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

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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.

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., 2013).
Table 1. Studies of Acupressure and Acupuncture Therapy for Cancer-Related Fatigue

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<td>Balk et al., 2009</td>
<td>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 (FACT-F score of 44 or less)</td>
<td><strong>Intervention:</strong> True acupuncture given once or twice weekly during the 4- to 6-week period of RT. <strong>Control:</strong> Sham acupuncture with the same frequency and duration as that of true acupuncture. Two acupuncturists involved</td>
<td>Treatment for 4–6 weeks during RT with post-treatment follow-up after four weeks</td>
<td>The intervention group showed greater improvement on the FACT-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 follow-up period but were not statistically significant between groups or within groups.</td>
<td>Small, underpowered pilot study; High dropout rate in the control group (27%); Sham acupuncture is an active control rather than an inert placebo.</td>
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<td>Deng et al., 2013</td>
<td>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</td>
<td><strong>Intervention:</strong> True acupuncture. <strong>Control:</strong> 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.</td>
<td>Treatment occurred weekly for six weeks, with post-treatment follow-up at six months.</td>
<td>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.</td>
<td>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.</td>
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<td>Johnston et al., 2011</td>
<td>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)</td>
<td><strong>Intervention:</strong> Combination of a patient education program on self-care with acupuncture as well as acupuncture with usual care from physicians. <strong>Control:</strong> Usual care from physicians. One acupuncturist involved.</td>
<td>Weekly treatment for eight weeks with post-treatment follow-up at week 10</td>
<td>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.</td>
<td>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.</td>
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<td>Lim et al., 2011</td>
<td>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</td>
<td><strong>Intervention:</strong> Weekly acupuncture. <strong>Control:</strong> Weekly nurse-led supportive care by an experienced palliative care nurse. One acupuncturist involved.</td>
<td>Weekly treatment for four weeks with post-treatment follow-up weekly for six weeks</td>
<td>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.</td>
<td>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.</td>
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BFI—Brief Fatigue Inventory; CI—confidence interval; CRF—cancer-related fatigue; CRT—chemoradiation therapy; ESAS—Edmonton Symptom Assessment System; FACT-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.
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| 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 III 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). |

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
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<td>Molassiotis et al., 2013</td>
<td>Nested, multicenter, three-armed, non-blinded, pragmatic RCT to assess the effectiveness of maintenance acupuncture with 197 patients with stage I, II, or III 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.</td>
<td><strong>Intervention:</strong> Acupuncturist-delivered maintenance group (AMG) or self-needling maintenance group (SMG) (participants were taught to needle themselves at two acupoints, ST36 and SP6).  <strong>Control:</strong> No maintenance group (NMG) as control. 12 acupuncturists involved</td>
<td>Maintenance therapy for four weeks, with post-maintenance therapy follow-up at week 18</td>
<td>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.</td>
<td>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.</td>
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<td>Smith et al., 2013</td>
<td>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</td>
<td><strong>Intervention:</strong> True acupuncture  <strong>Control:</strong> Sham acupuncture group using sham acupoints with sham needles or wait-list control group with no treatment  Six acupuncturists involved</td>
<td>Twice weekly treatment for three weeks followed by weekly treatment for three weeks with no post-treatment follow-up</td>
<td>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 to the treatment intensity. Better sleep, improved mood, and relaxation were identified as the explanations for fatigue improvement by the concurrent in-depth interviews.</td>
<td>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.</td>
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<td>Xu et al., 2010</td>
<td>Single-center, two-armed, nonblinded RCT with 80 hospitalized patients with breast cancer who underwent modified radical mastectomy</td>
<td><strong>Intervention:</strong> Combination of self-acupressure, abdominal breathing exercise, music therapy, as well as routine nursing care  <strong>Control:</strong> Routine nursing care</td>
<td>Treatment for 10 days with no post-treatment follow-up</td>
<td>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 &lt; 0.01).</td>
<td>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).</td>
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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
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<td>Zick et al., 2011</td>
<td>BFI was significantly reduced across all treatment arm groups. The HIS group had a mean reduction of 22% (SD = 11.6) for the BFI of 4 or greater.</td>
<td>Single-center, three-arm, blinded pilot trial with 43 participants who were predominantly breast and gynecologic cancer survivors; 12 weeks (except for ongoing hormone therapy).</td>
<td>High-intensity stimulation (HIS) group with 12 participants who self-administered acupuncture for 30 minutes twice a day for 12 weeks. Low-intensity stimulation (LIS) group with 12 participants who self-administered relaxation acupressure for 30 minutes twice a day for 12 weeks.</td>
<td>Subjects with BFI of 4 or greater and life expectancy of greater than six months.</td>
<td>Small, underpowered pilot study.ITT analysis was not strictly followed; no inert control. No sham controls. No placebo effects. No firm conclusion can be drawn about the efficacy of the two acupressure methods.</td>
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<td>Acupressure for a week followed by a week of no treatment. The majority of BFI improvement occurred during the first four weeks of treatment.</td>
<td>Three therapists involved. Three treatment methods. 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; Zick et al., 2011).</td>
<td>The dropout rate was 20% or above overall in one of the arms in six studies (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; 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 acupressure 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.</td>
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<td>High-intensity stimulation (HIS) group with 12 participants who self-administered acupuncture for 30 minutes twice a day for 12 weeks. Low-intensity stimulation (LIS) group with 12 participants who self-administered relaxation acupressure for 30 minutes twice a day for 12 weeks.</td>
<td>Three therapists involved. Three treatment methods. 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; Zick et al., 2011).</td>
<td>The dropout rate was 20% or above overall in one of the arms in six studies (Balk et al., 2009; Deng et al., 2013; Johnston et al., 2011; 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 acupressure 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.</td>
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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 acupuncture, 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., 2011; 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 “less than true” 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 acupunture 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 acupunture 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 acupunture 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 acupunture 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 acupunture 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 acupunture 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 acupunture was more significant than frequency in fatigue improvement (Zick et al., 2011). Daily acupunture was also adopted by Johnston et al. (2011) and Molassiotis et al. (2007), which appears to be more practical for self-acupunture 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. Acupuncture was found to have positive effects on sleep disturbance and depression in patients with cancer, and relaxation acupunture was more effective than stimulatory acupunture (Zick et al., 2011). Lim et al. (2011) and Dean-Clover et al. (2010) agreed that increased attention from the study acupunturists 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 acupunture and acupunture for CRF. Patient empowerment in self-care interventions, including self-acupunture, 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 acupunture 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 acupunture 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)
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.

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