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CLINICAL REVIEW

Review of Acupuncture Therapy for Cancer Related Fatigue: 2009-2019

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Abstract

Introduction

Cancer-related fatigue (CRF)—a subjective sense of tiredness related to cancer or cancer treatment—significantly impacts quality of life and is an important element of palliative care for cancer patients. It is the most prevalent, devastating, and debilitating symptom, affecting 70-100% of patients undergoing biotherapy, chemotherapy, and/or radiation.¹ The etiology of CRF is multidimensional, stemming from the cancer itself, its associated treatments, and the psychological stress of a cancer diagnosis. Within the last two decades, there has been a growing body of research studying the utilization of acupuncture in the treatment of CRF. Acupuncture is a major treatment modality in Eastern medicine and is widely used in palliative care globally.² There are many different traditions of acupuncture, including Japanese, traditional Chinese medicine (TCM), and Korean Saam. Treatment with acupuncture is usually personalized, and varies in terms of needle stimulation, type, and depth, frequency and length of treatment, and acupuncture point selection.

This paper reviews of the literature describing use of acupuncture in the treatment of CRF. Our goal is to develop future directions for integrative oncology research and clinical care.

Objectives

1. To review literature on cancer related fatigue during a recent 10-year period (2009-2019)
2. To analyze the available data on acupuncture in the treatment of cancer related fatigue
3. To propose proactive and concurrent use of acupuncture in patients undergoing chemotherapy

Methods

We searched CINAHL, EMBASE, MEDLINE, PubMed, PsycINFO, and Thomson Reuters Web of Science for relevant trials relating to the use of acupuncture in treatment of CRF within a 10-year period (2009-2019). Terms used were “acupuncture”, “cancer”, “neoplasm”, and “fatigue”.

Results

Eight studies with a total of 715 patients were included. Three studies were pilot randomized control trials, one study was an observational pilot study, and the remaining four studies were randomized control trials (RCTs).

Summary Table collates the highlights from the available research papers: (1) Study, (2) Design, (3) Sample, (4) Intervention, (5) Acupuncture Point Selection.

Conclusions

The rapid development of cancer treatments has extended overall survival of cancer patients but has also resulted in multiple cancer-related symptoms. Encouraging evidence has demonstrated the positive role acupuncture plays in integrative cancer care and improving cancer related fatigue. We reviewed seven RCTs and one observational study published over the past ten years. These trials all show acupuncture as an effective adjunct treatment for CRF. Of note, conclusions from our review are limited by the heterogeneity of the intervention and cancer population. Nevertheless, the positive results support future research to further elicit the role acupuncture may play in the treatment of CRF, and consideration for earlier incorporation of acupuncture in cancer patients undergoing chemotherapy.

Introduction

Cancer-related fatigue (CRF) is defined as a distressing, debilitating subjective sense of physical, emotional, and/or cognitive tiredness associated with cancer and its therapy that is not proportional to recent activity and is not relieved by rest.^{1,2} CRF is also associated with comorbidities including pain, nausea, vomiting, dyspnea, and lack of appetite to depression and anxiety.³ A systematic review of 40 CRF studies reported prevalence rates from 46% to 96% of patients undergoing chemotherapy, radiotherapy, and/or biotherapy.⁴ It may be a manifestation of the cancer alone, or a complex interplay of psychological distress from the diagnosis of cancer, cancer surgery, and medical treatments.

CRF commonly improves one-year post-treatment, but about 30% of patients continue to report fatigue that may persist more than 10 years after treatment.⁵ CRF affects all aspects of individuals' lives—impacting family life, employment, social relationships, and sexual life.⁶ In addition to limiting overall quality of life, CRF affects ability to perform activities of daily living with decreased functional status.⁷ Additionally, CRF is associated with decreased survival.

CRF can lead to increased health care utilization, including medications, physician visits, and hospital admissions. Currently, limited pharmaceutical agents are available for the treatment of CRF and are associated with multiple potential side effects.³ Pharmacologic therapies for CRF include psychostimulants, erythropoietin, and antidepressants.³ Numerous non-pharmacologic, integrative, and complementary treatments have shown promising results in helping patients with CRF.³ Of these treatments, acupuncture has gained increasing attention.

One of the most common reasons people choose acupuncture in the United States is to treat fatigue.⁸ Many patients with CRF consider acupuncture because of potential adverse effects (AEs) from pharmacologic intervention, including: fear that drugs may further worsen fatigue; general belief in or good experience with alternative medicine; and the feeling of having more control over one's own health.⁸ Regardless of the reasons for

acupuncture initiation, it is important to evaluate data establishing effectiveness for treatment of CRF.

The aim of our systematic review is to evaluate the evidence of efficacy of acupuncture managing CRF. Our goal is to develop future directions for integrative oncology research and clinical care.

Methods

We searched CINAHL, EMBASE, MEDLINE, PubMed, PsycINFO, and Thomson Reuters Web of Science for relevant trials relating to the use of acupuncture in treatment of CRF within a recent 10-year period (2009-2019). Terms used were “acupuncture”, “cancer”, “neoplasm”, and “fatigue”.

Results

Eight studies with a total of 715 patients were included. Four were pilot studies - 3 randomized control trials and 1 observational study, and the other four studies were randomized control trials. We summarize the results and limitations of each study below. Summary table (Table 1) describes the following: (1) Study, (2) Design and Sample, (3) Intervention, (4) Treatment, and (5) Findings.

Table 1: Tabular summary of 4 pilot studies—3 randomized control trials and 1 observational study—to assess the role of acupuncture in treatment of cancer related fatigue.

Study	Design	Sample	Interventions	Acupuncture Points
Balk et. al 2009 [9]	Pilot, modified, double-blind, placebo-controlled RCT to determine if true acupuncture versus sham acupuncture can improve CRF measured by FACIT-F	Women with localized cancer who had surgery alone or in combination with chemotherapy and were planning to undergo radiation Total participants: 27 subjects, 23 completed study	Intervention: 1-2 times per week acupuncture treatments (30-minute sessions) for 6 weeks Control: Sham group using Park Sham Device	Acupuncture: KI-3, SP-6, LI-4, ST-36, and CV-6
Johnston et. al 2011 [10]	Pilot RCT to assess feasibility of delivering patient education integrated with acupuncture for relief of CRF measured by BFI	Women who finished with primary therapy for breast cancer (free of cancer) but who still had fatigue Total participants: 12 study participants (5 in treatment group, 7 in control group)	Interventions: 1 time per week acupuncture treatments (50-minute sessions) for 8 weeks and self-care education, along with usual care of personal physicians Control: Usual care of personal physicians	Acupuncture: Four energy associated acupuncture points (LI-4, SP-6, ST-36, KI-3) were needed bilaterally Other points at discretion of acupuncturist
Smith et. al 2013 [11]	Pilot, single-center, mixed method RCT, comparing acupuncture with a sham and a wait list control in management of CRF measured by BFI	Women with breast cancer who have a score of 4 or more on BFI and completed chemotherapy at least 1 month previously Total of 30 participants divided into 3 groups: (1) acupuncture; (2) sham control; (3) waitlist control	Intervention: 2 times per week acupuncture treatments (20-minute sessions) over 3 weeks, then 1 time per week thereafter for total of 8 treatments Control: Sham control group received a non-invasive sham needle Waitlist control: subjects had a designated researcher who made contact with them every 2 weeks	Acupuncture: KI-3, KI-27, ST-36, SP-6, CV-4, and CV-6 Sham group: Sham needles placed in fixed designated points
Kim DJ et. al 2014 [12]	Pilot observational study to collect preliminary data on the effects of acupuncture with regard to immunity in cancer patients. CRF measured by FSS.	Patients with any malignancy with ECOG performance score of ≤ 2 who have received palliative operation and radio/chemotherapy at least 2 months prior to start of trial Total participants: 10 subjects	Intervention: 2 times per week acupuncture (20-minute sessions) for 2 weeks Control: No acupuncture	Acupuncture: LU-8, BL-66, SI-5, TE-4, and CV-12

*Randomized control Trial (RCT), Cancer Related Fatigue (CRF), Functional Assessment of Chronic Illness Therapy- Fatigue Subscale (FACIT-F), Brief Fatigue Inventory (BFI), Fatigue Severity Scale (FSS)

Table 1 (continued): Tabular summary of 4 randomized control studies to assess the role of acupuncture in the treatment of cancer related fatigue (CRF)

Study	Design	Sample	Interventions	Acupuncture Points
Molassiotis et. al 2012 [13]	Multicenter, two-armed, RCT to determine role of acupuncture in improving CRF measured by MFI	Breast cancer patients (Stage I, II or IIIa breast cancer) who experienced persistent fatigue of at least a moderate level Total participants: 302 (3:1 ratio of 227 in experimental, 75 in control group)	Intervention: 1 time per week acupuncture treatment (20-minute sessions) over 6 weeks in addition to enhanced usual care Control: Enhanced usual care (which includes providing detailed information booklet about coping with fatigue)	Acupuncture: ST-36, SP-6, and LI-4. Additional points were selected at discretion of acupuncturist (eg GB-34, SP-9, SP-11)
Molassiotis et. al 2013 [14]	Nested, multi-center, phase III unblinded, RCT to assess benefits of maintenance acupuncture (self or acupuncturist led) in managing CRF measured by MFI	Breast cancer patients from a prior trial (Molassiotis 2012) were re-randomized to 3 groups Total participants: 197 (divided into 3 groups: self delivered, acupuncturist delivered, no maintenance)	Intervention: <i>Acupuncturist led</i> – 1 time per week acupuncture (20-minute sessions) for 4 weeks <i>Self led</i> – Patient performed self-acupuncture 1 time per week for 4 weeks as instructed Control: No maintenance treatment provided	Acupuncture: ST-36, SP-6, LI-4
Deng 2013 [15]	Single-center, two armed, sham-controlled RCT aimed to determine if acupuncture reduces CRF measured by BFI	Subjects diagnosed with any malignancy who have completed a course of chemo at least 60 days prior; fatigue experienced after chemotherapy and not before Total participants 74 (34 true acupuncture; 40 sham control)	Intervention: 1 time per week acupuncture treatment (20-minute sessions) over 6 weeks Control: Sham needling near but not on acupuncture points by blunt-tipped needles	Acupuncture: CV-6, CV-4, KI-3, ST-36, SP-6, LI-11, HT-6, auricular point (anti-depression)
Mao et. al 2014 [16]	Single center, three arm RCT to evaluate the effects of electro-acupuncture on CRF measured by BFI	Post-menopausal women with history of early stage breast cancer (stages I-III) Total of 67 participants divided in 3 groups: (1) 22 to electro-acupuncture (EA); (2) 22 to sham acupuncture (SA); (3) 23 to waitlist control (WLC)	Interventions: 2 times per week for 2 weeks, then 1 per week for 6 weeks for total of 10 treatments Control: Sham acupuncture Waitlist Control (WLC): Received self care information. WLC group patients were able to receive treatment after week 12 follow-up (All groups received self-care information)	4 local points around the joint with the most pain (2 pairs of electrodes with two hertz electro-stimulation were connected to these needles) and 4 distal points (SP-6, ST-36, PC-6, LV-3) to address fatigue and emotional symptoms

*Randomized control Trial (RCT), Cancer Related Fatigue (CRF), Multidimensional Fatigue Inventory (MFI), Brief Fatigue Inventory (BFI)

Pilot studies

In their 2009 study, Balk J et al. performed a modified, double-blind, randomized, placebo-controlled trial. Twenty-seven subjects enrolled, and 23 subjects completed the study. The subjects were women with localized breast cancer planning to undergo radiation. The radiation treatment occurred after either surgery alone or surgery in combination with chemotherapy. Subjects received acupuncture once or twice weekly during the 6-week course of radiation therapy. Needles were placed for 30 minutes each session at the following locations: KI-3, SP-6, LI-4, ST-36, and CV-6. The Park Sham device was used for sham acupuncture. Data were collected at baseline, 3 weeks, 6 weeks, and 10 weeks (4 weeks after the last acupuncture session). Improvement in symptoms were measured by the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F). Both the true and sham acupuncture groups had improvement in fatigue, quality of life, depression from baseline to 10 weeks. The true acupuncture group improved 5.50 (SE, +/- 1.48) points on the FACIT-F scale, whereas the sham acupuncture group improved by 3.73 (SE +/- 1.92) points. This difference was not statistically significant ($p = 0.37$). All subjects believed they were in the true acupuncture group. The study was underpowered due to poor recruitment so no statistical significance could be drawn. Overall, while this study did find that true acupuncture may be more beneficial than sham acupuncture, improved recruitment, and power (with at least 75 subjects) would allow for further elucidation of benefit.

In a 2011 study, Johnston et al. performed a pilot RCT to assess the feasibility of patient education integrated with acupuncture for management of CRF. The group enrolled 12 breast cancer survivors. Seven subjects were randomized to the control arm, which included usual care by physicians with use of pharmacologic and non-pharmacologic options. Five subjects were randomized to the intervention arm, in which they received eight acupuncture sessions in addition to usual care by physicians. Each acupuncture session was 50 minutes in duration. The acupuncture points used were aimed at improving the subjects' energy level and included the following points: LI-4, SP-6, ST-36, KI-3. Of note, at the discretion of the acupuncturist, other points were also used to address individual problems such as gastrointestinal symptoms (P-6, SP-4), emotional symptoms (LU-7, KI-4, LV-3, Yintang, GV-20), or sleep (HT5-7, KI-4, UB-62). Improvements in symptoms were measured by the Brief Fatigue Inventory (BFI) scale. Compared to the control group who received usual care, the intervention was associated with a 2.38-point decline in fatigue as measured by the BFI (90% CI from 0.586 to 5.014; $p < 0.10$). There was no statistical significance between the two groups. The study was limited due to its

small sample size. The recruitment was also felt to be biased as many subjects were self-referred. Additionally, the study was non-blinded. As the study showed promising results, the authors suggested further investigation with a larger double blind RCT to further investigate the benefits of acupuncture for management of CRF.

In 2013, Smith et al. studied the effects of acupuncture compared to sham and wait list control in a pilot single-center, mixed method RCT. A total of 30 participants were divided into 3 groups: acupuncture, sham control, and waitlist control. The subjects were women who completed chemotherapy at least 1 month previously and had fatigue, with score of 4 or more on the Brief Fatigue Inventory (BFI). Patients received twice weekly acupuncture over the first 3 weeks and then weekly for two more weeks, for a total of 8 treatment sessions. Each acupuncture session was 20 minutes in duration. Clinical outcomes were assessed at baseline, 2, 4, and 6 weeks. The sham control group received a non-invasive sham needle. The waitlist control group (WLC) were contacted every two weeks. Practitioners were advised to demonstrate empathy, respect, and a pleasant manner with all study participants. The acupuncture group received needles in five of the primary points administered at each session (bilateral KI-3, KI-27, ST-36 and SP-6 and unilateral CV-4 and CV-6 – points used in past studies that have been shown to help fatigue) and three secondary points with stimulation of needles. The sham group received non-invasive sham needles using the Park Sham device placed in fixed sham points on the lower back, abdomen, foot, lower leg, and forearm. Clinical outcomes were assessed at baseline, 2, 4, and 6 weeks. Fatigue score was measured using the Brief Fatigue Inventory. There was a significant reduction in fatigue for women receiving acupuncture compared with control after 2 weeks mean difference (MD) 5.3, 95% CI 4.5 to 6.2, $p=0.05$, and a significant improvement in well-being at 6 weeks for acupuncture compared with the sham and wait list control, MD 2.7, 95% CI 2.1 to 3.2, $p=0.006$. Women described their experience of acupuncture positively, and interview data may also offer explanations for the improved outcomes of well-being, with women reporting an improvement in sleep, mood, and relaxation. As this was a pilot study with only a small number of patients, the study was underpowered. The study also relied on self-referral recruitment which may present bias. Comparability between groups was difficult to assess as patients had different malignancies, comorbidities, and functional status.

In 2014, Kim DJ et al. performed a pilot, observational study to assess the role of acupuncture on improving immunity and cancer related fatigue. Ten subjects enrolled and completed the study. The subjects had a history of

cancer with ECOG performance score of ≤ 2 and received palliative operation, radiation, or chemotherapy 2 months prior to start of trial. The subjects received 2 acupuncture sessions weekly for 2 weeks, for a total of 4 sessions. Each session was 20 minutes in duration; five acupoints were used, including LU-8, BL-66, SI-5, TE-4, and CV-12. The subjects were assessed before and after acupuncture and at 2 weeks follow-up. There was a statistically significant increase in the number of CD3+ ($P = 0.023$) and CD8+ cells ($P < 0.001$) and T-cell subsets, as well as a decrease in the fatigue severity scale (FSS) score ($P = 0.001$) after acupuncture. The authors concluded acupuncture may improve the immune system by increasing the counts of a few immune cells and relieve fatigue in cancer patients by decreasing FSS scores. The study was limited as there was no control group, and it was not blinded. Additionally, the sample size was also small with short follow-up of two weeks.

Randomized Control Trials

Molassiotis et al. conducted a multicenter, two-armed RCT in 2012 and found that acupuncture was an effective intervention for improving CRF and patient's quality of life. Three hundred two subjects with breast cancer—stage I, II, or IIIa—enrolled in the study. All subjects had completed chemotherapy at least 1 month but not >5 years previously. They also reported at least a moderate level of persistent fatigue on a single item 10-point scale. The researchers randomly assigned 75 patients to usual care and 227 patients to acupuncture in addition to usual care, a ratio of 1:3. The usual care group received a booklet with information about fatigue and its management. The intervention arm received usual care in addition to treatment by acupuncturists once a week for 6 weeks. Each 20-minute acupuncture session used three acupuncture points: ST 36, SP 6, LI 4. Additional points were selected by the acupuncturists at their discretion based on clinical exam, including Gb-34, SP-6, SP-9, and SP-11. The primary outcome was general fatigue assessment at 6 weeks, measured by the Multidimensional Fatigue Inventory (MFI). The MFI includes measures of General Fatigue, Physical Fatigue, Mental Fatigue, anxiety, depression, and quality of life. The difference in the mean General Fatigue score between the intervention arm and usual care arm was -3.11 ($P < .001$). The intervention also improved all other fatigue aspects measured by MFI, including Physical Fatigue and Mental Fatigue, anxiety and depression, and quality of life. The study did have limitations. There was no sham control group, and the trial was unblinded, with risk of assessment bias. Additionally, the subjects were self-referred with a highly selected sample.

In 2013, Molassiotis et al. performed a nested, multicenter, phase III unblinded, pragmatic, RCT using a three-group design to assess maintenance acupuncture

benefits vs. self-acupuncture in treating fatigue after initial course of in-clinic acupuncture. The subjects were the same breast cancer patients from their 2012 trial who had already completed 6 weekly sessions of clinic-based acupuncture; these subjects were re-randomized to 3 groups: with 65 to acupuncturist-delivered sessions, 67 to self-acupuncture/self-needling, and 65 to no further acupuncture sessions. A total of 197 subjects enrolled. The acupuncturist-delivered group received maintenance therapy weekly for 4 weeks with an acupuncturist. The acupuncture sessions were 20 minutes in duration, and needles were placed in 3 points: ST 36, SP 6, LI 4. The primary outcome was general fatigue, measured by Multidimensional Fatigue Inventory (MFI) at 4 weeks, 10 weeks, and 18 weeks. They reported self-acupuncture as an acceptable, feasible, and safe maintenance treatment for patients with CRF. However, maintenance acupuncture did not yield significant improvements beyond initial in-clinic acupuncture sessions. Primary outcome scores were equivalent between the acupuncturist-delivered acupuncture and self-acupuncture ($P > 0.05$). A non-significant trend in improving fatigue was observed at the end of 4 weeks in the combined acupuncture arms ($P = 0.07$). The study was limited by low power. Additionally, there was substantial missing data at week 10 (23.3%) and week 18 (29.9%), as many patients did not return for final assessments. This could represent non-adherence to therapy or decreasing clinical improvements with treatments. Furthermore, the study was non-blinded and cannot rule out possible placebo effect or assessment bias.

In a 2013 study, Deng et al. performed a single-center, two armed, randomized, sham-controlled study and found that both true and sham acupuncture helped reduce post-chemotherapy chronic fatigue. One hundred one patients initially enrolled, and 74 completed the study (34 in true acupuncture group, 40 in sham control). The subjects included any cancer patients reporting significant fatigue persisting for at least 2 months following the completion of chemotherapy. The subjects were randomized to either receive true or sham acupuncture. Both true and sham acupuncture were performed once weekly for 6 weeks. Each session was 20 minutes with 14 needles inserted at the following points: CV-6, CV-4, KI-3, ST-36, SP-6, LI-11, HT-6, auricular point (anti-depression). The primary endpoint was assessed using the Brief Fatigue Inventory (BFI) score at the end of 6 weeks, and at 6-month follow-up. At 6 weeks, BFI scores fell by about one point between baseline and post-intervention in both groups, with no statistically significant difference between the two groups. No long-term reduction of fatigue scores was observed at the 6-month evaluation. The study had multiple limitations. Firstly, the study had a number of patients (13 in acupuncture group, 11 in sham group) who did not complete post-treatment follow-up questionnaire. Treatments were

provided at a tertiary referral center in a large city, and many patients had travel difficulties to receive treatments. The comparability between groups of patients is difficult to assess as all had various malignancies and comorbidities.

In 2014, Mao studied the role of electroacupuncture for fatigue, sleep, and psychological distress in breast cancer patients with joint pain from aromatase inhibitors. The authors performed a single center, three arm RCT and demonstrated electroacupuncture to be beneficial in improving fatigue, anxiety, and depression. In contrast, sham acupuncture only improved depression for patients with aromatase induced arthralgias. Sixty-seven subjects were enrolled in the study, divided into 3 groups: 22 in the electro-acupuncture group, 22 to sham acupuncture group, and 23 into the wait list control group. The subjects were all postmenopausal women with breast cancer (stages I-III) who self-reported joint pain attributable to aromatase inhibitors (Anastrozole, Letrozole, Exemestane). The joint pain was present for at least 3 months and was assessed at a level of 4 or more on 0-10 numerical rating scale. Subjects received acupuncture twice a week for two weeks then weekly for six more weeks for a total of 10 treatments over 8 weeks. The electro-acupuncture group received acupuncture needles in 4 points around the most painful joint as well as 4 additional distal points to address depression, anxiety, and fatigue (SP-6, ST-36, PC-6, LV-3). Two pairs of electrodes were connected at the needles adjacent to the painful joint(s) with two hertz electrostimulation. Sham acupuncture was performed using Streitberger non-penetrating needles at non-acupuncture, non-trigger points at least 5 cm from the joint where pain was perceived to be maximal. The acupuncturists turned the dial of the electrostimulation unit to a different channel so subjects perceived a blinking light without electric current. The duration of needle placement for both treatment groups was 30 minutes. The waitlist control group received the same information as other groups regarding management of joint pain such as staying physically active and continuing current pharmacologic (over-the counter or prescription) therapies.

Clinical outcomes were assessed at 2, 4, and 8 weeks during treatment; and then 4 weeks post-treatment (week 12). Fatigue was measured by the Brief Fatigue Inventory (BFI). Of the 67 randomly assigned patients, baseline pain interference was associated with fatigue (Pearson correlation coefficient $r = 0.75$, $p < 0.001$), sleep disturbance ($r = 0.38$, $p = 0.0026$), and depression ($r = 0.58$, $p < 0.001$). Compared to the WLC, electro-acupuncture produced significant improvement in fatigue ($p = 0.0095$) during the 12-week intervention and follow up period. In contrast, sham acupuncture did not produce significant reduction in fatigue and anxiety symptoms but produced significant improvement in depression compared with WLC ($p = 0.0088$). The study was limited as it was

powered to detect a difference between electroacupuncture and waitlist control; however, was not powered to detect significant differences between electroacupuncture and sham acupuncture. Additionally, the follow-up period was too short to detect differences between electro-acupuncture and sham acupuncture. Of note, the choice of acupuncture points was primarily targeted for treating pain rather than addressing fatigue.

Discussion

Our systematic review was designed to evaluate the clinical applicability of acupuncture for symptom management, especially in managing cancer related fatigue (CRF). Fatigue is a common undertreated symptom in patients with cancer due to the lack of effective therapeutic options in conventional medicine. Cancer related fatigue is thought to be due to various somatic and psychological factors. The mechanism of acupuncture therapy for CRF is unknown, but researchers theorize that acupuncture may help with the downregulation of pro-inflammatory cytokines or an increase of T lymphocytes.³ Another possible explanation may involve nonspecific placebo effects related to the patient's beliefs that the treatment intervention will produce benefits as well as the therapeutic alliance between acupuncturist and patient. The placebo effect though, may not provide a complete explanation for observed benefit as some studies reported sham acupuncture to be less effective.

We identified 7 randomized control trials (RCTs) and 1 observational study with a total of 715 patients from 2009-2019. Three of the trials were pilot RCTs, and the other four were larger scale RCTs. Due to the heterogeneity of the data, the varying study designs, and the differences between the participants, meta-analysis could not be performed.

These 8 trials all favored acupuncture as an adjunct treatment for CRF. All the trials described the treatment acupoints. Of the eight trials, seven of the trials included SP-6, (a convergent acupuncture point for multiple meridian channels) and ST-36, (classic acupoint to improve energy). Both of these points are considered energy-associated points. Six of the trials utilized weekly acupuncture for 20- to 30-minute sessions, while 2 utilized twice weekly acupuncture sessions. Given that CRF is a more entrenched symptom, Deng et al proposed that more frequent therapies (e.g. 2 to 3 times weekly) may be needed to see improvement in symptoms.¹⁵ This is especially relevant as community acupuncturists who treat CRF often see patients 2-3 times per week through the course of cancer treatments.

These published RCTs also have limitations. Six of the eight studies had a sample size < 100 and four had sample sizes < 30 . Due to the small sample size, these 4 pilot studies were underpowered. Although these studies showed positive results, four of the eight RCTs reported statistically non-significant improvement due to the limited power. Two trials had larger sample sizes (197 participants and 302 participants) and relatively high methodological quality.^{13,14} Another limitation

that was not fully addressed were the various associated symptoms that may play a role in fatigue, such as pain, sleep disturbance, nutrition, and activity level. The severity of these symptoms and other factors may have impacted the severity of fatigue and the study outcomes on the role of acupuncture.

Additionally, given the nature of the study intervention and design, the studies were potentially subject to a high risk of bias. Four of the studies (Johnston, Kim, Molassiotis 2012, Molassiotis 2013) were not blinded and did not have a sham control and may have introduced assessment bias.^{10,12-14} Furthermore, participation in the studies relied on self-referral with selection bias and may have skewed results towards more positive outcomes.

Our review has several limitations. First, while we utilized an extensive search methodology, we do not know if we have identified all relevant trials. We did not search for trials published in different languages. Secondly, publication bias may also have prevented negative studies from being published. Thirdly, comparisons were difficult to elicit due to the heterogeneous interventions and cancer populations. This precluded performing a formal meta-analysis.

All the trials had differences with regards to design, sample size, intervention, fatigue measurement, and treatment modalities. The diversity and relatively few number of randomized control trials (RCTs) in the literature limit our conclusions. A uniform acupuncture protocol and fatigue measurement tool should be developed for future studies.

In conclusion, though the evidence from current RCTs investigating acupuncture for treating CRF is not definitive, it does show trends toward positive results and promising potential. All studies have attempted to recruit patients after the development of debilitating cancer-related fatigue and worsening quality of life. The positive results demonstrated by the current studies utilizing acupuncture for patients with CRF suggest consideration for the proactive and concurrent use of acupuncture in addressing cancer related fatigue, especially if utilized for those undergoing chemotherapy treatments. The early integration of acupuncture into oncologic treatment may not only reduce fatigue, but also serve as a potential therapeutic means of preventing other debilitating cancer related symptoms.

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