Effects of Acupuncture and Acupressure on Cancer-Related Fatigue: A Systematic Review

Wai-man Ling, MScN, RN, FHKAN, Liza Y.Y. Lui, MN, RN, Winnie K.W. So, PhD, RN, and Kuen Chan, MBBS, FRCR, FHKCR, FHKMA

Purpose/Objectives: To critically examine the evidence for acupuncture and acupressure in the management of cancer-related fatigue (CRF) in adult patients with cancer.

Data Sources: 18 databases were searched for randomized, controlled trials published in English and Chinese through April 2014.

Data Synthesis: Given the heterogeneity of data, meta-analysis was not conducted. A six-step thematic analysis method was used to synthesize the results.

Conclusions: Although results are inconclusive, acupuncture and acupressure tend to be effective in relieving CRF, with the former producing a greater improvement. Future research is recommended to contribute further evidence.

Implications for Nursing: Nurses should know about the relative effectiveness of acupuncture and acupressure in the management of CRF to educate and support their patients.

Key Words: fatigue; cancer; acupuncture; acupressure; systematic review

ONF, 41(6), 581–592. doi: 10.1188/14.ONF.581-592

The National Comprehensive Cancer Network ([NCCN], 2014) defined cancer-related fatigue (CRF) as a "distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and interferes with usual functioning" (p. FT-1). CRF is one of the most common and distressing symptoms in patients with cancer (Chan & Molassiotis, 2000; Given, 2008; Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003; Kohara et al., 2004; Stone & Minton, 2008) that affects 50%–100% of patients (Campos, Hassan, Riechelmann, & Del Giglio, 2011; Newton, Hickey, & Marrs, 2009; Prue, Rankin, Allen, Gracey, & Cramp, 2006; So et al., 2009) and is a complex and multidimensional phenomenon (Chan, Chair, & Chui, 2009; Escalante & Manzullo, 2009; Given, 2008; Kirshbaum, 2010; Morrow, 2007). Contrary to acute fatigue, CRF is unlikely to be relieved by rest, sleep, food, or water (Chan et al., 2009; Given, 2008; Kirshbaum, 2010; National Cancer Institute [NCI], 2012; Prue et al., 2006). It may last for 5–10 years after the completion of treatment in many cancer survivors (Andrykowski, Donovan, Laronga, & Jacobsen, 2010; Bower et al., 2006; Crom, Hinds, Gattuso, Tyc, & Hudson, 2005; Given, 2008; Stone & Minton, 2008).

Patients with CRF may find it difficult to perform even simple daily activities (Curt et al., 2000). They may also suffer from psychological side effects (Curt et al., 2000; Morrow, 2007; NCI, 2012) and be forced to quit their jobs and limit social interaction (Chan & Molassiotis, 2000; Curt et al., 2000). These adverse effects can extend to the primary caregivers and family who will be required to spend more time taking care of patients (Chan & Molassiotis, 2000; Curt et al., 2000). It then undermines the family's financial well-being, giving rise to anxiety, worry, and feelings of guilt (Chan & Molassiotis, 2000; Curt et al., 2000).

The exact etiology of CRF remains unclear (Given, 2008; NCCN, 2014; Wang, 2008), and CRF has no single cause (Chan & Molassiotis, 2000; Ryan et al., 2007; Stricker, Drake, Hoyer, & Mock, 2004). A number of contributory factors have been identified, including tumor burden, treatment-related effects, and comorbidities (e.g., malnutrition, infection, organ failure, renal insufficiency, thyroid dysfunction, pain, sleep disturbance, psychological challenges, ineffective personal coping) (Kirshbaum, 2010; Wang, 2008). Coexistence of and interplay between fatigue, pain, sleep disturbance, and psychological challenges have been frequently reported in the literature (Beck, Dudley, & Barsevick, 2005; Dodd, Miaskowski, & Paul, 2001; Fox, Lyon, & Farace, 2007; Maliski, Kwan, Elashoff, & Litwin, 2008; Prue et al., 2006; So et al., 2009).

Management of CRF includes pharmacotherapy, elevation of hemoglobin, exercise, energy conservation, activity management, psycho-educational interventions, diet and nutrition management, sleep therapy, management of distressing symptoms, and complementary and

alternative medicine (Mitchell, Beck, Hood, Moore, & Tanner, 2007). However, a lack of robust evidence exists to inform the best management (Payne, Wiffen, & Martin, 2012), and evidence for many strategies is limited or mixed (Mitchell et al., 2007; NCCN, 2014). In addition, the potential side effects and contraindications of some interventions may limit clinical use (Campos et al., 2011; NCCN, 2014). Caregiver-initiated interventions, including acupuncture and acupressure, are of special value for patients with cancer who are too weak or otherwise not suited for exercise (Mitchell et al., 2007), and evidence is evolving to support their use (Campos et al., 2011; Lee & Frazier, 2011; Mitchell et al., 2007; NCCN, 2014).

Although a few systematic reviews on acupuncture have been published (Finnegan-John, Molassiotis, Richardson, & Ream, 2013; Garcia et al., 2013; He, Wang, & Li, 2013; Posadzki et al., 2013), the current review is warranted for several reasons. First, the period of the literature search extends to April 2014, and four new randomized, controlled trials (RCTs) published in 2013 are included in the current study (Deng et al., 2013; Liu, Liu, & Tu, 2013; Molassiotis et al., 2013; Smith, Carmady, Thornton, Perz, & Ussher, 2013). Second, this review includes 11 RCTs on CRF, more than appear in the other reviews listed previously. Only four studies were not included in the review, but one was an underpowered, low-quality unpublished master's thesis written in Korean (Oh, 2009), which was not accessible to or understood by the authors. The other three were on moxibustion (Chen, Wang, Xue, & Xu, 2011; Qin & Liu, 2012; Yang, Yu, Xu, Wang, & Jing, 2012) and beyond the scope of the interventions concerned in the authors' clinical question. Third, unlike some reviews (Finnegan-John et al., 2013; Garcia et al., 2013; Posadzki et al., 2013), the current review deliberately includes acupressure as an intervention for CRF because its noninvasive nature renders it more adaptive to nursing practice. Acupressure is safer than acupuncture and free of risk of infection, is suitable for patients with a phobia of needles, is easy to learn and use, can be done anywhere by patients or caregivers after simple training, and is more affordable for patients (Gooneratne, 2008; Lun, 2012; Tsay, 2004). In addition, as a noninvasive substitute for acupuncture (Lun, 2012), the inclusion of acupressure in this review can provide additional information about the effectiveness of acustimulation on CRF.

The authors intended to critically examine the evidence for the use of acupuncture and acupressure in managing CRF in adult patients with cancer. Research questions included

- Are acupuncture and acupressure effective in managing CRF in adult patients with cancer?
- Do differences exist in the effectiveness of acupuncture and acupressure in dealing with CRF, and what is the magnitude of the differences?
- What is the optimal intensity and duration of treatment required?

Methods

Literature Search

An electronic search was performed using the following databases: AMED, British Nursing Index, CINAHL®, Evidence Based Medicine Reviews, Embase, Journals@Ovid, MEDLINE®, Physiotherapy Evidence Database, ProQuest, PubMed, ScienceDirect, SpringerLink, TRIP, Wiley Online Library, China Academic Journals Full-Text Database, and Wanfang Data China Online Journals. By means of the PICO (population, intervention, comparison, and outcome) format, the key words *fatigue, cancer, acupuncture,* and *acupressure* were derived from the research questions for use in the literature search. The use of synonyms, wildcard characters, and Boolean operators were also considered. The final search strategy employed for the English databases was *fatigue* AND *acup** AND (*cancer** OR *neoplas** OR *malignan**). Equivalent terms in Chinese were used for the two Chinese databases. The review period was from the inception of each database through April 2014, and the reference lists of all selected articles were searched for additional studies. OpenSIGLE and Wanfang Data Conference Papers Full-Text Database were used to retrieve unpublished studies.

Articles to be included were RCTs of acupuncture and acupressure for CRF in adult patients with cancer regardless of the type of cancer, duration of disease, and type of treatment received. CRF was a key outcome to be clearly measured and reported. Only studies published in English or Chinese were included. Articles whose sole target participants were patients with fatigue other than CRF were excluded. Studies using shiatsu or reflexology for therapeutic intervention were also excluded because these two therapies are not congruent with acupressure in their theoretical basis or manipulation methods.

Two reviewers independently appraised the methodologic quality of the full texts of all potentially eligible articles by means of the standard checklist for RCTs developed by the Scottish Intercollegiate Guidelines Network ([SIGN], 2014). The 10 appraisal criteria for internal validity in the SIGN checklist were equally weighted. To provide an overall assessment, users were asked to code a study as "high quality," "acceptable," or "unacceptable–reject," according to its rigor in minimizing bias. Both reviewers then independently extracted the relevant information from the articles included for final review, using a standard data extraction form. Any disagreements between the reviewers throughout the process of quality appraisal and data extraction were resolved by a third reviewer.

A total of 716 potentially relevant studies were identified. Of these, 137 duplicates were removed, leaving 579 articles for further consideration. After a review of titles and abstracts, 17 articles were found to meet the full inclusion criteria. However, only 16 gave access to the full-text article and were retrieved for detailed examination. Five studies were excluded because they focused on animals. Consequently, 11 studies were included in the final review (see Figure 1).

Given the heterogeneity of these studies in terms of the stage of cancer, onset of CRF, its measurement and baseline level, intervention design and control used, meta-analysis was not conducted. The characteristics and results of the studies were analyzed by the six-step thematic analysis method advocated by Aveyard (2010). Findings were reported in tabular and narrative forms.

Eleven studies (Balk, Day, Rosenzweig, & Beriwal, 2009; Deng et al., 2013; Johnston et al., 2011; Lim, Wong, & Aung, 2011; Liu et al., 2013; Molassiotis, Sylt, & Diggins, 2007; Molassiotis et al., 2012, 2013; Smith et al., 2013; Xu, Gu, & Qiao, 2010; Zick et al., 2011) were analyzed in the current review (see Table 1). They were published from 2007–2013 and originated from five countries: the United States (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; Zick et al., 2011), the United Kingdom (Molassiotis et al., 2007, 2012, 2013), China (Liu et al., 2013; Xu et al., 2010), Australia (Smith et al., 2013), and Canada (Lim et al., 2011). In studies, 731 participants were found in total, with 13–302 participants per study. Recruited mainly from outpatient centers, the participants had an average age range of 52–59.4 years, with the youngest being age 20 years and the oldest being age 81 years. They had a wide range of cancer diagnoses, with breast cancer the most common, and suffered from different degrees of fatigue before the study.

Measures

A variety of outcome measurement tools were used in the studies. Those used for measuring fatigue were the Brief Fatigue Inventory (BFI) (Deng et al., 2013; Johnston et al., 2011; Liu et al., 2013; Smith et al., 2013; Zick et al., 2011), the Multidimensional Fatigue Inventory (MFI) (Molassiotis et al., 2007, 2012, 2013), the fatigue score of the Edmonton Symptom Assessment System (ESAS) (Lim et al., 2011), the Piper Fatigue Scale (PFS) (Xu et al., 2010), the Functional Assessment of Chronic Illness Therapy–Fatigue Subscale (FACIT-F), and the Cancer-Related Fatigue Distress Scale (CRFDS) (Balk et al., 2009).

Of the 11 trials, eight used acupuncture in the study arm (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007, 2012, 2013; Smith et al., 2013), and five used acupressure (Johnston et al., 2011; Liu et al., 2013; Molassiotis et al., 2007; Xu et al., 2010; Zick et al., 2011). In Johnston et al.'s (2011) study, acupuncture was a major therapy in the study arm, with acupressure being a minor auxiliary intervention as a component in the patient self-care education program. This was the only study that adopted a combination of acupuncture and acupressure. Molassiotis et al. (2007) made a direct comparison of acupuncture and acupressure by using a three-arm RCT design, with a true acupuncture group, a true acupressure group, and a sham acupressure group. It was the only study to conduct such a valuable comparison.

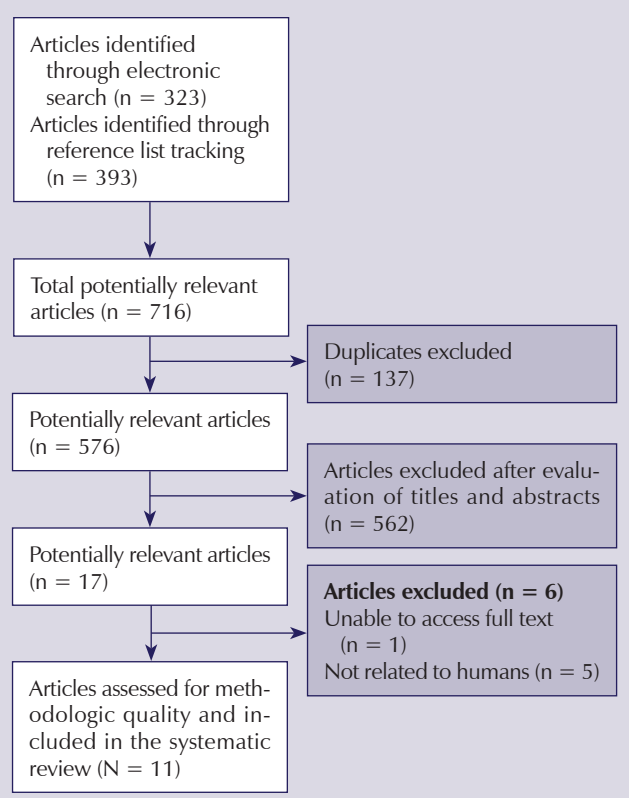

Figure 1. Flow Diagram of Systematic Review Process

Three studies adopted a multimodal therapeutic protocol in their study arms (Johnston et al., 2011; Liu et al., 2013; Xu et al., 2010). Johnston et al. (2011) added a patient self-care education program with self-conducted acupressure to acupuncture treatment. Liu et al. (2013) offered CRF education and aerobic exercise in addition to auricular acupressure. Xu et al. (2010) added abdominal breathing exercise and music therapy to self-conducted acupressure. A great variety of acupoints were used across the 11 studies, with ST36, SP6, and KI3 being the most commonly chosen.

All of the included studies were acceptable in quality but had methodologic flaws with an associated risk of bias. Eight were underpowered, six being pilot studies with a small sample size (range = 13–47) (Balk et al., 2009; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007; Smith et al., 2013; Zick et al., 2011). Two were underpowered because of a high attrition rate (Deng et al.,

Table 1. Studies of Acupressure and Acupuncture Therapy for Cancer-Related Fatigue

Study	Design and Sample	Interventions	Treatment	Findings	Limitations
Balk et al., 2009	Single-center, two-armed, blinded RCT with 27 participants who were predominantly women with localized breast cancer undergoing postoperative RT but not concurrent CRT and having fatigue (FACIT-F score of 44 or less)	**Intervention:** True acupuncture given once or twice weekly during the 4- to 6-week period of RT. **Control:** Sham acupuncture with the same frequency and duration as that of true acupuncture. Two acupuncturists involved	Treatment for 4–6 weeks during RT with post-treatment follow-up after four weeks	The intervention group showed greater improvement on the FACIT-F score (5.5, SE = 1.48) than the control group (3.73, SE = 1.92) at week 10, but it was not statistically significant (p = 0.37). CRF distress and QOL improved during the study period but were not statistically significant between groups or within groups.	Small, underpowered pilot study High dropout rate in the control group (27%) Sham acupuncture is an active control rather than an inert placebo
Deng et al., 2013	Single-center, two-armed, blinded RCT with 98 patients with cancer having significant fatigue (BFI of 4 or greater) for at least two months post-chemotherapy	**Intervention:** True acupuncture **Control:** Sham acupuncture using sham acupoints with sham needles (participants were allowed to cross over to true acupuncture at week 7) More than one acupuncturist, but exact number not reported	Treatment occurred weekly for six weeks, with post-treatment follow-up at six months.	Fatigue was measured by BFI, and participants showed small improvements at weeks 6–7 in both groups with no statistically significant difference between groups. Mean difference was 0.04 (95% CI [–0.57, 0.66], p = 0.9). No long-term improvement in fatigue was found from the time immediately after true acupuncture to the six-month follow-up. Mean difference was –0.14 (95% CI [–0.84, 0.56], p = 0.7). Baseline fatigue, depression, anxiety, gender, age, and hemoglobin did not relate to outcome.	Underpowered study because of high dropout rate (25% overall) Comparability between groups at the start of study is questionable because stage of cancer, activity level, and performance status between the groups are unclear. ITT analysis was not strictly followed.
Johnston et al., 2011	Single-center, two-armed, nonblinded RCT with 13 breast cancer survivors who completed primary therapy, were cancer-free, and were having significant fatigue (BFI of 4 or greater)	**Intervention:** Combination of a patient education program on self-care with acupressure as well as acupuncture with usual care from physicians **Control:** Usual care from physicians One acupuncturist involved	Weekly treatment for eight weeks with post-treatment follow-up at week 10	Compared to the control group, the intervention group was associated with a 2.38-point decline in fatigue measured by BFI (90% CI [0.586, 5.014], p = 0.078), which was statistically significant and clinically meaningful. No statistically significant improvement was found in the cognitive complaints.	Small, underpowered pilot study As a multimodal therapy, precise effect of acupuncture alone is unknown. Nonblinded study with inadequate control for assessment bias and placebo effects Sampling bias may exist (high refusal rate of 54%) Comparability between groups at the start of the study is questionable because comorbidities between groups are unclear. ITT analysis was not employed.
Lim et al., 2011	Single-center, two-armed, nonblinded, pilot RCT with 20 participants with cancer in palliative care with an estimated survival rate of at least three months	**Intervention:** Weekly acupuncture **Control:** Weekly nurse-led supportive care by an experienced palliative care nurse One acupuncturist involved	Weekly treatment for four weeks with post-treatment follow-up weekly for six weeks	For the immediate effect, ESAS score for tiredness was reduced by 2, on average, after each acupuncture session in the intervention group compared to no change in the control group. At the end of the follow-up, the ESAS score for tiredness was reduced by 1.25, on average, for the intervention group and 1.5 for the control group.	Small, underpowered pilot study High rate of attrition (20% overall) Nonblinded study with inadequate control for assessment bias and placebo effects Only descriptive statistics reported Comparability between groups at the start of the study is questionable. ITT analysis was not employed.

(Continued on the next page)

BFI—Brief Fatigue Inventory; CI—confidence interval; CRF—cancer-related fatigue; CRT—chemoradiation therapy; ESAS—Edmonton Symptom Assessment System; FACIT-F—Functional Assessment of Chronic Illness Therapy–Fatigue; ITT—intent to treat; MFI—Multidimensional Fatigue Inventory; NA—not available; PFS—Piper Fatigue Scale; QOL—quality of life; RCT—randomized, controlled trial; RT—radiation therapy; SE—standard error

Table 1. Studies of Acupressure and Acupuncture Therapy for Cancer-Related Fatigue *(Continued)*

Study	Design and Sample	Interventions	Treatment	Findings	Limitations
Liu et al., 2013	Single-center, two-armed, nonblinded RCT with 72 patients with all-stage ovarian cancer undergoing postoperative chemotherapy	**Intervention:** Usual discharge advice plus CRF education, auricular acupressure, and aerobic exercise **Control:** Usual discharge advice	Treatment lasted for 30 days with no post-treatment follow-up	Fatigue was measured by the BFI and was significantly improved in the intervention group by day 30 ($p < 0.01$)	Nonblinded study with unclear method of randomization and no concealment. Effectiveness study on a package of interventions; precise efficacy of auricular acupressure is unclear Low reporting quality, such as the lack of demographic characteristics of the two groups of participants Comparability between the groups is questionable (e.g., activity level, performance status).
Molassiotis et al., 2007	Single-center, three-armed, blinded RCT with 47 participants with cancer having significant fatigue (single-item fatigue score of 5 or greater) who were at least one month post-chemotherapy, had a life expectancy of greater than three months, and no cancer treatments scheduled during the study period	**Intervention:** Acupuncture group with 20-minute sessions three times per week for two weeks and acupressure group that was taught to do self-acupressure for one minute to each acupoint daily for two weeks **Control:** Sham acupressure group who were taught self-acupressure to three acupoints not associated with energy with the same frequency and duration as the acupressure group One acupuncturist involved	Treatment for two weeks with post-treatment follow-up after two weeks	General fatigue score, measured by the MFI, significantly improved in acupuncture and acupressure groups. General fatigue score showed a 36% improvement in the acupuncture group, 19% in the acupressure group, and 0.6% in the sham acupressure group at the end of the two-week intervention. Improvements were still observed two weeks after the final treatment (22%, 15%, and 7%, respectively).	Small, underpowered pilot study High overall dropout rate (26%) Inadequate control of the placebo effect for the acupuncture group Risk of selection bias and undertreatment may exist. Comparability among the groups is questionable (e.g., stage of cancer, comorbidities). ITT analysis was not strictly followed; randomized participants with missing outcomes were excluded.
Molassiotis et al., 2012	Multicenter, two-armed, nonblinded RCT with 302 participants with stage I, II, or IIIa breast cancer having significant fatigue (single-item fatigue score of 5 or greater), having completed chemotherapy for at least one month and up to five years, and not planning chemoradiation during the study period	**Intervention:** Weekly acupuncture in addition to usual care using a detailed information booklet about coping with fatigue **Control:** Usual care using a detailed information booklet about coping with fatigue only 12 acupuncturists involved	Weekly treatment for six weeks with post-treatment follow-up at weeks 10 and 18	Reduction in general fatigue score, measured by the MFI, at week 6 was significantly greater in the intervention group. Difference in the mean general fatigue score between the intervention and control groups was –3.11 (95% CI [–3.97, –2.25], $p < 0.001$). Acupuncture had beneficial effects on all secondary outcomes (i.e., mental fatigue, activity, motivation, anxiety, depression, and QOL). Baseline fatigue, age, maintenance hormone therapies, and expectation of effect did not relate to outcome.	Placebo effects and assessment bias cannot be totally eliminated. Sampling bias may be possible. Comparability between the groups is questionable (e.g., activity level, performance status).

(Continued on the next page)

BFI—Brief Fatigue Inventory; CI—confidence interval; CRF—cancer-related fatigue; CRT—chemoradiation therapy; ESAS—Edmonton Symptom Assessment System; FACIT-F—Functional Assessment of Chronic Illness Therapy–Fatigue; ITT—intent to treat; MFI—Multidimensional Fatigue Inventory; NA—not available; PFS—Piper Fatigue Scale; QOL—quality of life; RCT—randomized, controlled trial; RT—radiation therapy; SE—standard error

Table 1. Studies of Acupressure and Acupuncture Therapy for Cancer-Related Fatigue *(Continued)*

Study	Design and Sample	Interventions	Treatment	Findings	Limitations
Molassiotis et al., 2013	Nested, multicenter, three-armed, nonblinded, pragmatic RCT to assess the effectiveness of maintenance acupuncture with 197 patients with stage I, II, or IIIa breast cancer who had significant fatigue, completed chemotherapy at least one month and up to five years, and were not planning to undergo CRT during the study.	**Intervention:** Acupuncturist-delivered maintenance group (AMG) or self-needling maintenance group (SMG) (participants were taught to needle themselves at two acupoints, ST36 and SP6) **Control:** No maintenance group (NMG) used as control. 12 acupuncturists involved	Maintenance therapy for four weeks, with post-maintenance therapy follow-up at week 18	No statistically significant difference was found in the mean change of the general fatigue score, as measured by the MFI, between AMG and SMG at week 10 ($p = 0.18$) and week 18 ($p = 0.36$). The difference in general fatigue score at week 10 between intervention groups and the control group was –0.76 (95% CI [–1.5, 0.06], $p = 0.07$) and 0.57 (95% CI [–0.49, 1.64], $p = 0.29$) at week 18. Intervention groups failed to demonstrate extra maintenance effect. Effects of the initial six weekly acupuncture treatments were maintained in all three groups. Improvement seen in intervention groups at week 10 was clinically nonsignificant.	Placebo effects and assessment bias (a nonblinded study) cannot be totally eliminated. Underpowered study because of high overall dropout rate (23% at week 10, 30% at week 18) Comparability among the groups is questionable (e.g., activity level, performance status). ITT analysis was not strictly followed; randomized participants with missing outcomes were excluded.
Smith et al., 2013	Single-center, two-armed, blinded RCT with 29 participants with breast cancer having significant fatigue (BFI of 4 or greater) for at least one month postchemotherapy	**Intervention:** True acupuncture **Control:** Sham acupuncture group using sham acupoints with sham needles or wait-list control group with no treatment Six acupuncturists involved	Twice weekly treatment for three weeks followed by weekly treatment for three weeks with no post-treatment follow-up	Fatigue was measured by BFI and showed statistically significant improvement at week 2 for the true acupuncture group. Mean difference was 5.3 (95% CI [4.5, 6.2], $p = 0.05$). The improvements were not statistically significant at weeks 4 and 6. Fatigue improvement by true acupuncture was most prominent at week 2 but plateaued after week 4, which was attributed it to the treatment intensity. Better sleep, improved mood, and relaxation were identified as the explanations for fatigue improvement by the concurrent in-depth interviews.	Small, underpowered pilot study Comparability between groups at the start of study is questionable because stage of cancer, comorbidities, activity level, and performance status between the groups are unclear.
Xu et al., 2010	Single-center, two-armed, nonblinded RCT with 80 hospitalized patients with breast cancer who underwent modified radical mastectomy	**Intervention:** Combination of self-acupressure, abdominal breathing exercise, music therapy, as well as routine nursing care **Control:** Routine nursing care	Treatment for 10 days with no post-treatment follow-up	Fatigue was measured by the PFS and was significantly improved in the intervention group compared to the control group. PFS on day 10 was 57.58 (SD = 8.94) for the intervention group and 66.03 (SD = 6.47) for the control group ($p < 0.01$).	Nonblinded study with randomization done by simple drawing; no concealment reported. As a multimodal therapy, precise effect of acupressure alone is unknown. Comparability between the groups is questionable (e.g., postoperative complications, concurrent medications).

(Continued on the next page)

BFI—Brief Fatigue Inventory; CI—confidence interval; CRF—cancer-related fatigue; CRT—chemoradiation therapy; ESAS—Edmonton Symptom Assessment System; FACIT-F—Functional Assessment of Chronic Illness Therapy–Fatigue; ITT—intent to treat; MFI—Multidimensional Fatigue Inventory; NA—not available; PFS—Piper Fatigue Scale; QOL—quality of life; RCT—randomized, controlled trial; RT—radiation therapy; SE—standard error

Table 1. Studies of Acupressure and Acupuncture Therapy for Cancer-Related Fatigue *(Continued)*

Study	Design and Sample	Interventions	Treatment	Findings	Limitations
Zick et al., 2011	Single-center, three-armed, blinded pilot randomized trial with 43 participants who were predominantly breast and gynecologic cancer survivors with therapies completed for at least 12 weeks (except for ongoing hormone therapy), having significant fatigue (BFI of 4 or greater), and life expectancy of greater than six months	**Intervention:** High-intensity stimulatory (HIS) group that self-administered acupressure for 30 minutes twice a day for 12 weeks, low-intensity stimulatory (LIS) group that self-administered acupressure for 30 minutes three times a week for 12 weeks, and relaxation acupressure (RA) group that self-administered acupressure for 27 minutes twice a day for 12 weeks No inert control Three therapists involved	Treatment for 12 weeks with no post-treatment follow-up	BFI was significantly reduced across all treatment groups, with significantly greater reductions in the RA group at week 12. Mean reduction in BFI was 2.2 (SD = 1.6) for HIS group, 2.7 (SD = 2.2) for LIS group, and 4 (SD = 1.5) for RA group (p = 0.027). The effects remained significant after controlling for age, cancer type, cancer stage, and cancer treatment (p = 0.013). Regardless of study group, the majority of BFI improvement occurred during the first four weeks of acupressure, followed by a small additional reduction between weeks 4 and 7. Compliance was highest in the LIS group, but statistical significance was not achieved. No significant relationship was found between beliefs and expectations of acupressure and the decrease in BFI.	Small, underpowered pilot study Overall dropout rate was 19%, with 20% in the HIS group. Without inert control, effects of confounding variables (e.g., staff attention) cannot be ruled out, and placebo effect cannot be assessed. Comparability among the groups is questionable (e.g., activity level, performance status). ITT analysis was not strictly followed; randomized participants with missing outcome were excluded.

BFI—Brief Fatigue Inventory; CI—confidence interval; CRF—cancer-related fatigue; CRT—chemoradiation therapy; ESAS—Edmonton Symptom Assessment System; FACIT-F—Functional Assessment of Chronic Illness Therapy–Fatigue; ITT—intent to treat; MFI—Multidimensional Fatigue Inventory; NA—not available; PFS—Piper Fatigue Scale; QOL—quality of life; RCT—randomized, controlled trial; RT—radiation therapy; SE—standard error

2013; Molassiotis et al., 2013); the dropout rate was 20% or above overall in one of the arms in six studies (Balk et al., 2009; Deng et al., 2013; Lim et al., 2011; Molassiotis et al., 2007, 2013; Zick et al., 2011). Four studies used a double-blind design (Balk et al., 2009; Deng et al., 2013; Smith et al., 2013; Zick et al., 2011), and four had sham controls (Balk et al., 2009; Deng et al., 2013; Molassiotis et al., 2007; Smith et al., 2013). Without adequate blinding and good use of active and inert control, observer bias and placebo effects can hardly be excluded, and no firm conclusion can be drawn about the efficacy of the two acustimulation methods. Three studies used combination therapy in the experimental arm, which made the specific efficacy of acupuncture or acupressure unclear (Johnston et al., 2011; Liu et al., 2013; Xu et al., 2010). Intent-to-treat analysis was not strictly followed in six studies because of the exclusion of missing outcomes (Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007, 2013; Zick et al., 2011). Although the proper management of missing outcomes is difficult and controversial (Moher et al., 2012), sensitivity analysis with a "last value carried forward" approach, as in Molassiotis et al. (2012, p. 4,472), can render the results more convincing.

Effectiveness of Acupuncture and Acupressure

Seven out of eight acupuncture studies (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007, 2012; Smith et al., 2013) reported improvement in CRF, but only four were statistically significant (Johnston et al., 2011; Molassiotis et al., 2007, 2012; Smith et al., 2013). All four acupressure studies (Liu et al., 2013; Molassiotis et al., 2007; Xu et al., 2010; Zick et al., 2011) showed statistically significant improvement in CRF. Six studies conducted post-treatment follow-up assessments (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007; 2013). The four studies with a positive initial result for the main course of treatment (Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007, 2013) found that the CRF improvement could be maintained for as long as 12 weeks after treatment completion. However, results of the maintenance therapy study from Molassiotis et al. (2013) showed that the four-week maintenance of acupuncture following the six-week initial course of treatment gave no extra benefit in CRF improvement. Three studies did not provide any report of adverse events after treatment (Liu et al., 2013; Smith et al., 2013; Xu et al., 2010); for the other studies, either no adverse event or only minor transient events were reported. Therefore, acupuncture and acupressure are seen to be safe and well tolerated.

Only one trial studied the difference in effectiveness between acupuncture and acupressure in managing CRF (Molassiotis et al., 2007) and found statistically significant improvements in acupuncture and acupressure groups. In comparison with true and sham acupressure, acupuncture showed a significantly greater improvement in general fatigue score at the end of a two-week intervention (Molassiotis et al., 2007).

Optimal Intensity and Duration of Treatment

Great variation existed in the duration of treatment, from 2–10 weeks for acupuncture (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2007, 2012, 2013; Smith et al., 2013) and 10 days to 12 weeks for acupressure (Liu et al., 2013; Molassiotis et al., 2007; Xu et al., 2010; Zick et al., 2011). Except in the case of two studies (Johnston et al., 2011; Smith et al., 2013), the length of each acupuncture session was similar (about 20–30 minutes). Five of eight acupuncture studies adopted a weekly regimen for the entire course of treatment (Deng et al., 2013; Johnston et al., 2011; Lim et al., 2011; Molassiotis et al., 2012, 2013). For acupressure, the time spent on massaging each acupoint and the frequency varied to a great extent. Therefore, except for the length and frequency of acupuncture sessions, no consensus existed among the investigators, and no definite conclusions can be drawn regarding optimal intensity and duration of treatment.

Discussion

Some related studies may not have been identified, including unpublished studies, because of differences in search strategies and databases used. Because the search was limited to journals in English or Chinese, studies reported in other languages were not included.

The twin threats of placebo effects and observer bias are common in acupuncture and acupressure studies. To address these issues, the use of sham interventions and a double-blind design is indispensable. However, long and intense debates exist on sham control, and no consensus has been reached (Azad & John, 2013; Ernst & Canter, 2005; Molassiotis, 2013a, 2013b; Molassiotis & Richardson, 2013). One issue is the authenticity of sham-control methods. The sham intervention is not as inert as expected (the "more than sham" effect) because manipulation of the skin without puncturing the acupoints can produce certain physiologic effects (Balk et al., 2009, p. 10; Molassiotis et al., 2012). To keep participants blinded, practitioners using true intervention may need to sacrifice normal interactions with participants to confirm the *de qi* sensation (the "less than true" effect) (Balk et al., 2009, p. 10).

The existence of placebo effects cannot be negated in acupuncture or acupressure (Kaptchuk et al., 2008; Molassiotis & Richardson, 2013). Appropriate control and rigor in the assessment of placebo effects are needed. Molassiotis and Richardson (2013) have called for a consensus among professionals in the field, and Molassiotis et al. (2012) advocated the concurrent use of active (for attention control) and inert (without treatment at all) controls in future studies. Researchers should make clear whether they aim at an efficacy or effectiveness trial, as well as the rationale and the limitations inherent in these different lines of inquiry. In addition, treatment characteristics (e.g., intensity, timing, duration, acupoint selection, acupoint manipulations) are important in determining treatment effects (Molassiotis & Richardson, 2013). The wide variation in treatment characteristics across these studies makes the results less comparable and makes it difficult to draw conclusions about the effectiveness of acupuncture and acupressure.

Ernst (2009) noted that acupuncture was ineffective for many conditions, including fatigue, by referencing Cochrane Reviews. In the current review, all 10 studies investigating an initial main course of acupuncture or acupressure found improvements in CRF. Caution should be exercised when interpreting these results because of methodologic flaws; however, seven studies did show statistically significant improvements. Being the only adequately powered multicenter trial, Molassiotis et al. (2012) provided good evidence for the effectiveness of acupuncture versus enhanced standard care. However, bearing in mind the limitation of its pragmatic design, no firm conclusions can be drawn about the efficacy of acupuncture (Ernst & Canter, 2005).

Molassiotis et al.'s (2007) results support that acupuncture is more effective than acupressure in relieving CRF. The study hypothesized that acupuncture produced stronger stimulation and led to a better response. However, the results should be interpreted with caution because of the study's methodologic flaws. In addition, studies dealing with other symptoms show an inconsistent picture. For chemotherapy-induced nausea and vomiting (CINV), Ezzo et al.'s (2005) systematic review revealed that acupuncture was more effective than acupressure in reducing acute vomiting, but acupressure showed better results in reducing the severity of acute nausea. Further studies are needed to draw firm conclusions.

The study from Johnston et al. (2011) noted that the combination of acupuncture and acupressure may have specific value in CRF management. Though limited by the methodologic flaws, the study achieved a greater CRF improvement (66%) than the majority of the other studies. Early work on CINV has also supported that the use of acupressure following acupuncture prolongs the antiemetic effect (Dundee & Yang, 1990). Although Molassiotis et al. (2013) found weekly maintenance

acupuncture produced no extra effect on CRF relief after the main course of therapy, but it remains unclear whether maintaining acupressure with a different intensity and duration would also be without value.

The optimal intensity and duration of treatment are unclear for acupuncture and acupressure. According to their data set, Zick et al. (2011) found that at least four weeks were needed to obtain significant effects from acupressure, and seven weeks were needed to reach maximum effects; further study would be needed to determine if this can be extrapolated to acupuncture. All of the studies published in 2012 or later delivered acupuncture and acupressure for four to six weeks as the main course of therapy (Deng et al., 2013; Liu et al., 2013; Molassiotis et al., 2012; Smith et al., 2013); therefore, advocating treatment for four weeks or longer in future studies is warranted.

Acupuncture was carried out weekly in the majority of studies, which is supported by an earlier pioneer study from Vickers, Straus, Fearon, and Cassileth (2004). That study found that weekly acupuncture was as effective as performing acupuncture twice weekly and was more convenient for patients. Most of the investigators offered acupuncture for 20–30 minutes per session, which is a common practice recommended by the traditional Chinese medicine textbook (Liu, Liu, Fan, & Zhang, 2009).

Great variation existed in the intensity of acupressure in the four studies (Liu et al., 2013; Molassiotis et al., 2007; Xu et al., 2010; Zick et al., 2011), which was also seen in acupressure studies for other symptoms (Sun, Sung, Huang, Cheng, & Lin, 2010; Tsay, Rong, & Lin, 2003; Wu, Wu, Lin, & Lin, 2004). Lun (2012) recommended that the massage for each acupoint to last for two or three minutes until the *de qi* sensation occurs. A similar practice has been adopted by other seasoned acupressure researchers in fatigue management (Cho & Tsay, 2004; Tsay, 2004). Although two to three minutes per acupoint can be a good reference point for setting the massage time, details of the manipulation should also be mentioned with justification in future studies because the length of massage on an acupoint have therapeutic implications, according to the Chinese medicine theory (Lun, 2012).

No standard practice exists in acupressure frequency, which ranges from three times per week to once daily in studies for other symptoms (Reza et al., 2010; Sun et al., 2010; Tsay et al., 2003; Wu et al., 2004). Zick et al. (2011) found that patient adherence was poorer in high-frequency acupressure groups; twice daily was specified, but some patients reduced it to daily. In addition, that study's data set supported the argument that the duration of acupressure was more significant than frequency in fatigue improvement (Zick et al., 2011). Daily acupressure was also adopted by Johnston et al. (2011) and Molassiotis et al. (2007), which appears to be more practical for self-acupressure by patients.

CRF is associated with various comorbidities, including pain, nausea, vomiting, dyspnea, poor appetite, anxiety, and depression (Posadzki et al., 2013). Interplay between CRF, pain, sleep disturbance, and anxiety and depression has been frequently reported in the literature (Beck et al., 2005; Dodd et al., 2001; Fox et al., 2007; Maliski et al., 2008; Prue et al., 2006; So et al., 2009). Although these conditions may not have common underlying mechanisms, their coexistence gives rise to the concept of symptom clusters (Cleeland, 2007; Cleeland et al., 2000; Dodd et al., 2001; So et al., 2009). The importance of this interplay has been supported by a study by Vickers et al. (2004), which found that improvement in fatigue by means of acupuncture decreased by 6.5% for every one-point increase in the depression score.

Three of the studies included used combination therapy (multimodal approach) in the experimental arm (Johnston et al., 2011; Liu et al., 2013; Xu et al., 2010). Those additional interventions target the patient's psychological distress, sleep disturbance, and pain. Smith et al. (2013) identified better sleep, improved mood, and relaxation as the explanation for CRF improvement by way of in-depth patient interviews. Acupressure was found to have positive effects on sleep disturbance and depression in patients with cancer, and relaxation acupressure was more effective than stimulatory acupressure (Zick et al., 2011). Lim et al. (2011) and Dean-Clower et al. (2010) agreed that increased attention from the study acupuncturists and the relaxing environment of the acupuncture suite may contribute to CRF improvement. Molassiotis et al. (2007), Xu et al. (2010), and Zick et al. (2011) also highlighted the importance of sleep quality in the effects of acupuncture and acupressure for CRF. Patient empowerment in self-care interventions, including self-acupressure, could enhance self-efficacy and be conducive to CRF improvement (Johnston et al., 2011). Findings from these studies supported the significance of psychological distress and sleep disturbance in CRF management, and provided the grounds for a multimodal approach.

Acupuncture and acupressure are potentially effective interventions for managing multiple symptoms simultaneously (Capodice, 2010; Lee & Frazier, 2011; Molassiotis et al., 2012; O'Regan & Filshie, 2010; Sagar, 2008). Studies of acupuncture or acupressure for other symptoms have revealed these concurrent effects as well (Tsay, 2004; Tsay, Cho, & Chen, 2004). According to the Chinese medicine theory, an acupoint often produces multiple therapeutic effects for various symptoms (Liu et al., 2009; Wu & Gao, 2010). Acupoints ST36, SP6, and KI3, those commonly used in the reviewed studies, are also effective for insomnia and anxiety (Liu et al., 2009; Lun, 2012; Wu & Gao, 2010). Mao et al. (2009)

Knowledge Translation

Evidence supports the effectiveness of acupuncture on cancer-related fatigue (CRF), but the evidence is inadequate for its efficacy. ST36, SP6, and KI3 are the most commonly used acupoints with relation to CRF.

To exert its full effect, acupuncture or acupressure for CRF should last at least four weeks. Weekly acupuncture in 20- to 30-minute sessions is suggested.

Daily self-acupressure is more acceptable to patients, and a combination of acupuncture and acupressure may enhance effectiveness.

suggested that the decrease in psychological distress because of the endogenous serotonin modulation effects induced by acupuncture was a mediating factor in the resultant fatigue improvement. Similar mechanisms relating to modulation in the nervous or related systems have been suggested by authors for many other symptoms (Capodice, 2010; Sagar, 2008; Tsay, 2004).

Previous non-RCT studies revealed that age and confidence in therapy may predict the CRF outcome (Dean-Clower et al., 2010; Vickers et al., 2004). Studies in the current review showed mixed results. Age and patient expectations did not relate to the outcome of acupuncture in the Molassiotis et al. (2012) cohort. Deng et al. (2013) found no relationship between age and CRF outcome. By contrast, acupressure was found to be more effective in younger women (aged 50–59 years), and patients' confidence in acupuncture approached statistical significance in predicting the acupressure response (Zick et al., 2011). Because of the methodologic flaws, this question remains unanswered, and more studies are needed.

Implications for Practice and Research

CRF has been recognized as an undertreated problem (Mitchell et al., 2007). Although many questions remain unanswered, information from this review may help nurses to have a better understanding of the effects of acupuncture and acupressure, and to have a more informed decision-making process for these interventions. Current research shows that acupressure and acupuncture tend to be effective, but additional well-designed RCTs are needed to confirm their efficacy.

In designing future studies, researchers should maintain rigor with respect to (a) adequate sample size (taking into account an expected attrition rate of 25% or more); (b) appropriate control of placebo effects or, at least, an assessment of the magnitude of such effects; (c) enhanced management of missing outcomes by means of sensitivity analysis; (d) adequate control of the known confounders, including the patient's activity level, stage of cancer, and comorbidities (such as thyroid dysfunction); and (e) justified treatment characteristics, including dose, intensity, duration, acupoints, and manipulation. A consensus on sham control among clinicians and researchers is also needed (Molassiotis & Richardson, 2013). In addition, researchers may consider the combined use of acupuncture and acupressure, with appropriate objective physiologic outcome measures.

Conclusions

Limited by the methodologic flaws of the studies included in this review, no firm conclusions can be drawn in answering the authors' three research questions. However, acupuncture and acupressure seem to be effective in relieving CRF with a good selection of acupoints and an adequate length of intervention. Future research is recommended to contribute further evidence in this important topic of symptom management for patients with cancer.

The authors gratefully acknowledge Jan Fischer, PhD, for his support in developing the initial plan of this review.

Wai-man Ling, MScN, RN, FHKAN, is a nurse consultant in the Department of Clinical Oncology at Pamela Youde Nethersole Eastern Hospital; Liza Y.Y. Lui, MN, RN, is an RN in the Department of Medicine at Yan Chai Hospital; Winnie K.W. So, PhD, RN, is an associate professor in the Nethersole School of Nursing at the Chinese University of Hong Kong; and Kuen Chan, MBBS, FRCR, FHKCR, FHKMA, is an associate consultant in the Department of Clinical Oncology at Pamela Youde Nethersole Eastern Hospital, all in Hong Kong, China. No financial relationships to disclose. Ling can be reached at lingwm1@ha.org.hk, with copy to editor at ONFEditor @ons.org. (Submitted March 2014. Accepted for publication June 8, 2014.)

References

Andrykowski, M.A., Donovan, K.A., Laronga, C., & Jacobsen, P.B. (2010). Prevalence, predictors, and characteristics of off-treatment fatigue in breast cancer survivors. *Cancer, 116,* 5740–5748.

Aveyard, H. (2010). *Doing a literature review in health and social care: A practical guide* (2nd ed.). Maidenhead, United Kingdom: Open University Press.

Azad, A., & John, T. (2013). Do randomized acupuncture studies in patients with cancer need a sham acupuncture control arm? *Journal of Clinical Oncology, 31,* 2057–2058. doi:10.1200/jco.2012.47.8750

Balk, J., Day, R., Rosenzweig, M., & Beriwal, S. (2009). Pilot, randomized, modified, double-blind, placebo-controlled trial of acupuncture for cancer-related fatigue. *Journal of the Society for Integrative Oncology, 7,* 4–11. doi:10.2310/7200.2009.0004

Beck, S., Dudley, W.N., & Barsevick, A. (2005). Pain, sleep disturbance, and fatigue in patients with cancer: Using a mediation model to test a symptom cluster [Online exclusive]. *Oncology Nursing Forum, 32,* E48–E55. doi:10.1188/05.ONF.E48-E55

Bower, J.E., Ganz, P.A., Desmond, K.A., Bernaards, C., Rowland, J.H.,

Meyerowitz, B.E., & Belin, T.R. (2006). Fatigue in long-term breast carcinoma survivors: A longitudinal investigation. *Cancer, 106,* 751–758. doi:10.1002/cncr.21671

Campos, M.P., Hassan, B.J., Riechelmann, R., & Del Giglio, A. (2011). Cancer-related fatigue: A practical review. *Annals of Oncology, 22,* 1273–1279. doi:10.1093/annonc/mdq458

Capodice, J.L. (2010). Acupuncture in the oncology setting: Clinical trial update. *Current Treatment Options in Oncology, 11,* 87–94.

Chan, C.W., Chair, S.Y., & Chui, Y.Y. (2009). End of life experience of symptom cluster and their management in Hong Kong Chinese patients with lung cancer who receive palliative radiotherapy. *Chinese Journal of Lung Cancer, 12,* 361–368.

Chan, C.W., & Molassiotis, A. (2000). The impact of fatigue on Chinese cancer patients in Hong Kong. *Supportive Care in Cancer, 9,* 18–24. doi:10.1007/s005200000192

Chen, F.R., Wang, M., Xue, J., & Xu, J. (2011). Study on influence of ginger separated moxibustion on quality of life of elderly patients with advanced cancer. *Chinese Nursing Research, 25,* 2951–2952.

Cho, Y.C., & Tsay, S.L. (2004). The effect of acupressure with massage on fatigue and depression in patients with end-stage renal disease. *Journal of Nursing Research, 12,* 51–59.

Cleeland, C.S. (2007). Symptom burden: Multiple symptoms and their impact as patient-reported outcomes. *Journal of the National Cancer Institute. Monographs, 37,* 16–21.

Cleeland, C.S., Mendoza, T.R., Wang, X.S., Chou, C., Harle, M.T., Morrissey, M., & Engstrom, M.C. (2000). Assessing symptom distress in cancer patients: The MD Anderson Symptom Inventory. *Cancer, 89,* 1634–1646.

Crom, D.B., Hinds, P.S., Gattuso, J.S., Tyc, V., & Hudson, M.M. (2005). Creating the basis for a breast health program for female survivors of Hodgkin disease using a participatory research approach. *Oncology Nursing Forum, 32,* 1131–1141. doi:10.1188/05.ONF.1131-1141

Curt, G.A., Breitbart, W., Cella, D., Groopman, J.E., Horning, S.J., Itri, L.M., . . . Vogelzang, N.J. (2000). Impact of cancer-related fatigue on the lives of patients: New findings from the Fatigue Coalition. *Oncologist, 5,* 353–360. doi:10.1634/theoncologist.5-5-353

Dean-Clower, E., Doherty-Gilman, A.M., Keshaviah, A., Baker, F., Kaw, C., Lu, W., . . . Rosenthal, D.S. (2010). Acupuncture as palliative therapy for physical symptoms and quality of life for advanced cancer patients. *Integrative Cancer Therapies, 9,* 158–167.

Deng, G., Chan, Y., Sjoberg, D., Vickers, A., Yeung, K.S., Kris, M., . . . Cassileth, B. (2013). Acupuncture for the treatment of post-chemotherapy chronic fatigue: A randomized, blinded, sham-controlled trial. *Supportive Care in Cancer, 21,* 1735–1741.

Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum, 28,* 465–470.

Dundee, J.W., & Yang, J. (1990). Prolongation of the antiemetic action of P6 acupuncture by acupressure in patients having cancer chemotherapy. *Journal of the Royal Society of Medicine, 83,* 360–362.

Ernst, E. (2009). Acupuncture: What does the most reliable evidence tell us? *Journal of Pain and Symptom Management, 37,* 709–714.

Ernst, E., & Canter, P.H. (2005). Limitations of "pragmatic" trials. *Post-Graduate Medical Journal, 81*(954), 203. doi:10.1136/pgmj.2004.026807

Escalante, C.P., & Manzullo, E.F. (2009). Cancer-related fatigue: The approach and treatment. *Journal of General Internal Medicine, 24*(Suppl.), S412–S416. doi:10.1007/s11606-009-1056-z

Ezzo, J., Vickers, A., Richardson, M.A., Allen, C., Dibble, S.L., Issell, B., . . . Zhang, G. (2005). Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting. *Journal of Clinical Oncology, 23,* 7188–7198. doi:10.1002/14651858.CD002285.pub2

Finnegan-John, J., Molassiotis, A., Richardson, A., & Ream, E. (2013). A systematic review of complementary and alternative medicine interventions for the management of cancer-related fatigue. *Integrative Cancer Therapies, 12,* 276–290. doi:10.1177/1534735413485816

Fox, S.W., Lyon, D., & Farace, E. (2007). Symptom clusters in patients with high-grade glioma. *Journal of Nursing Scholarship, 39,* 61–67.

Garcia, M.K., McQuade, J., Haddad, R., Patel, S., Lee, R., Yang, P., . . . Cohen, L. (2013). Systematic review of acupuncture in cancer care: A synthesis of the evidence. *Journal of Clinical Oncology, 31,* 952–960. doi:10.1200/jco.2012.43.5818

Given, B. (2008). Cancer-related fatigue: A brief overview of current nursing perspectives and experiences. *Clinical Journal of Oncology Nursing, 12*(Suppl.), 7–9. doi:10.1188/08.CJON.S2.7-9

Gooneratne, N.S. (2008). Complementary and alternative medicine for sleep disturbances in older adults. *Clinics in Geriatric Medicine, 24,* 121–138. doi:10.1016/j.cger.2007.08.002

Haghighat, S., Akbari, M.E., Holakouei, K., Rahimi, A., & Montazeri, A. (2003). Factors predicting fatigue in breast cancer patients. *Supportive Care in Cancer, 11,* 533–538.

He, X.R., Wang, Q., & Li, P.P. (2013). Acupuncture and moxibustion for cancer-related fatigue: A systematic review and meta-analysis. *Asian Pacific Journal of Cancer Prevention, 14,* 3067–3074.

Johnston, M.F., Hays, R.D., Subramanian, S K., Elashoff, R.M., Axe, E.K., Li, J.J., . . . Hui, K.K. (2011). Patient education integrated with acupuncture for relief of cancer-related fatigue randomized controlled feasibility study. *BMC Complementary and Alternative Medicine, 11,* 49. doi:10.1186/1472-6882-11-49

Kaptchuk, T.J., Kelley, J.M., Conboy, L.A., Davis, R.B., Kerr, C.E., Jacobson, E.E., . . . Lembo, A.J. (2008). Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *BMJ, 336,* 999–1003. doi:10.1136/bmj.39524.439618.25

Kirshbaum, M. (2010). Cancer-related fatigue: A review of nursing interventions. *British Journal of Community Nursing, 15,* 214–219.

Kohara, H., Miyauchi, T., Suehiro, Y., Ueoka, H., Takeyama, H., & Morita, T. (2004). Combined modality treatment of aromatherapy, footsoak, and reflexology relieves fatigue in patients with cancer. *Journal of Palliative Medicine, 7,* 791–796. doi:10.1089/jpm.2004.7.791

Lee, E.J., & Frazier, S.K. (2011). The efficacy of acupressure for symptom management: A systematic review. *Journal of Pain and Symptom Management, 42,* 589–603.

Lim, J.T., Wong, E.T., & Aung, S.K. (2011). Is there a role for acupuncture in the symptom management of patients receiving palliative care for cancer? A pilot study of 20 patients comparing acupuncture with nurse-led supportive care. *Acupuncture in Medicine, 29,* 173–179. doi:10.1136/aim.2011.004044

Liu, Q., Liu, X., & Tu, M. (2013). Effect of aerobic exercises and auricular acupoint pressing on cancer-related fatigue among oophoroma patients during intermittent chemotherapy. *Journal of Nursing Science, 28,* 44–45. doi:10.3870/hlxzz.2013.15.044

Liu, Z.W., Liu, L., Fan, W., & Zhang, S. (2009). *Essentials of chinese medicine* (vol. 2). London, England: Springer.

Lun, X. (2012). *Dian xue liao fa* [Therapy of acupressure]. Hong Kong: Wan Li Book Co.

Maliski, S.L., Kwan, L., Elashoff, D., & Litwin, M.S. (2008). Symptom clusters related to treatment for prostate cancer. *Oncology Nursing Forum, 35,* 786–793. doi:10.1188/08.ONF.786-793

Mao, J.J., Styles, T., Cheville, A., Wolf, J., Fernandes, S., & Farrar, J.T. (2009). Acupuncture for nonpalliative radiation therapy-related fatigue: Feasibility study. *Journal of the Society for Integrative Oncology, 7,* 52–58.

Mitchell, S.A., Beck, S.L., Hood, L.E., Moore, K., & Tanner, E.R. (2007). Putting Evidence Into Practice: Evidence-based interventions for fatigue during and following cancer and its treatment. *Clinical Journal of Oncology Nursing, 11,* 99–113. doi:10.1188/07.CJON.99-113

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gøtzsche, P.C., Devereaux, P.J., . . . Altman, D.G. (2012). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery, 10,* 28–55.

Molassiotis, A. (2013a). Evidence is in the eye of the beholder. *Supportive Care in Cancer, 21,* 3259–3260.

Molassiotis, A. (2013b). Managing cancer-related fatigue with acupuncture: Is it all good news for patients? *Acupuncture in Medicine, 31,* 3–4. doi:10.1136/acupmed-2012-010292

Molassiotis, A., Bardy, J., Finnegan-John, J., Mackereth, P., Ryder, D.W., Filshie, J., . . . Richardson, A. (2012). Acupuncture for cancer-related fatigue in patients with breast cancer: A pragmatic randomized controlled trial. *Journal of Clinical Oncology, 30,* 4470–4476.

Molassiotis, A., Bardy, J., Finnegan-John, J., Mackereth, P., Ryder, W.D., Filshie, J., . . . Richardson, A. (2013). A randomized, controlled trial of acupuncture self-needling as maintenance therapy for cancer-related fatigue after therapist-delivered acupuncture. *Annals of Oncology, 24,* 1645–1652. doi:10.1093/annonc/mdt034

Molassiotis, A., & Richardson, A. (2013). Reply to A. Azad et al. *Journal of Clinical Oncology, 31,* 2058–2059. doi:10.1200/jco.2013.49.2470

Molassiotis, A., Sylt, P., & Diggins, H. (2007). The management of cancer-related fatigue after chemotherapy with acupuncture and acupressure: A randomised controlled trial. *Complementary Therapies in Medicine, 15,* 228–237. doi:10.1016/j.ctim.2006.09.009

Morrow, G.R. (2007). Cancer-related fatigue: Causes, consequences, and management. *Oncologist, 12*(Suppl. 1), 1–3.

National Cancer Institute. (2012). Fatigue (PDQ®). Retrieved from http://1.usa.gov/XV4Wcd

National Comprehensive Cancer Network. (2014). *NCCN clinical practice guidelines in oncology: Cancer-related fatigue* [v.1.2014]. Retrieved from http://bit.ly/1oqi1BH

Newton, S., Hickey, M., & Marrs, J. (2009). *Mosby's oncology nursing advisor: A comprehensive guide to clinical practice.* St. Louis, MO: Mosby Elsevier.

Oh, D. (2009). *The pilot study on the effect of SAAM acupuncture treatment for patients with cancer-related fatigue: Randomized, a single-blind, controlled trial* (Unpublished master's thesis). Kyung-Hee University, South Korea.

O'Regan, D., & Filshie, J. (2010). Acupuncture and cancer. *Autonomic Neuroscience, 157,* 96–100. doi:10.1016/j.autneu.2010.05.001

Payne, C., Wiffen, P.J., & Martin, S. (2012). Interventions for fatigue and weight loss in adults with advanced progressive illness. *Cochrane Database of Systematic Reviews, 18,* CD008427.

Posadzki, P., Moon, T.W., Choi, T.Y., Park, T.Y., Lee, M.S., & Ernst, E. (2013). Acupuncture for cancer-related fatigue: A systematic review of randomized clinical trials. *Supportive Care in Cancer, 21,* 2067–2073. doi:10.1007/s00520-013-1765-z

Prue, G., Rankin, J., Allen, J., Gracey, J., & Cramp, F. (2006). Cancer-related fatigue: A critical appraisal. *European Journal of Cancer, 42,* 846–863. doi:10.1016/j.ejca.2005.11.026

Qin, X.Y., & Liu, Z.H. (2012). Clinical observation of wen moxibustion therapy of cancer-related fatigue of advanced cancer. *China Journal of Chinese Medicine, 27,* 273–274.

Reza, H., Kian, N., Pouresmail, Z., Masood, K., Sadat Seyed Bagher, M., & Cheraghi, M.A. (2010). The effect of acupressure on quality of sleep in Iranian elderly nursing home residents. *Complementary Therapies in Clinical Practice, 16,* 81–85.

Ryan, J.L., Carroll, J.K., Ryan, E.P., Mustian, K.M., Fiscella, K., & Morrow, G.R. (2007). Mechanisms of cancer-related fatigue. *Oncologist, 12*(Suppl. 1), 22–34. doi:10.1634/theoncologist.12-S1-22

Sagar, S.M. (2008). Acupuncture as an evidence-based option for symptom control in cancer patients. *Current Treatment Options in Oncology, 9,* 117–126. doi:10.1007/s11864-008-0063-3

Scottish Intercollegiate Guidelines Network. (2014). *Critical appraisal: Notes and checklists.* Retrieved from http://bit.ly/1rzfjfD

Smith, C., Carmady, B., Thornton, C., Perz, J., & Ussher, J.M. (2013). The effect of acupuncture on post-cancer fatigue and well-being for women recovering from breast cancer: A pilot randomised controlled trial. *Acupuncture in Medicine, 31,* 9–15.

So, W.K., Marsh, G., Ling, W.M., Leung, F.Y., Lo, J.C., Yeung, M., & Li, G.K. (2009). The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: A multicenter study [Online exclusive]. *Oncology Nursing Forum, 36,* E205–E214.

Stone, P.C., & Minton, O. (2008). Cancer-related fatigue. *European Journal of Cancer, 44,* 1097–1104. doi:10.1016/j.ejca.2008.02.037

Stricker, C.T., Drake, D., Hoyer, K.A., & Mock, V. (2004). Evidence-based practice for fatigue management in adults with cancer: Exercise as an intervention. *Oncology Nursing Forum, 31,* 963–976.

Sun, J.L., Sung, M.S., Huang, M.Y., Cheng, G.C., & Lin, C.C. (2010). Effectiveness of acupressure for residents of long-term care facilities with insomnia: A randomized controlled trial. *International Journal of Nursing Studies, 47,* 798–805. doi:10.1016/j.ijnurstu.2009.12.003

Tsay, S.L. (2004). Acupressure and fatigue in patients with end-stage renal disease–A randomized controlled trial. *International Journal of Nursing Studies, 41,* 99–106. doi:10.1016/S0020-7489(03)00079-8

Tsay, S.L., Cho, Y.C., & Chen, M.L. (2004). Acupressure and transcutaneous electrical acupoint stimulation in improving fatigue, sleep quality and depression in hemodialysis patients. *American Journal of Chinese Medicine, 32,* 407–416. doi:10.1142/S0192415X04002065

Tsay, S.L., Rong, J.R., & Lin, P.F. (2003). Acupoints massage in improving the quality of sleep and quality of life in patients with end-stage renal disease. *Journal of Advanced Nursing, 42,* 134–142.

Vickers, A.J., Straus, D.J., Fearon, B., & Cassileth, B.R. (2004). Acupuncture for postchemotherapy fatigue: A phase II study. *Journal of Clinical Oncology, 22,* 1731–1735. doi:10.1200/JCO.2004.04.102

Wang, X.S. (2008). Pathophysiology of cancer-related fatigue. *Clinical Journal of Oncology Nursing, 12*(Suppl.), 11–20.

Wu, C.Z., & Gao, S.W. (2010). *Shu xue ding wei su cha* [Quick reference for locating the acupoints]. Beijing, China: People's Military Medical Press.

Wu, H.S., Wu, S.C., Lin, J.G., & Lin, L.C. (2004). Effectiveness of acupressure in improving dyspnoea in chronic obstructive pulmonary disease. *Journal of Advanced Nursing, 45,* 252–259. doi:10.1046/j.1365-2648.2003.02886.x

Xu, J.J., Gu, L.X., & Qiao, H. (2010). Effect of traditional Chinese and western medicine joint exercise therapy on cancer-related fatigue after operation of mammary cancer. *Chinese General Practice, 13,* 3225–3226.

Yang, J.L., Yu, L., Xu, L., Wang, J., & Jing, N.C. (2012). The effect observation of moxibustion for cancer-related fatigue in elderly patients suffered from advanced cancer. *Chinese Journal of Gerontology, 32,* 4408–4410. doi:10.3969/j.issn.1005-9202.2012.20.025

Zick, S.M., Alrawi, S., Merel, G., Burris, B., Sen, A., Litzinger, A., & Harris, R.E. (2011). Relaxation acupressure reduces persistent cancer-related fatigue. *Evidence-Based Complementary and Alternative Medicine, 8,* 1–10. doi:10.1155/2011/142913