

Acupuncture for Cancer-Related Fatigue in Patients With Breast Cancer: A Pragmatic Randomized Controlled Trial

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ABSTRACT

Purpose

We aimed to assess the effectiveness of acupuncture for cancer-related fatigue (CRF) in patients with breast cancer.

Patients and Methods

We conducted a pragmatic, randomized controlled trial comparing acupuncture with enhanced usual care. Three hundred two outpatients with breast cancer participated. We randomly assigned 75 patients to usual care and 227 patients to acupuncture plus usual care (random assignment of 1:3 respectively) with minimization controlling for baseline general fatigue and maintenance treatment. Treatment was delivered by acupuncturists once a week for 6 weeks through needling three pairs of acupoints. The usual care group received a booklet with information about fatigue and its management. Primary outcome was general fatigue at 6 weeks, measured with the Multidimensional Fatigue Inventory (MFI). Other measurements included the Hospital Anxiety and Depression Scale, Functional Assessment of Cancer Therapy–General quality-of-life scale, and expectation of acupuncture effect. Analyses were by intention to treat.

Results

Two hundred forty-six of 302 patients randomly assigned provided complete data at 6 weeks. The difference in the mean General Fatigue score, between those who received the intervention and those who did not, was -3.11 (95% CI, -3.97 to -2.25 ; $P < .001$). The intervention also improved all other fatigue aspects measured by MFI, including Physical Fatigue and Mental Fatigue (acupuncture effect, -2.36 and -1.94 , respectively; both at $P < .001$), anxiety and depression (acupuncture effect, -1.83 and -2.13 , respectively; both at $P < .001$), and quality of life (Physical Well-Being effect, 3.30; Functional Well-Being effect, 3.57; both at $P < .001$; Emotional Well-Being effect, 1.93; $P = .001$; and Social Functioning Well-Being effect, 1.05; $P < .05$).

Conclusion

Acupuncture is an effective intervention for managing the symptom of CRF and improving patients' quality of life.

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INTRODUCTION

Persistent cancer-related fatigue (CRF) is a significant problem in as many as 40% of disease-free patients with breast cancer, who experience moderate to severe levels of fatigue even several years after treatment,^{1,2} impacting quality of life. Evidence to underpin its management is scarce. Patients with cancer often display an interest in complementary therapies,^{3,4} and a systematic review showed that acupuncture is promising in the management of fatigue,⁵ with further supporting evidence from cancer⁶ and noncancer studies.^{7,8} These preliminary

studies had small sample sizes and methodologic limitations. Our feasibility trial assessed the effects of acupuncture in a mixed sample of fatigued patients with cancer ($n = 47$) randomly assigned to receive six sessions of acupuncture, daily self-acupressure, or daily sham self-acupressure over 2 weeks.⁹ General fatigue improved by 36% at the end of the 2-week intervention in the acupuncture group (compared with 19% in the acupressure group and 0.6% in the sham acupressure group); however, the effect decreased a month later (22%, 15%, and 7% improvement, respectively), suggesting that patients may have been undertreated. The aim of this study

was to assess the effectiveness of a course of acupuncture for managing CRF in a sample of patients with breast cancer who had completed adjuvant chemotherapy.

PATIENTS AND METHODS

Design

A two-group, randomized controlled trial design was used, with participants receiving either enhanced usual care or acupuncture. A computer program allocated patients to groups and used minimization with a random element over the margins of the following two factors: baseline Multidimensional Fatigue Inventory (MFI) General Fatigue score (≤ 16 , 17 or 18, or 19 or 20) and maintenance therapy (none, biologic [trastuzumab], and/or hormonal [tamoxifen, goserelin]). The allocation ratio was 3:1 to the acupuncture and control groups, respectively.

Sample and Settings

Patients with breast cancer experiencing persistent fatigue of at least a moderate level were the focus of the study. Patients were screened for fatigue through a single-item 10-point scale (where 0 is not fatigued at all and 10 is extremely fatigued) to identify patients with significant fatigue (ie, those with score ≥ 5), who were then assessed for eligibility to participate in the study. We have validated this single item compared with a fatigue scale, and correlations were $r = 0.75$.⁹ Recruitment took place at two specialist cancer hospitals in the United Kingdom, four cancer centers, and three treatment centers of a national voluntary breast cancer organization.

Eligible patients had a diagnosis of stage I, II, or IIIA breast cancer; had completed chemotherapy at least 1 month and up to 5 years previously (to recruit those with persistent/long-term fatigue); had not planned to receive chemoradiotherapy during the study; had a score ≥ 5 on a 0 to 10 screening scale; and were willing to participate and be randomly assigned to one of the study groups. Patients with previous local recurrence were eligible, but not patients with distant metastasis.

Exclusion criteria included the following: needle phobia; low platelet count ($< 50,000/\mu\text{L}$); comorbidity with a bleeding disorder or thyroid dysfunction; pregnancy; hemoglobin less than 10 g/dL; hematocrit less than 30%; active treatment for anemia with erythropoietin or blood transfusions; corticosteroid use; and a life expectancy less than 6 months. In addition, the ipsilateral arm of patients who had undergone axillary dissection was excluded from needling, as were lymphedematous limbs.

Intervention

All trial patients received usual care. Because there is no recognized standard care for fatigue, all patients were offered a fatigue information booklet. In addition, the intervention group was offered six acupuncture sessions over 6 weeks. On the basis of the Standards for Reporting Interventions in Clinical Trials of Acupuncture recommendations for reporting acupuncture trials,¹⁰ patients received a standardized 20-minute acupuncture session needling bilaterally or unilaterally three points (ST36, SP6, and LI4), with some flexibility in case points could not be punctured (eg, in case of lymphedema). Alternative points were selected by therapists at their discretion to maintain an equal dose of treatment. These points could include GB34 and SP9.^{6,9,11} This approach mimics current acupuncture practice and ensured replicability of the technique across therapists, which was assessed through regular audits of the therapists' records. Patients were observed for 18 weeks. Points were punctured perpendicularly, with a depth of 0.5 to 1 inch,¹¹ depending on patients' size, sensitivity, and health state. Needles were manufactured by Seirin (Kyoto, Japan) with guide tubes for single use (size, 36 gauge; point, 16 to 30 mm). No flicking or rotation of the needle took place once inserted. Each session was based on a strict protocol, and conversation between acupuncturists and patients was kept to minimum. Immediately after each session, therapists completed a form verifying the exact treatment given and any issues that needed to be reported (eg, adverse effects). These forms were checked regularly by the investigators for consistency across therapists. No other complementary therapy use was recommended during the course of acupuncture (although

any such use was documented). Therapists ($n = 12$) were educated in acupuncture to degree level, were registered with a professional body, and had a minimum of 2 years of clinical experience.

The control group received enhanced usual care. In the absence of any guidelines about how to manage fatigue and the limited available research evidence, usual care inevitably varied and depended on the clinicians treating patients with breast cancer at the study sites. To control this current practice, we chose to enhance usual care by providing all patients with a detailed information booklet about coping with fatigue developed by Macmillan/CancerBackup (London, United Kingdom), which included details about fatigue and cancer; causes and effects of fatigue; coping with fatigue at work; diet, exercise, and sleep; planning the day; and management of fatigue.

The ratio of patients in the experimental and control groups was 3:1, respectively, to allow us to randomly assign acupuncture patients again at the end of treatment to one of three groups to test the effectiveness of self-acupuncture/self-needling as a maintenance therapy (not reported here).

Procedures

The study received ethical approval from a research ethics committee and all hospitals and centers involved. Patients were referred by clinicians or health professionals; were self-referred after responding to media publicity, Web site information, or posters displayed within the hospitals and satellite centers; were referred directly by researchers during outpatient visits; or responded to mailshot. Patients willing to participate signed a consent form and were randomly assigned after completion of baseline data. Researchers telephoned a central service (hospital clinical trials unit), and operators there used a bespoke computer system to obtain the allocations. Stratification took place based on main center. Patients in the acupuncture group visited the treatment setting to receive the intervention weekly. Trial participants' travel expenses were reimbursed. Assessments were completed at baseline and at the end of 6, 10, and 18 weeks after baseline (data for 10- and 18-week follow-ups are reported elsewhere). The trial was monitored by a trial steering/data monitoring committee that included independent members and a patient representative.

Outcome Measures

The primary outcome measure was the difference in general fatigue, as self-reported by patients with the MFI¹² at 6 weeks (treatment completion). The MFI is a brief 20-item well-validated scale measuring general fatigue and the dimensions of physical and mental fatigue, activity, and motivation. Secondary outcomes included mental fatigue, activity, and motivation (using the MFI); anxiety and depression using the 14-item Hospital Anxiety and Depression Scale (HADS)¹³; and quality of life using the Functional Assessment of Cancer Therapy-General and the Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B) module.¹⁴

Sociodemographic and treatment characteristics were obtained at baseline from patients' records and patients themselves. Use of complementary therapies in the past and during the study participation was recorded with a self-report questionnaire at 6 weeks. Patients were asked about their treatment expectations, how much they believed this method would help them alleviate fatigue, and how much faith they have in acupuncture, using three 10-point scales. Patients completed the questionnaires at home, and these were mailed back to the researchers using prepaid envelopes. We monitored adverse events by patient reports and review of therapists' records.

Sample Size

Our earlier study⁹ was used to inform the sample size calculation. The planned sample size was 320 patients, randomly assigned at a ratio of 3:1 with 240 patients in the experimental group and 80 patients in the control group, unbalanced to allow for 80% power for the second part of the trial (another random assignment of acupuncture patients to maintenance therapy with self-needling, not reported here, for which we needed 192 patients). A 20% attrition rate was anticipated. With this sample size, there would be in excess of 95% power to detect a half standard deviation (SD) difference in fatigue change scores. The power was for a two-tailed test of equal mean change scores at the 5% level of significance. The SD was anticipated to be approximately 4, and thus, the study was planned to have high power to detect a 2-unit difference in change scores. Recruitment stopped at 302 patients because the target

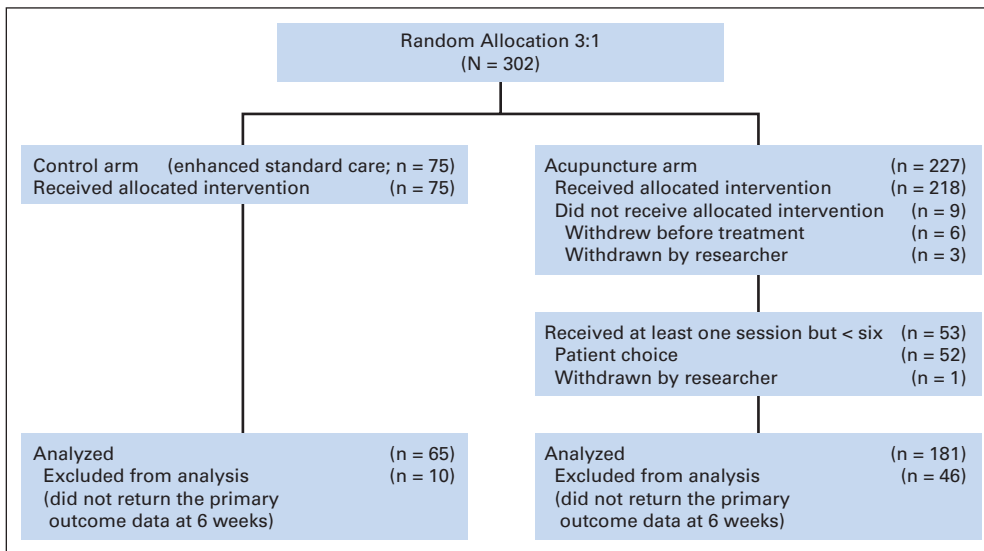


Fig 1. Flow of participants through each stage of the trial.

numbers for the second phase of the trial ($n = 192$) had been achieved, with sample power ($> 90\%$) for the first random assignment.

Data Analysis

Descriptive statistics were used to summarize the data. A simple t test was applied to fatigue change scores (week 6 – baseline), but the primary analysis was an analysis of covariance (ANCOVA) of week 6 fatigue scores with the baseline fatigue score as a covariate and trial arm as grouping factor. Similar analyses were performed for secondary outcomes (ie, subscales from the MFI, HADS, and FACT-B). A last value carried forward approach was used as a sensitivity analysis for patients missing the primary outcome. Sample sizes were adequate to justify t tests (the sampling distribution of the mean tends to normality irrespective of the distribution of the observations by the central limit theorem). Intent-to-treat analysis was performed. Normality assumptions in the data were assessed using residual plots against fitted values and a quantile-quantile plot of the residuals.

RESULTS

Sociodemographic and Clinical Characteristics

Three hundred two patients were enrolled and randomly assigned, 227 to acupuncture and 75 to usual care (Fig 1). The sample was predominantly white, married, and with college or higher education. The mean age of the enhanced usual care group was 53 years (range, 25 to 80 years), and the mean age of the acupuncture group was 52 years (range, 30 to 75 years). Time since diagnosis was 20.5 months for both groups, with a range of 6 to 84 months in the usual care group and 5 to 161 months in the acupuncture group. The mean duration of fatigue was 18 months (range, 4 to 58 months) in the usual care arm and 15 months (range, 2 to 69 months) in the acupuncture arm. Other details are listed in Table 1.

Primary Outcome Analysis

Fifty-six (18.5%) of 302 patients were missing the primary outcome, 46 (20.3%) of 227 patients in the acupuncture arm and 10 (13.3%) of 75 patients in the control arm. The trial arm effect was highly significant ($P < .001$), with an estimated difference in week 6 score (acupuncture – control) given equal baseline scores of -3.11 (95% CI, -3.97 to -2.25 ; Fig 2).

An assumption of no improvement for patients missing the 6-week general fatigue score (ie, baseline value carried forward) was postulated, providing a conservative sensitivity analysis for the primary outcome. On fitting such a model, the magnitude of the acupuncture effect was reduced to -2.49 (95% CI, -3.29 to -1.69), but this remained highly significant ($P < .001$; Table 2). ANCOVA for the primary outcome is presented in Table 3.

Assessment of a center effect was performed with the addition of two random effects (an intercept and trial arm contrast) within each of the 11 centers. This extended mixed-effects model was fitted and found not to significantly improve the fit ($P = .39$). Under the extended model, the mean treatment contrast was -2.99 , with an estimated SD of the random effect of 0.30.

Primary analysis yielded a treatment contrast of -3.11 fitted to 246 patients. Adding additional covariates of baseline FACT-B, HADS-Anxiety, and HADS-Depression in an ANCOVA model yielded a treatment contrast of -2.93 fitted to 221 patients (missing data in 25 patients), which was similar to the estimate without the covariates and highly significant ($P < .001$).

ANCOVA regression models were fitted for MFI, HADS, and FACT-B subscales. In each case, the week 6 value was the response and the baseline value was used as covariate. The key results are listed in Table 3, showing that the acupuncture intervention had beneficial effects on all secondary outcomes assessed.

Subgroup analyses were carried out with regard to the screening fatigue score (5 to 6 [moderate fatigue] v 7 to 10 [severe fatigue]), age (median cutoff point of 52 years), and whether patients were receiving or not receiving maintenance hormone therapies. Significance was assessed by adding appropriate interaction terms to ANCOVA. None of the results were significant (test of heterogeneity, 0.23, 0.23, and 0.34 for fatigue score, age, and receipt of hormone therapy, respectively).

Participants were asked before random assignment how much they expected acupuncture to help them alleviate fatigue. Expectation of effect did not relate to outcome, as the Spearman rank correlations were $r_s = -0.18$ ($n = 62$, $P = .15$) in the control group and $r_s = -0.03$ ($n = 175$, $P = .74$) in the acupuncture group.

Table 1. Sociodemographic and Clinical Characteristics of the Patient Sample

Characteristic	Usual Care Group (n = 75)		Acupuncture Group (n = 227)	
	No. of Patients	%	No. of Patients	%
Marital status				
Single	17	23	47	21
Married	46	61	124	55
Divorced or separated	8	11	49	22
Widowed	4	5	7	3
Living arrangements				
Living alone	15	20	51	22
Living with husband or partner	51	68	140	63
Other	9	12	36	16
Educational attainment				
Secondary school	13	17	64	28
College/diploma	25	33	81	36
University/degree	23	31	45	20
Postgraduate	14	19	36	16
Missing	0	0	1	< 1
Race or ethnicity				
White	71	95	212	93
Black	1	1	3	1
Asian/Chinese	0	0	9	4
Mixed	3	4	2	1
Missing	0	0	1	< 1
Religious affiliation				
Christian	57	76	173	76
Muslim	0	0	5	2
Hindu	0	0	2	1
None	16	21	36	16
Prefer not to say	0	0	3	1
Other	2	3	8	4
Occupational status				
Employed full-time	19	25	59	26
Employed part-time	21	28	74	33
Retired	19	25	30	13
Unemployed	0	0	5	2
Casual worker	1	1	0	0
Not working because of ill health	10	13	39	17
Housewife	3	4	12	5
Other	0	0	8	4
Missing	2	3	0	0
Cancer treatment				
Surgery and chemotherapy	12	16	45	20
Chemotherapy and radiotherapy	1	1	2	1
Surgery, chemotherapy, and radiotherapy	62	83	180	79
Chemotherapy type				
CMF	1	1	4	2
Anthracyclines	32	43	99	44
Taxanes	8	11	16	7
CMF and anthracyclines	10	13	44	19
Anthracyclines and taxanes	20	27	48	21
CMF, anthracyclines, and taxanes	0	0	2	1
Missing	4	5	14	6
Baseline General Fatigue score				
≤ 16	36	48	113	50
17 or 18	24	32	68	30
19 or 20	15	20	46	20

(continued in next column)

Table 1. Sociodemographic and Clinical Characteristics of the Patient Sample (continued)

Characteristic	Usual Care Group (n = 75)		Acupuncture Group (n = 227)	
	No. of Patients	%	No. of Patients	%
Question rating				
Faith in acupuncture				
Median	7		7	
Range	0-10		0-10	
No. of patients with missing data	2		8	
Expectations of acupuncture in general				
Median	7		7	
Range	0-10		0-10	
No. of patients with missing data	2		7	
Expectations of acupuncture with fatigue				
Median	7		7	
Range	0-10		0-10	
No. of patients with missing data	3		8	

Abbreviation: CMF, cyclophosphamide, methotrexate, and fluorouracil.

DISCUSSION

This study determined that women with breast cancer and CRF reported significant improvements in overall fatigue, physical and mental fatigue, activity, motivation, psychological distress, and all domains of quality of life after 6 weeks of acupuncture. To our knowledge, this is the first large multisite trial of its kind and provides some evidence of the effects of acupuncture.

This trial confirms preliminary and promising evidence obtained from an uncontrolled single-arm trial⁶ and our own pilot study.⁹ Although the magnitude of the improvement in the current trial in absolute numbers was lower than previous preliminary studies, it is nevertheless both statistically and clinically important. The approach used in this study not only improved physical fatigue and physical and functional quality of life, but also improved mental fatigue, which has

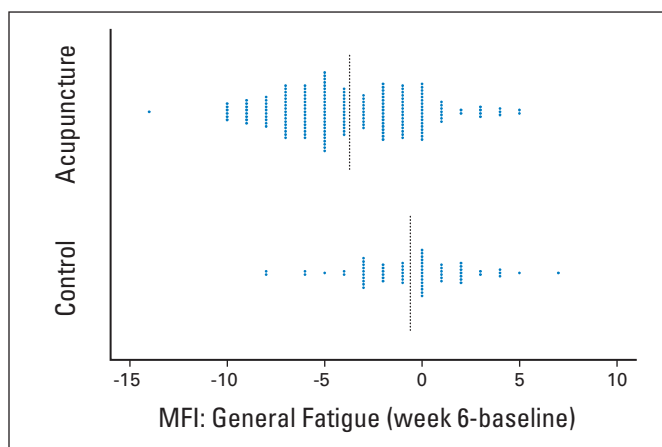


Fig 2. Change in Multidimensional Fatigue Inventory (MFI): General Fatigue scores from baseline to 6 weeks.

Table 2. Fatigue Change Scores Analyses

Measure	Complete Patients (n = 246)	LVCF (n = 302)
Mean score (GF.6–GF.0), SC	–0.62	–0.53
Mean score (GF.6–GF.0), Acu	–3.72	–2.96
Difference (Acu–SC) in mean change in GF (GF.6–GF.0)	–3.10	–2.43
95% CI	–3.98 to –2.23	–3.19 to –1.67
P	< .001	< .001
Covariance model estimates for GF		
Baseline GF		
Estimate		0.47
SE		0.07
Acupuncture		
Estimate	–3.11	
SE		0.44

Abbreviations: Acu, acupuncture arm; GF, General Fatigue; GF.0, General Fatigue at baseline; GF.6, General Fatigue at 6 weeks; LVCF, last value carried forward; SC, standard care.

been a difficult area in the past in which to demonstrate an improvement.⁹ The improvements in psychological distress and emotional adjustment are also interesting, particularly because fatigue has been shown to be part of symptom clusters alongside anxiety and depression,¹⁵ and acupuncture could be an approach to manage clusters of symptoms rather than only single symptoms.

The evidence around the role of acupuncture for supportive care in cancer is increasing, and positive trials exist for the management of hot flushes, aromatase inhibitor–induced arthralgia, chemotherapy–induced nausea and vomiting, and xerostomia.^{16,17} Why acupuncture helps to reduce fatigue is not known, and this should be the focus of future work. However, we know acupuncture has an effect on inflammatory cytokines, T lymphocytes, and various peptides,¹⁸ and recent

results suggest that cytokines and tumor necrosis factor α signaling are contributing factors in the development of fatigue.^{19,20}

Although it is acknowledged that a placebo effect in an acupuncture trial may be possible, a sham acupuncture needling method was not included because of debate surrounding sham methods. It is increasingly believed a sham controlled trial is only appropriate when two acupuncture interventions are compared. In addition, sham acupuncture designs cannot detect the whole placebo effect, may generate false-negative results,^{21–24} and may introduce ethical and practical dilemmas.²⁵ Experimental and clinical studies have also shown that minimal or sham acupuncture used as placebo control is not necessarily inert from a physiologic perspective, and its relevance as placebo acupuncture must be questioned,^{26,27} even when it is not used as per acupuncture principles.^{22,28} Instead of reducing bias, sham designs may introduce bias against the treatment being tested.²⁹ To regard placebo acupuncture as a universally effective super placebo would be inappropriate, and results should be interpreted with care.^{30,31}

We followed a pragmatic design focusing on effectiveness rather than efficacy that best reflects the likely clinical response in practice, but we acknowledge that acupuncture may have a placebo effect.³² We enhanced usual care by providing participants with a booklet about fatigue management options, therapists in the acupuncture group communicated and stayed with patients only to facilitate treatment, and there was no evidence of expectancy in the results; these facts partly control for placebo effects as a result of increased contact and expectation. Future acupuncture trials should include an active control arm, such as attention control, educational intervention, or exercise, alongside a no treatment arm or wait-list arm, so nonspecific and placebo effects of acupuncture can be assessed more appropriately.

Findings need to be set in context of the study’s limitations. Because of self-referral and the multiplicity of sites involved in recruitment, it was not possible to obtain data on how many patients were approached for participation; hence, we do not know whether our

Table 3. Difference in Outcomes at Week 6 for Fatigue, Quality of Life, Anxiety, and Depression

Scale	Score Range	No. of Patients Missing Data	Equal Slopes P	Trial Arm P	Acupuncture Effect*	SE	95% CI
MFI							
GF	0-20	56	.23	< .001	–3.11	0.44	–3.97 to –2.25
GF (LVCF)	0-20	0	.35	< .001	–2.49	0.44	–3.29 to –1.69
PF	0-20	56	.40	< .001	–2.36	0.45	–3.25 to –1.47
RA	0-20	61	.68	< .001	–2.29	0.41	–3.10 to –1.48
RM	0-20	60	.93	< .001	–2.02	0.40	–2.82 to –1.22
MF	0-20	61	.14	< .001	–1.94	0.44	–2.81 to –1.07
HADS							
Anxiety	0-21	70	.94	< .001	–1.83	0.44	–2.69 to –0.97
Depression	0-21	67	.67	< .001	–2.13	0.36	–2.85 to –1.41
FACT-B							
PWB	0-28	63	.006	< .001	3.30	0.57	2.17 to 4.43
SFWB	0-28	63	.08	.05	1.05	0.54	–0.01 to 2.11
EWB	0-24	62	.04	< .001	1.93	0.49	0.96 to 2.90
FWB	0-28	85	.29	< .001	3.57	0.61	2.38 to 4.76

NOTE. Analysis of covariance was used with baseline values as covariate and trial arm as grouping factor. For conciseness, only the trial arm estimates are given here.

Abbreviations: EWB, Emotional Well-Being; FACT-B, Functional Assessment of Cancer Therapy–Breast Cancer; FWB, Functional Well-Being; GF, General Fatigue; HADS, Hospital Anxiety and Depression Scale; LVCF, last value carried forward; MF, Mental Fatigue; MFI, Multidimensional Fatigue Inventory; PF, Physical Fatigue; PWB, Physical Well-Being; RA, Reduced Activity; RM, Reduced Motivation; SFWB, Social/Family Well-Being.

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

sample is highly selected or whether it differs from those who were ineligible. One of the difficulties in recruitment was to identify women with moderate or severe fatigue levels; despite the literature showing high incidence of CRF, much of the fatigue reported by patients in our study was of low severity, and we needed to screen many hundreds of patients to identify those with at least moderate CRF. It is also important to emphasize that acupuncture is not just a simple needling technique eliciting specific physiologic effects, but wide improvements in patient-reported outcomes may indicate nonspecific placebo effects. We also need to recognize that improvements in outcome variables in an unblinded trial may be susceptible to assessment bias, although the secondary patient-reported outcomes we have used are well known to co-occur with fatigue and impact on quality of life.³³⁻³⁵ There was a 20% missing data rate (which was expected and incorporated at the time of sample size calculations), which was partly addressed through sensitivity analysis; however, a 7% difference in missingness between the two arms, although not statistically significant, needs to be considered when results are interpreted. Also, the trial was powered for the primary outcome analysis; all other analyses on secondary outcomes need to be considered corroborative or hypothesis generating rather than definitive. Finally, lack of blinding may be a concern, but in the absence of credible controls for an acupuncture trial, we chose a pragmatic trial design. Inclusion of objective physiologic data in future trials will provide stronger evidence of effect in acupuncture trials.

The trial shows that patients in the intervention group reported better fatigue, anxiety, depression, and quality-of-life scores, but the design of the trial does not allow the specific effect of acupuncture to be distinguished from other elements and effects of the intervention. Although this trial provides some evidence of effectiveness, further effectiveness trials using appropriate controls, where hypotheses and

study design are formulated based on conditions in routine practice, and outcomes essential for clinical decisions are warranted before recommending widespread use of acupuncture in patients with breast cancer. Acupuncture could be a treatment option for CRF, although its availability may be an issue in many health care services and patients may not be able to afford private costs. Future research should concentrate on cost-effectiveness of acupuncture, because potentially expensive acupuncture treatments may be offset by reduced societal costs and health care utilization in those suffering significant and protracted fatigue after treatment. Future studies should collect long-term outcome data for fatigue that could make results more convincing. The use of acupuncture should also be tested in other cancer diagnostic groups.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Provision of study materials or patients: Peter Mackereth, Jacqueline Filshie

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Data analysis and interpretation: Alexander Molassiotis, David W. Ryder

Manuscript writing: All authors

Final approval of manuscript: All authors

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