related fatigue.

‘Fatigue’ is a very brushed-off symptom in medicine because it is used so frequently and ambiguously. However, there is a distinct difference in fatigue in a healthy individual and fatigue in a cancer patient. Fatigue can eventually be alleviated in a healthy person with adequate rest and sleep, which does not warrant further treatment in most cases. However in a cancer patient, fatigue is not alleviated by rest and can persist up to months to years after treatment. It has a

profound impact on the patient's quality of life and ability to perform the roles they have in their family, communities and careers. Fatigue is commonly the most experienced symptom of cancer and cancer treatment, but the least reported. It is commonly thought that fatigue is an inevitable consequence of cancer and therefore often goes without being properly addressed. Another issue for not addressing fatigue is due to cost. Because there is not one proven treatment for cancer-related fatigue, and many therapies are still experimental, insurance companies are not likely to pay for treatment for the fatigue itself. Acupuncture could be a legitimate treatment option for CRF, although its availability may be an issue for health care services and patients may not be able to afford private costs⁶. The median cost of one acupuncture session is about \$100, and without insurance coverage, cost can make it difficult to sustain this form of therapy.

All three of the articles reviewed displayed some evidence that acupuncture has the potential of being an accepted form of therapy to treat cancer-related fatigue. Although differing in statistical significance, these studies can be a stepping stone for future research. Outliers of the reviewed studies included cancer patients under the age of 50. Also, all three studies had exclusion criteria of patients actively going through chemotherapy or radiation therapy. A limitation of the experiments was finding an adequate control to compare to acupuncture. Between sham acupuncture, sham acupressure, and enhanced usual care, there was not a standard control. This has the possibility of having small discrepancies while comparing the different studies.

CONCLUSION

At this time, data is suggesting that acupuncture is an effective course of treatment for improving cancer-related fatigue in adult cancer patients. The amount of improvement differed

between the three studies; however each acupuncture experimental group did improve in some degree in comparison to the control group. More evidence can always be collected with a greater number of participants in a study and if the duration is longer. Future studies can add another dimension of research by including adolescent and young adult cancer patients and see how they would respond to the treatment. Future studies can explore the effect of acupuncture in patients actively going through cancer treatment. Molassiotis et al⁶ was the only study out of the three that had a specification of a type of cancer that was included in that particular experiment. However future studies could also target specific cancer forms to see if acupuncture is more beneficial in patients with a particular malignancy. The future of cancer-related fatigue treatment has a wide arena of research and potential in its future.

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