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Investigation of 2 Types of Self-administered Acupressure for Persistent Cancer-Related Fatigue in Breast Cancer Survivors
A Randomized Clinical Trial

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IMPORTANCE Fatigue is a common and debilitating late-term effect of breast cancer that is associated with poor sleep and decreased quality of life, yet therapies remain limited. Acupressure has reduced fatigue in previous small studies, but rigorous clinical trials are needed.

OBJECTIVES To investigate if 6 weeks of 2 types of self-administered acupressure improved fatigue, sleep, and quality of life vs usual care in breast cancer survivors and to determine if changes were sustained during a 4-week washout period.

DESIGN, SETTING, AND PARTICIPANTS Phase 3 randomized, single-blind, clinical trial conducted from March 1, 2011, through October 31, 2014. Women were recruited from the Michigan Tumor Registry.

INTERVENTIONS Randomization (1:1:1) to 6 weeks of daily self-administered relaxing acupressure, stimulating acupressure, or usual care.

MAIN OUTCOMES AND MEASURES The primary outcome was change in the Brief Fatigue Inventory score from baseline to weeks 6 and 10. Secondary analyses were sleep (Pittsburgh Sleep Quality Index) and quality of life (Long-Term Quality of Life Instrument).

RESULTS A total of 424 survivors of stages 0 to III breast cancer who had completed cancer treatments at least 12 months previously were screened, and 288 were randomized, with 270 receiving relaxing acupressure (n = 94), stimulating acupressure (n = 90), or usual care (n = 86). One woman withdrew owing to bruising at the acupoints. At week 6, the percentages of participants who achieved normal fatigue levels (Brief Fatigue Inventory score <4) were 66.2% (49 of 74) in relaxing acupressure, 60.9% (42 of 70) in stimulating acupressure, and 31.3% (26 of 84) in usual care. At week 10, a total of 56.3% (40 of 71) in relaxing acupressure, 60.9% (42 of 69) in stimulating acupressure, and 30.1% (25 of 83) in usual care continued to have normal fatigue. At neither time point were the 2 acupressure groups significantly different. Relaxing acupressure, but not stimulating acupressure, showed significant improvements in sleep quality compared with usual care at week 6, but not at week 10. Only relaxing acupressure significantly improved quality of life vs usual care at weeks 6 and 10.

CONCLUSIONS AND RELEVANCE Both acupressure arms significantly reduced persistent fatigue compared with usual care, but only relaxing acupressure had significant effects on sleep quality and quality of life. Relaxing acupressure offers a possible low-cost option for managing symptoms.

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Many breast cancer survivors experience negative late-term physical and psychological effects from their cancer therapies.[1,2] Persistent fatigue is one of the most common and bothersome symptoms.[3,4] Moreover, persistent fatigue in breast cancer survivors is emerging as a potential independent risk factor associated with shorter times to breast cancer recurrence and overall survival.[5] Approximately one-third of women experience moderate to severe persistent fatigue up to 10 years after the end of treatment.[6-8] Persistent fatigue is associated with higher rates of depression,[9-11] poor sleep,[12] and decreased quality of life.[13] While the etiology of persistent fatigue is unknown, recent data suggest dysfunction within the central nervous system, including elevations in specific neurotransmitters and metabolites.[14,15]

Despite the high burden of persistent fatigue in breast cancer survivors, treatments remain limited and have challenges to implementation.[16] For instance, cancer-related fatigue is one of the most commonly reported barriers to starting or maintaining physical activity.[17,18] Behavioral treatments have been hindered by the poor availability of mental health programs, limited insurance coverage, and the stigma associated with psychological problems.[19-22] Therefore, there is a need for inexpensive, easy-to-initiate, self-care treatments for persistent fatigue in breast cancer survivors.

Acupressure, a method derived from traditional Chinese medicine (TCM), is a treatment in which pressure is applied with fingers, thumbs, or a device to acupoints on the body. Acupressure has shown promise for treating fatigue in patients with cancer,[23] and in a study[24] of 43 cancer survivors with persistent fatigue, our group found that acupressure decreased fatigue by approximately 45% to 70%. Furthermore, acupressure points termed *relaxing* (for their use in TCM to treat insomnia) were significantly better at improving fatigue than another distinct set of acupressure points termed *stimulating* (used in TCM to increase energy).[24] Despite such promise, only 5 small studies[24-28] have examined the effect of acupressure for cancer fatigue.

To develop an inexpensive, easy-to-initiate, self-care treatment for persistent fatigue, we conducted a 10-week phase 3 randomized, single-blind, clinical trial from March 1, 2011, through October 31, 2014, to test the hypothesis that self-administered relaxing acupressure would be significantly better at reducing fatigue, improving sleep, and increasing quality of life than either stimulating acupressure or usual care in persistently fatigued breast cancer survivors. We also examined the carryover effects on fatigue, sleep, and quality of life during a 4-week washout period.

Key Points

Question What is the efficacy of 2 types of self-administered acupressure compared with usual care for treating chronic fatigue, poor sleep, and low quality of life in fatigued breast cancer survivors?

Findings In this randomized clinical trial that included 288 breast cancer survivors, the percentages of women who achieved normal fatigue levels at week 6 were 66.2% in relaxing acupressure, 60.9% in stimulating acupressure, and 31.3% in usual care. Only women in the stimulating acupressure arm experienced significant improvement in both sleep quality and quality of life vs usual care.

Meaning Self-administered relaxing acupressure may be a useful treatment for improving fatigue, sleep, and quality of life.

Methods

The study design has been previously reported.[29] The trial protocol (Supplement 1) was approved by the University of Michigan Medical School, Michigan State University, and Michigan Department of Public Health institutional review boards, and participants provided written informed consent.

Trial Design

A 10-week randomized, single-blind trial comparing self-administered relaxing acupressure with stimulating acupressure once daily for 6 weeks vs usual care with a 4-week follow-up was conducted. There were 5 research visits: at screening, baseline, 3 weeks, 6 weeks (end of treatment), and 10 weeks (end of washout phase). The Pittsburgh Sleep Quality Index (PSQI) and Long-Term Quality of Life Instrument (LTQL) were administered at baseline and weeks 6 and 10. The Brief Fatigue Inventory (BFI) score was collected at baseline and weeks 1 through 10. Study visits were conducted at the Michigan County Extension Office in the county where women resided.

Participants

Women were recruited from the Michigan Tumor Registry. The registry sent letters to women diagnosed as having stages 0 to III breast cancer between January 1, 2006, and December 31, 2010, from 6 Michigan counties. Eligible women had to report persistent fatigue starting on or after their cancer diagnosis and a score of 4 or higher on the BFI.[30] They also had to be cancer free and have completed cancer treatments (except hormone therapy) at least 12 months previously. Women were ineligible if (1) they had untreated major depressive disorder, other fatigue-causing comorbidities, or a cancer diagnosis other than breast cancer or skin cancer within the previous 10 years; (2) they were planning on changing or starting a new medication during the study period; or (3) they were taking any medications for insomnia or had received acupuncture or acupressure within the previous 6 months.

Interventions

Usual care was defined as any treatment women were receiving from health care professionals for fatigue. At baseline, women were taught to self-administer acupressure by a trained acupressure educator.[29] The 13 acupressure educators were taught by one of the study's principal investigators (R.E.H.), an acupuncturist with National Certification Commission for Acupuncture and Oriental Medicine training. This training included a 30-minute session in which educators were taught point location, stimulation techniques, and pressure intensity.

Relaxing acupressure points consisted of *yin tang*, *anmian*, heart 7, spleen 6, and liver 3. Four acupoints were performed bilaterally, with *yin tang* done centrally. Stimulating acupressure points consisted of *du* 20, conception vessel 6, large intestine 4, stomach 36, spleen 6, and kidney 3. Points

were administered bilaterally except for *du* 20 and conception vessel 6, which were done centrally (eFigure in Supplement 2). Women were told to perform acupressure once per day and to stimulate each point in a circular motion for 3 minutes.

The assessments for fidelity of both acupressure educators and participants have been previously described.[31] Participants were assessed for how well they performed acupressure at their baseline visits and at weeks 3 and 6. Participants were asked to locate all acupoints and demonstrate the amount of stimulation and treatment duration. These items were scored from 0 (no answers correct) to 100 (all answers correct). The acupressure educators were assessed in the same way as the participants at least twice by the acupuncturist.

Outcome Measures

For the outcome of fatigue, we selected the BFI,[30] a scale validated with Cronbach α > .95 in patients with cancer,[32] which correlates well with other fatigue measures.[33] The BFI assesses the severity and effect of fatigue in patients with cancer during the past 24 hours. The instrument consists of 9 items, each measuring fatigue on a scale of 0 to 10, and the score is calculated from the mean of completed items. Scores of 4 or higher indicate clinically relevant fatigue.[30] A 3-point change or a drop below 4 is considered a clinically meaningful change.[34]

To assess sleep quality, the 19-item PSQI was used. It evaluates sleep disturbance during the past month. The PSQI yields a global score (Cronbach α = .81).[32] In women with breast cancer, a score of 8 or higher suggests poor sleep quality.[32] A 3-point change or a drop below 8 is considered clinically meaningful.[35]

Quality of life was measured by the LTQL, a 34-item questionnaire evaluating functional impairment and its effect on quality of life in female cancer survivors during the past month. The LTQL is composed of 4 subscales, including somatic, spiritual and philosophical, fitness, and social support.[36] The Cronbach α ranges from α = .86 to α = .92 for the 4 subscales.[36]

Women in the acupressure arms were given a study logbook. In it, they were instructed to record adherence to acupressure treatments.

Sample Size

The power to detect differences between the 2 types of acupressure and between the 2 acupressure arms and usual care was computed via simulation using linear mixed models (LMMs), with a group, week, group by week interaction, and a random participant effect. The mean BFI scores at baseline were taken to be 6 across all 3 arms and decreased to 2, 3, and 4 at week 6 for usual care, stimulating acupressure, and relaxing acupressure, respectively. The between-participant variance was assumed to be 4 at all time points, while the variance of the random participant component was also 4, with a 0.5 intraclass correlation.[24] For this configuration, the power for detecting group differences is greater than 0.95, and the power for detecting a significant group by week interaction is 0.82, with a sample size of 100 per treatment arm and a 5% level of significance.

Randomization, Allocation, and Blinding

Randomization (1:1:1) was computer generated by the study statistician (A.S.) in blocks of 6 and by county. Women were classified into 1 of 2 strata based on sleep quality at baseline (PSQI <8 or ≥8).[32,37,38] Participants were enrolled and assigned the next randomization number in their county by the study coordinator. Before enrolling any participants into the study, randomization numbers were written on the outside of opaque envelopes that contained treatment assignments. These envelopes were created by study staff who had no contact with participants. All study staff were blinded. Those randomized to usual care knew their study assignment, but the women randomized to acupressure (and their acupressure educators) were unaware if they were receiving relaxing or stimulating acupressure.

Statistical Analysis

Baseline characteristics were analyzed by treatment groups using means (SDs) for continuous variables and counts and percentages for categorical variables. Balance between groups on baseline characteristics was tested using analysis of variance or a Pearson χ^2 test, as appropriate. Adverse events, fidelity, and adherence between groups were analyzed using a Pearson χ^2 test.

An intent-to-treat analysis was used, as suggested by White and colleagues.[39] This method included performing an analysis of key sociodemographic and clinical characteristics comparing those who completed the trial with those who withdrew and using LMMs. The LMMs were used to investigate the primary outcome of fatigue (BFI score). In the LMMs, a random participant intercept was included to account for participant clustering, and week, group, and the interaction term (group by week) were included as fixed effects. To examine the percentage of women by group who were no longer clinically fatigued at weeks 6 and 10, a Pearson χ^2 test was conducted. The LMMs were also used to analyze the global PSQI and the LTQL subscales. For fatigue analyses, multiple testing (change in BFI score and BFI clinical responders) was accounted for using a Bonferroni adjustment such that $P \leq .025$ was considered significant. In all other analyses, $P \leq .05$ was considered statistically significant. No adjustment was made for other outcomes, which were considered hypothesis generating. All tests were 2 sided.

Results

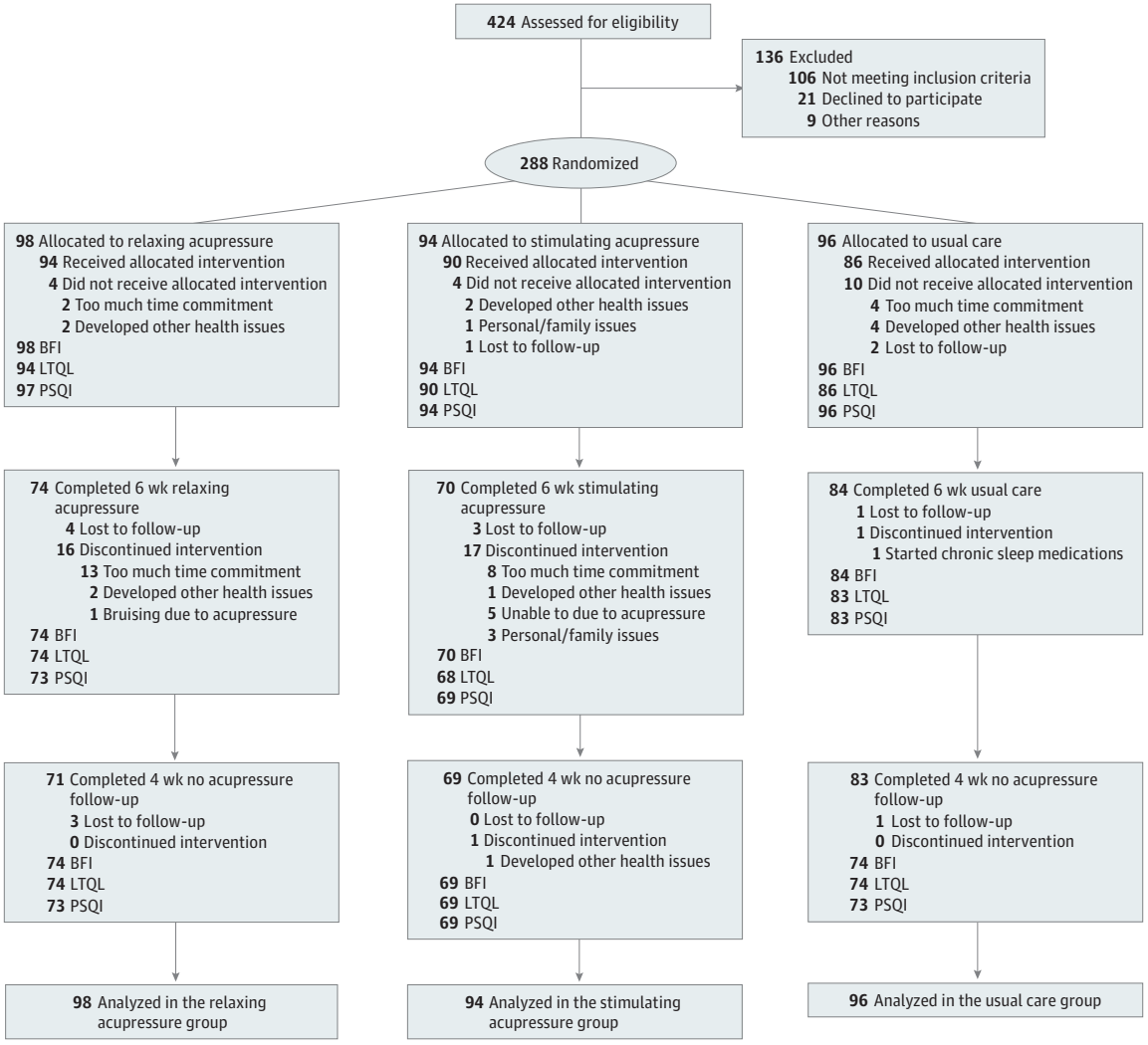
Screening, Enrollment, and Withdrawals

Of the 424 women screened, 288 were randomized. All study visits were completed by 72.4% (71 of 98) in relaxing acupressure, 73.4% (69 of 94) in stimulating acupressure, and 86.5% (83 of 96) in usual care ($P = .04$ for acupressure groups vs usual care). There were no significant differences in any sociodemographic or clinical characteristics, including baseline fatigue, between women who completed the study and those who withdrew. **Figure 1** shows exclusions and reasons for discontinuing interventions.

Sociodemographic and Clinical Characteristics

No significant baseline differences were found across study groups for any variables. These results are shown in the eTable in Supplement 2.

Figure 1. Consolidated Standards of Reporting Trials Flow Diagram



BFI indicates Brief Fatigue Inventory; LTQL, Long-Term Quality of Life Instrument; and PSQI, Pittsburgh Sleep Quality Index.

Fatigue

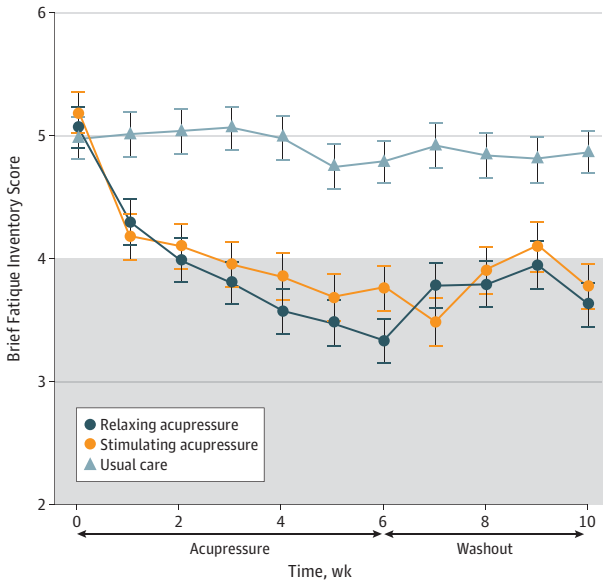
At week 6, the change in BFI score from baseline was significantly greater in relaxing acupressure and stimulating acupressure compared with usual care (mean [SD], −2.6 [1.5] for relaxing acupressure, −2.0 [1.5] for stimulating acupressure, and −1.1 [1.6] for usual care; $P < .001$ for both acupressure arms vs usual care), and there was no significant difference between acupressure arms ($P = .29$). At week 10, the change in BFI score from baseline was greater in relaxing acupressure and stimulating acupressure compared with usual care (mean [SD], −2.3 [1.4] for relaxing acupressure, −2.0 [1.5] for stimulating acupressure, and −1.0 [1.5] for usual care; $P < .001$ for both acupressure arms vs usual care), and there was no significant difference between acupressure arms ($P > .99$) (**Figure 2**). The mean percentage fatigue reductions at 6 weeks were 34%, 27%, and −1% in relaxing acupressure, stimulating acupressure, and usual care, respectively.

The percentages of study participants who achieved normal fatigue levels (BFI score <4) at week 6 were 66.2% (49 of 74) in relaxing acupressure, 60.9% (42 of 70) in stimulating acupressure, and 31.3% (26 of 84) in usual care ($P < .001$ for comparison across study arms). Similarly, 56.3% (40 of 71) in relaxing acupressure, 60.9% (42 of 69) in stimulating acupressure, and 30.1% (25 of 83) in usual care continued to have normal fatigue levels at week 10 ($P < .001$ for comparison across study arms).

Sleep Quality

At week 6, participants randomized to relaxing acupressure had significantly lower PSQI scores compared with usual care but were not significantly different from those randomized to stimulating acupressure. The stimulating acupressure arm was not significantly different from the usual care arm. There was no significant difference between the 3 study arms at week 10 (**Table**). Only relaxing acupressure significantly improved quality of life vs usual care at weeks 6 and 10.

Figure 2. Fatigue by Week and Group Assignment



The Brief Fatigue Inventory consists of 9 items, each measuring fatigue on a scale of 0 to 10, and the score is calculated from the mean of completed items. Scores of 4 or higher indicate clinically relevant fatigue. The shaded area represents nonclinical or normal levels of fatigue.

Long-term Quality of Life

Participants in the relaxing acupressure arm improved significantly compared with the usual care arm for 3 of the 4 quality-of-life subscales, including somatic, fitness, and social support at both 6 and 10 weeks. Stimulating acupressure was not significantly different from usual care for any subscale at either time point. There were no significant differences between the relaxing and stimulating acupressure arms for any subscale at either week 6 or 10 (Table).

Fidelity, Adherence, and Adverse Events

At week 6, the mean (SD) fidelity ratings were 94.6% (10.2%) and 95.3% (8.1%) in the relaxing acupressure and stimulating acupressure arms, respectively (P = .23). There was no significant difference in adherence between acupressure arms (P = .11): women in relaxing acupressure self-administered a mean (SD) of 73% (29%) of all possible sessions, while those in the stimulating acupressure self-administered a mean (SD) of 65% (32%) of their sessions. Six adverse events were related to the acupressure treatment. All were nonserious cases of mild bruising at acupressure sites.

Discussion

Six weeks of daily self-administered relaxing and stimulating acupressure led to significant fatigue reductions compared with usual care in persistently fatigued breast cancer survivors. At posttreatment, 66.2% (49 of 74) of relaxing acupressure participants and 60.9% (42 of 70) of stimulating acupressure participants achieved normal fatigue levels compared with 31.3% (26 of 84) of usual care participants. While both acupressure treatments demonstrated significant, sustained improvements in fatigue, only relaxing acupressure significantly improved both sleep and quality of life compared with usual care.

Why might both acupressure arms significantly improve fatigue? In our group's previous work, we had seen that cancer fatigue may arise through multiple distinct mechanisms.[15] Similarly, it is also known in the acupuncture literature that true and sham acupuncture can improve symptoms equally, but they appear to work via different mechanisms.[40] Therefore, relaxing acupressure and stimulating acupressure could elicit improvements in symptoms through distinct mechanisms, including both specific and nonspecific effects. These results are also consistent with TCM theory for these 2 acupoint formulas, whereby the relaxing acupressure acupoints were selected to treat insomnia by providing more restorative sleep and improving fatigue and the stimulating acupressure acupoints were chosen to improve daytime activity levels by targeting alertness.

How could acupressure lead to improvements in fatigue? The etiology of persistent fatigue in cancer survivors is related to elevations in brain glutamate levels, as well as total creatine levels in the insula.[15] Studies in acupuncture research have demonstrated that brain physiology,[41] chemistry,[42] and function[43] can also be altered with acupoint stimulation. We posit that self-administered acupressure may have similar effects.

Self-administered acupressure appeared to be safe, acceptable, and easy to learn. After a 15-minute training session, women were able to accurately locate their acupoints and apply the correct amount of pressure. Women on average performed more than 70% of daily acupressure sessions and reported few, transient, and minor occurrences of bruising at the acupressure site. Given the brief training required to learn acupressure, this intervention could be a low-cost option for treating fatigue.

Our results are consistent with other investigations in which acupressure was significantly better than usual care at decreasing fatigue. However, these studies[25-28] had limitations, including small sample sizes, inclusion of multimodal treatment approaches, patients currently receiving or recently completing cancer treatment, and no examination of carryover effects of acupressure. Moreover, to our knowledge, only one study[26] examined acupressure in breast cancer survivors, and our study addressed these limitations and improved fatigue to a greater extent. However, fatigue reduction in our study was considerably less than what was observed in a pilot study,[24] despite using the same 2 acupressure treatments and similar baseline fatigue severity. In addition, the pilot study found a significant difference in fatigue reduction between stimulating (45%) and relaxing (70%) acupressure. There are several possible reasons for the discrepant findings. The pilot study included a mixed cancer population, with only some participants being diagnosed as having breast cancer. Cancer-related fatigue in other cancer populations could have different etiologies and mechanisms, making it more amenable to acupressure treatments. We also recruited women from the community in this study, in contrast to a National Cancer Institute–designated comprehensive cancer center. As a consequence, women in this study were on average older, had more comorbidities, and were more racially/ethnically diverse than pilot study participants. Certain comorbidities[6,44] and nonwhite race[44] are predictors of more severe fatigue in breast cancer sur-

Table. Sleep Quality and Quality of Life by Group Assignment and Study Visit

Variable	Baseline Visit Mean (SD)			Week 6 Visit at End of Acupressure Mean (SD), (95% CI)[a]			Week 10 Visit at End of Washout Mean (SD), (95% CI)[a]		
	Relaxing Acupressure	Stimulating Acupressure	Usual Care	Relaxing Acupressure	Stimulating Acupressure	Usual Care	Relaxing Acupressure	Stimulating Acupressure	Usual Care
Global PSQI	8.3 (3.8)	8.6 (3.4)	8.2 (3.9)	6.3 (2.9) (−0.47 to 2.11)[b]	7.2 (3.1) (−2.59 to −0.92)[c]	7.6 (3.33) (−1.78 to 0.74)[d]	6.3 (3.0) (−1.89 to 0.69)[b]	7.0 (2.7) (−2.03 to 0.47)[c]	7.0 (3.0) (−1.44 to 1.08)[d]
LTQL somatic	41.1 (8.6)	42.2 (9.3)	42.7 (8.1)	44.4 (8.7) (−1.48 to 1.95)	44.2 (8.3) (0.17 to 3.43)	42.9 (7.9) (−0.11 to 3.24)	44.6 (7.5) (−0.13 to 3.17)	43.4 (8.5) (0.05 to 3.18)	43.3 (8.1) (−1.49 to 1.68)
LTQL spiritual and philosophical	32.2 (8.4)	30.8 (8.8)	30.6 (8.7)	32.8 (8.4) (−2.63 to 1.36)	31.8 (8.9) (−1.32 to 2.48)	30.9 (8.6) (−0.72 to 3.15)	34.2 (8.1) (−0.57 to 3.36)	31.3 (8.9) (−0.56 to 3.20)	31.7 (8.4) (−1.97 to 1.81)
LTQL fitness	10.0 (5.3)	10.3 (5.1)	10.6 (5.4)	11.4 (5.7) (−1.02 to 1.46)	10.8 (5.6) (0.08 to 2.44)	10.5 (5.6) (−0.17 to 2.25)	12.2 (5.7) (−0.73 to 1.96)	11.2 (5.5) (0.40 to 3.00)	11.0 (5.9) (−0.23 to 2.37)
LTQL social support	9.1 (4.5)	9.4 (4.3)	9.5 (4.8)	9.2 (4.9) (−0.41 to 1.57)	9.0 (4.9) (0.11 to 2.00)	8.7 (4.7) (−0.49 to 1.44)	9.1 (5.2) (−0.30 to 1.79)	8.6 (5.2) (0.15 to 1.85)	8.8 (4.9) (−0.90 to 1.11)

Abbreviations: LTQL, Long-Term Quality of Life Instrument; PSQI, Pittsburgh Sleep Quality Index.

[a] Derived from a linear mixed model.

[b] Relaxing acupressure compared with stimulating acupressure.

[c] Relaxing acupressure compared with usual care.

[d] Stimulating acupressure compared with usual care.

vivors. Also, older age may diminish responsiveness to acupressure treatment for fatigue.[34]

This study had several limitations, including limited participation of minority women. Most participants (89.6% [258 of 288]) were white non-Hispanic women, and almost all nonwhite participants were African Americans. However, this study's racial makeup is similar to the demographics of breast cancer cases reported in Michigan.[45] Another limitation is that some women (11.9% [23 of 192]) found that self-administering daily acupressure was too time consuming and discontinued the study for this reason. Other time-intensive study requirements could also explain why participants found the study too burdensome; however, only 4.2% (4 of 96) of women in usual care indicated that they withdrew owing to time conflicts. These attrition rates are not dissimilar to those of exercise and diet interventions in breast cancer survivors.[46] However, unlike other behavioral changes, women may not need to continue doing acupressure to have prolonged benefit. This consideration could be a significant advantage of acupressure because the maintenance of behavioral changes after the end of an intervention is a significant challenge for lifestyle interventions, such as exercise.[47] Still, it is difficult to know the long-term efficacy of this treatment beyond 4 weeks. Also, for a small number (6 of 288), this intervention was a suboptimal treatment owing to complaints of bruising or difficulty doing acupressure.

Future acupressure studies should investigate how to best implement acupressure in real-world clinical settings and in the community or more broadly disseminate the therapy through web-based or mobile applications. There is also a lack of studies examining the mechanisms of how acupressure affects fatigue. Such studies could contribute important insights into underlying acupressure mechanisms and chronic fatigue in cancer survivors. Last, investigations of which cancer survivors are most likely to benefit from acupressure would help guide clinical recommendations and improve evidence-based treatment for fatigued breast cancer survivors.

Conclusions

In summary, both acupressure arms significantly reduced fatigue compared with usual care, but only relaxing acupressure had a significant effect on improving both sleep and quality of life. Improvements in fatigue, sleep, and quality of life were sustained for 4 weeks after cessation of acupressure. Self-administered relaxing acupressure could offer an inexpensive, easy-to-learn intervention for improving fatigue, sleep, and quality of life in fatigued breast cancer survivors.

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Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Zick, Harris.
Critical revision of the manuscript for important intellectual content: All authors.
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Administrative, technical, or material support: Zick, Wyatt, Harris.
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