

Acupuncture Versus Venlafaxine for the Management of Vasomotor Symptoms in Patients With Hormone Receptor–Positive Breast Cancer: A Randomized Controlled Trial

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ABSTRACT

Purpose

Vasomotor symptoms are common adverse effects of antiestrogen hormone treatment in conventional breast cancer care. Hormone replacement therapy is contraindicated in patients with breast cancer. Venlafaxine (Effexor), the therapy of choice for these symptoms, has numerous adverse effects. Recent studies suggest acupuncture may be effective in reducing vasomotor symptoms in menopausal women. This randomized controlled trial tested whether acupuncture reduces vasomotor symptoms and produces fewer adverse effects than venlafaxine.

Patients and Methods

Fifty patients were randomly assigned to receive 12 weeks of acupuncture ($n = 25$) or venlafaxine ($n = 25$) treatment. Health outcomes were measured for up to 1 year post-treatment.

Results

Both groups exhibited significant decreases in hot flashes, depressive symptoms, and other quality-of-life symptoms, including significant improvements in mental health from pre- to post-treatment. These changes were similar in both groups, indicating that acupuncture was as effective as venlafaxine. By 2 weeks post-treatment, the venlafaxine group experienced significant increases in hot flashes, whereas hot flashes in the acupuncture group remained at low levels. The venlafaxine group experienced 18 incidences of adverse effects (eg, nausea, dry mouth, dizziness, anxiety), whereas the acupuncture group experienced no negative adverse effects. Acupuncture had the additional benefit of increased sex drive in some women, and most reported an improvement in their energy, clarity of thought, and sense of well-being.

Conclusion

Acupuncture appears to be equivalent to drug therapy in these patients. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use in patients with breast cancer.

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INTRODUCTION

There were approximately 182,460 new cases of breast cancer in the United States in 2008, and a recent National Cancer Institute report estimates that one in eight women in the United States will develop breast cancer in her lifetime.¹ Conventional medical treatment commonly involves the use of chemotherapy and hormone therapy (eg, tamoxifen or aromatase inhibitors). The recommended duration of initial hormone therapy is 5 years. With such a long course of treatment, adverse effects can become a major cause of decreased quality of life and treatment discontinuation. The most prevalent debilitating adverse effects experienced by breast cancer patients receiving hormone therapy are vaso-

motor symptoms (hot flashes, night sweats, and so on). A survey conducted to determine the prevalence and severity of vasomotor, gynecologic, and other symptoms in women with a history of breast cancer² found that of women taking tamoxifen, 52% had night sweats and 78% had hot flashes (described as a sudden, brief sensation of heat, often over the entire body, and characteristic of menopause). Furthermore, they often reported more severe symptoms than menopausal women not taking tamoxifen. Increasing severity of hot flashes and night sweats was also associated with increased feelings of depression or difficulty sleeping.

Hormone replacement therapy, normally used in postmenopausal women to treat vasomotor symptoms, is contraindicated in estrogen-sensitive

breast cancer patients because of the potential increased risk of recurrent cancer. Other pharmacologic agents used to decrease vasomotor symptoms include steroids (megestrol acetate) and clonidine (transdermal patch).³ Many patients are noncompliant with these medications as a result of their adverse effects (ie, weight gain and hypotension, respectively).

The antidepressant, venlafaxine (Effexor; Wyeth Pharmaceuticals, Collegeville, PA), a selective serotonin reuptake inhibitor, is currently the pharmacologic therapy of choice for hot flashes. A double-blind, placebo-controlled, randomized study⁴ comparing placebo to 37.5, 75, or 150 mg daily venlafaxine over 4 weeks of treatment showed decreases in hot flash scores of 27% in the placebo group and 37%, 61%, and 61%, respectively, in the venlafaxine groups. Adverse effects of venlafaxine treatment included mouth dryness, decreased appetite, nausea, and constipation; adverse effects were significantly higher in the groups receiving 75 and 150 mg. Although venlafaxine has been shown effective in treating vasomotor symptoms, many women refuse this approach because of the potential adverse effects or because they do not want any more medication. However, research shows that a

large proportion of women feel their breast cancer exacerbated physical or emotional problems related to menopause, and 50% feel they need treatment.² Thus, effective nonpharmacologic treatments with minimal or no adverse effects are urgently needed to improve quality of life for breast cancer patients and support conventional breast cancer therapy.

Acupuncture, a complementary and alternative medicine therapy that has been used successfully to treat a variety of health problems, is a promising alternative to venlafaxine because it has few or no adverse effects and preliminary studies indicate its effectiveness in decreasing vasomotor symptoms. Two pilot studies showed that acupuncture treatment for 5 to 8 weeks decreased vasomotor symptoms by approximately 50% in menopausal women.^{5,6} A randomized controlled trial (RCT)⁷ showed that acupuncture reduced the number of hot flashes significantly more than a placebo. However, although acupuncture seems to significantly reduce the number of hot flashes in menopausal women, studies that compared acupuncture to sham acupuncture found significantly greater decreases in severity, but not frequency, of hot flashes in the acupuncture groups compared with

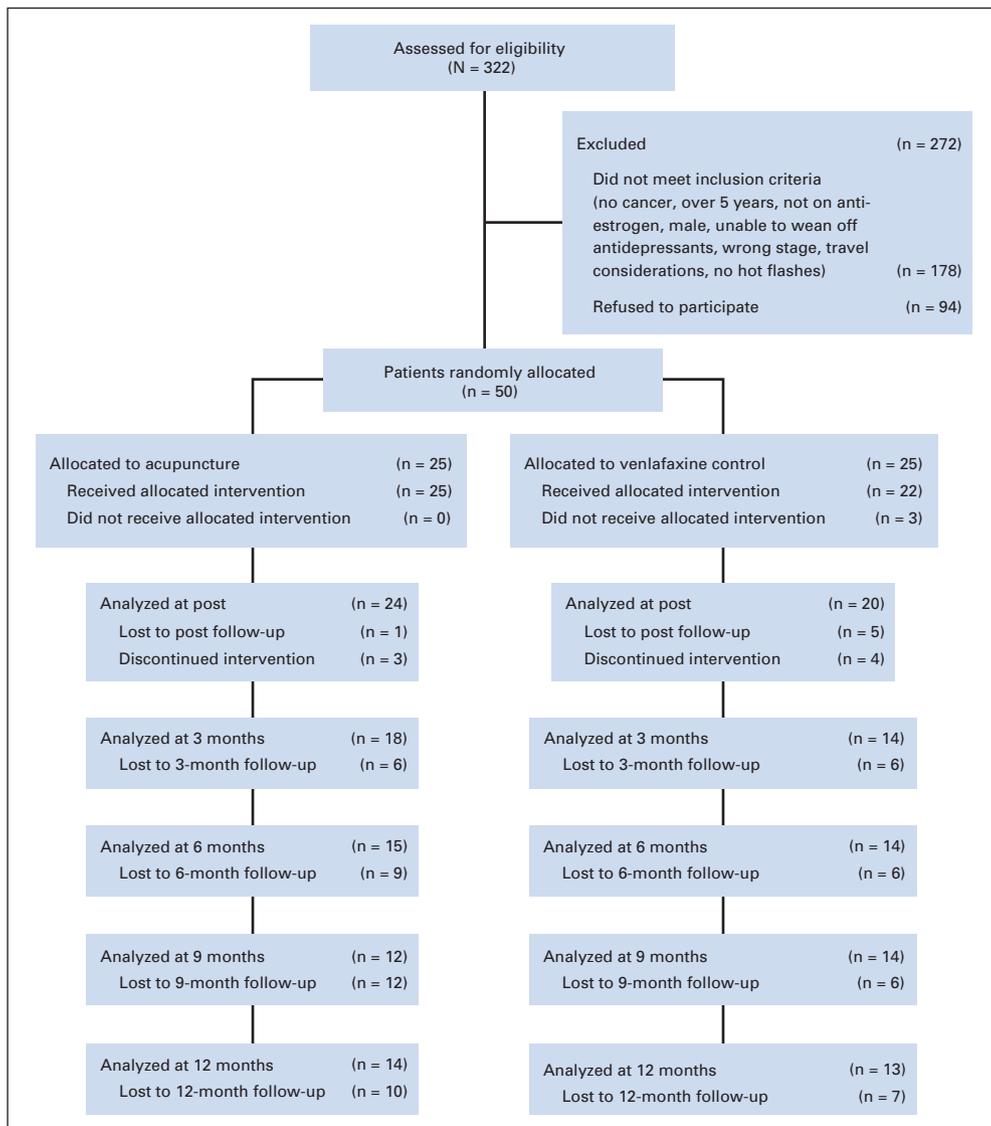


Fig 1. CONSORT diagram.

the sham controls.⁸⁻¹⁰ Given the need for finding nonpharmacologic treatment options for women, we conducted an RCT to evaluate the effect of acupuncture in reducing/eliminating vasomotor symptoms in patients with breast cancer who received antiestrogen hormone therapy as compared with venlafaxine and to determine whether acupuncture has fewer adverse effects.

PATIENTS AND METHODS

Study Participants

Patients were recruited from oncology clinics of Henry Ford Health System (numerous locations in Michigan). Informed consent was obtained before participant enrollment. This study was approved by the hospital institutional review board. Recruitment took place September 2004 through June 2007. Inclusion and exclusion criteria are listed below and shown in Appendix Table A1 (online only). The inclusion criteria were as follows: (1) stage 0-III pre- or postmenopausal breast cancer patients on hormone therapy with tamoxifen or arimidex (premenopausal patients must not have menstruated for at least 6 months); (2) ≥ 14 hot flashes per week; (3) ≥ 18 years of age; (4) may have been treated locally with surgery and/or radiation and must have completed chemotherapy; (5) may be receiving radiation therapy but otherwise must be within 5 years after treatment; (6) must be on a stable dose of hormone therapy for 4 weeks or more without plans to discontinue therapy for the duration of the study; (7) Karnofsky performance status (KPS) > 70 ; (8) life expectancy > 6 months.

Figure 1 shows the number of patients assessed for eligibility, randomly assigned, and evaluated. Fifty patients were assigned to either venlafaxine ($n = 25$; control arm) or acupuncture ($n = 25$; study arm). At the end of 12 weeks of treatment, all patients stopped therapy and were observed for 1 year.

Study Design

This RCT compared 12 weeks of acupuncture or venlafaxine treatment. The primary end point was hot flash frequency. Patients were observed for 1 year post-treatment. Figure 2 shows the general study design.

Outcome Measures

The following published, reliable, and validated measures were used to assess health outcomes: the Hot Flash Diary¹¹ measured the number and severity of hot flashes; the Menopause Specific Quality of Life Questionnaire (MenQOL)^{6,12} measured health status related to menopause-like symptoms; the Short Form 12-Item Survey (SF-12)^{13,14} measured general health status; the Beck Depression Inventory-Primary Care (BDI-PC)^{15,16} measured mental health/mood; and the National Cancer Institute Common Toxicity Criteria scale¹⁷ measured adverse effects of treatment.

Venlafaxine Control

Patients in the control arm took venlafaxine 37.5 mg orally at night for 1 week, then 75 mg at night for the remaining 11 weeks. Patients who could not tolerate the higher dose remained at 37.5 mg. This dosing schedule is similar to that of the venlafaxine study mentioned previously.⁴

Acupuncture Intervention

Acupuncture therapy was provided at two locations, the Henry Ford Center for Integrative Medicine and the Walter B. Ford Department of Radiation Oncology at Henry Ford Hospital. Patients in the acupuncture arm received treatments twice per week for the first 4 weeks, then once per week for the remaining 8 weeks. On the initial visit of 60 minutes, a full health intake and evaluation was given, including a traditional Chinese medicine (TCM) evaluation of tongue and pulse, which is diagnostic for TCM. All other sessions were 40 minutes, 30 minutes of which were spent in treatment. Acupuncture was given using stainless steel 34 gauge (Japanese size: 0.20 \times 30 mm) filiform needles (Seirin; Shizuoka City, Japan; and Carbo, Toronto, Canada). Skin was swabbed with an alcohol prep pad before acupuncture was administered. Needles were inserted 0.25 to 0.5 inches deep into the skin and gently manipulated to create the *de qi* sensation. No electrical stimulation was used. Far-infrared heat lamps were used if needed to prevent the participant from

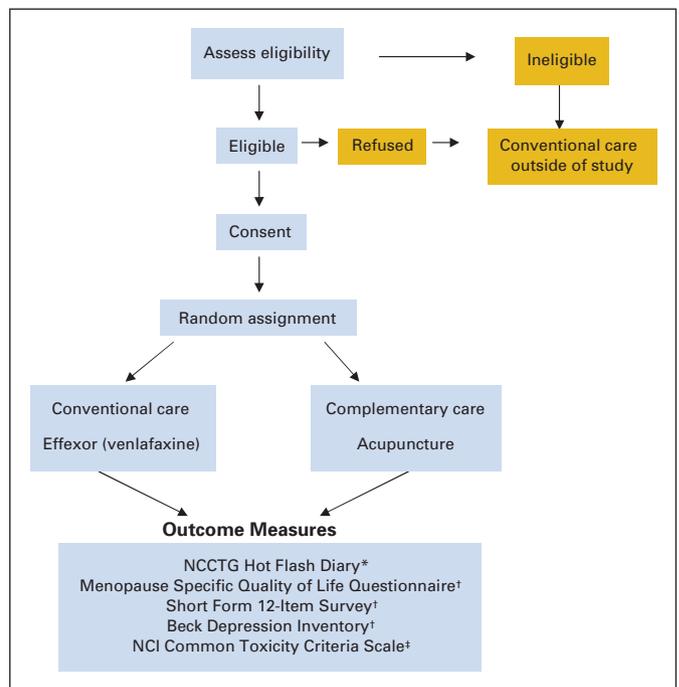


Fig 2. Study design. NCCTG, North Central Cancer Treatment Group; NCI, National Cancer Institute. (*) Assessed at baseline; throughout treatment; for 4 weeks post-treatment; and at 3-, 6-, 9-, and 12-month post-treatment follow-ups. (†) Assessed at baseline; at the end of treatment; and at 3-, 6-, 9-, and 12-month follow-ups. (‡) Assessed throughout treatment, and at 3-, 6-, 9-, and 12-month follow-ups.

becoming cold during treatment in rooms where heat regulation was not possible. All rooms were dimly lit for comfort.

Primary and Secondary Points

All patients were treated using primary acupuncture points of urinary bladder 23, kidney 3, and spleen 6 for general menopausal symptoms. Secondary points were used as needed according to the TCM diagnosis: du 14, gallbladder 20, lung 9, liver 3, du 20, stomach 36, ren 6, pericardium 7, and heart 7. Table 1 lists primary and secondary point details.

Statistical Methods

The various health outcome measures were examined using a mixed model analysis of variance (ANOVA) methodology. Tests for main effects of time and group were examined along with a group by time interaction. Results of the test for interaction were used to identify differential effects of the treatments. The PROC MIXED procedure in SAS (SAS Institute, Cary, NC) was used, as it allows for missing data points conducive to the intent-to-treat approach we used.

A second analysis was completed for hot flashes to examine a special observation period of pretreatment, post-treatment and weeks 1 through 4 post-treatment. The various pair-wise comparisons between results for the differing time periods were done using paired *t* tests.

The difference between groups in adverse effects rates was compared using a ratio test from sampling theory. This approach estimates the rates and their standard deviations and computes a test statistic comparing the two.

RESULTS

Study participants ranged in age from 35 to 77 years, with a median of 55 years; 82% were postmenopausal. Regarding race and ethnicity, 64% were white, 32% were African American, and 4% were Hispanic (Appendix Table A2, online only). Patients were evenly distributed between the two arms, although the median age in the

Table 1. Acupuncture Points Used in the Study

| Point Name | Location | Function |
|--------------------|--|---|
| Kidney 3 | In the depression between the medial malleolus and tendo calcaneus, at the level of the tip of the medial malleolus | Supplements kidney yin to decrease hot flashes |
| Urinary bladder 23 | 1.5 cun* lateral to du 4, at the level of the lower border of the spinous process of the second lumbar vertebra | Back shu point† of the kidney energy |
| Spleen 6 | 3 cun directly above the tip of the medial malleolus, on the posterior border of the medial aspect of the tibia | Tones body energy and blood to help decrease flashes |
| Gallbladder 20 | In the depression between the upper portion of m. sternocleidomastoideus and m. trapezius, on the same level with du 16 | Decreases extreme hot flashes and relaxes musculature |
| Du 14 | Below the spinous process of the seventh cervical vertebra, approximately at the level of the shoulders | Decreases extreme flashes, regulates immunity |
| Du 20 | On the midline of the head, 7 cun directly above the posterior hairline, approximately on the midpoint of the line connecting the apexes of the two auricles | Uplifts energy to alleviate depression signs and symptoms |
| Stomach 36 | 3 cun below ST 35, 1 fingerbreadth from the anterior crest of the tibia, in m. tibialis anterior | Supplements energy and blood, supports digestion |
| Liver 3 | On the dorsum of the foot, in the depression distal to the junction of the first and second metatarsal bones | Moves energy to alleviate depression |
| Heart 7 | At the ulnar end of the transverse crease of the wrist, in the depression on the radial side of the tendon of m. flexor carpi ulnaris | Reduces palpitations and insomnia, supports healthy sleep patterns, decreases anxiety |
| Pericardium 7 | In the middle of the transverse crest of the wrist, between the tendons of m. palmaris longus and m. flexor carpi radialis | Reduces palpitations and insomnia |
| Ren 6 | On the midline of the abdomen, 1.5 cun below the umbilicus | Regulates the lower abdomen and decreases fatigue |
| Lung 9 | At the radial end of the transverse crease of the wrist, in the depression on the lateral side of the radial artery | Regulates excess sweating and decreases symptoms of grief |

*A cun is a measurement used in finding acupuncture points. It is equivalent to the width of the distal phalanx of the participant's thumb.

†Shu points are acupuncture points located 1.5 cun lateral to the midline of the back that relate to and directly affect specific meridians (systems of energy).

venlafaxine arm was slightly older than that in the acupuncture arm (56 v 50 years, respectively). Appendix Table A3 (online only) shows the groups' baseline characteristics, including age and hot flash frequency and severity.

Of 94 eligible patients who declined to participate (Fig 1), 30 did so because they were unwilling to participate if assigned to venlafaxine (none declined because of acupuncture). Of the patients assigned to the acupuncture arm, several were lost to follow-up for the following reasons: noncompliance with the follow-up schedule, scheduling conflicts, and inability to be contacted. In the venlafaxine arm, three patients dropped out because of adverse effects; others either did not start treatment or were noncompliant with follow-up.

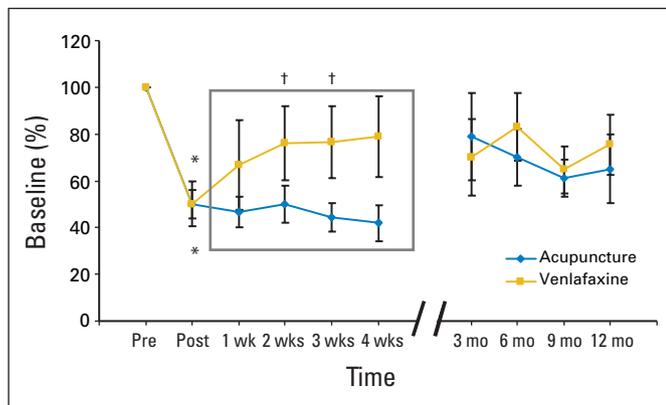


Fig 3. Hot flash frequency (mean ± SE of the mean) as a percentage of baseline for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and follow-up times of 1, 2, 3, and 4 weeks and 3, 6, 9, and 12 months post-treatment. Boxed area highlights the additional analysis of the first 4 weeks post-treatment. (*) $P < .05$, significantly different from Pre; (†) $P < .05$, significantly different from Post.

The participant flow through the trial is shown in Figure 2. The primary outcome was hot flash frequency from pre- to post-treatment and at 3-, 6-, 9-, and 12-month follow-up points. ANOVA showed a significant effect of group ($P < .036$) and time ($P < .001$), but no significant interaction effect. This indicated that although groups started out differently (the acupuncture group had more hot flashes at pretreatment), both groups experienced similar changes across time, including significant decreases in hot flashes from pre- to post-treatment of 50%, followed by a return toward baseline at follow-up time points (Fig 3).

To determine whether the beneficial effects of acupuncture or venlafaxine were longer lasting, we also evaluated hot flashes for the first 4 weeks post-treatment (boxed area in Fig 3). ANOVA indicated a significant time effect ($P < .001$) and interaction effect ($P < .029$), indicating differences in the pattern of change in the groups across time. Although both groups experienced a 50% decrease in hot flashes at post-treatment, by 2 weeks post-treatment the venlafaxine group experienced significant increases in hot flashes, whereas the acupuncture group remained low. Because hot flash diaries were not collected between 4 weeks and 3 months post-treatment, a retrospective chart review was conducted to determine when hot flash frequency began to increase in the acupuncture group. At a 2-month follow-up visit, acupuncture patients reported to the physician that hot flash frequency was similar to their 1-month values, whereas at the 3-month follow-up, they reported that frequency had recently increased, which corroborated the data seen in Figure 3.

The results of the ANOVA for secondary outcome measures showed a significant effect of time for hot flash severity ($P < .001$; Fig 4), BDI-PC ($P < .001$; Fig 5), MenQOL ($P < .002$; Fig 6), and SF-12: Mental ($P < .007$; data not shown). There were no significant effects of group or significant interactions. Thus, both groups had similar

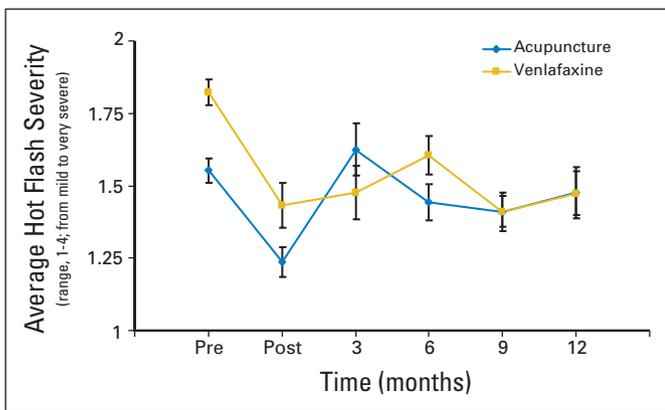


Fig 4. Hot flash severity (mean \pm SE of the mean) for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and 3, 6, 9, and 12 months follow-up with significant effect of time, but no group or interaction effects.

changes over time in each outcome measure. That is, they experienced improvements at post-treatment, followed by a return toward baseline values at follow-up times. There were no significant effects for SF-12: Physical.

In summary, both groups exhibited significant decreases in hot flashes, depressive symptoms, and other menopausal quality-of-life symptoms, as well as significant improvements in mental health from pre- to post-treatment. These changes were similar in both groups, indicating that acupuncture was at least as effective as venlafaxine.

National Cancer Institute Common Toxicity Criteria scale data showed there were 18 incidences of adverse effects (eg, nausea, headache, difficulty sleeping, dizziness, and so on) in the venlafaxine-treated group, in contrast to zero adverse effects in the acupuncture group (Appendix Table A4, online only). Rates, estimated by a ratio estimator, are 0.72 ± 0.20 and 0 ± 0.04 , respectively. These estimates are significantly different ($P \leq .002$).

DISCUSSION

To our knowledge, this is the first RCT to compare acupuncture to drug therapy for treatment of vasomotor symptoms in patients with breast cancer who receive antiestrogen hormone therapy. Our results

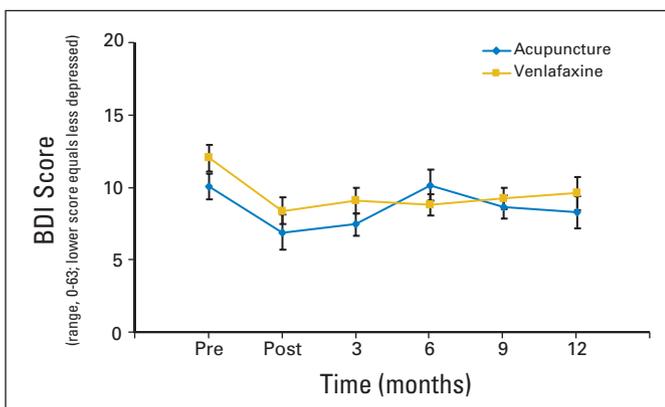


Fig 5. Beck Depression Inventory (BDI) scores (mean \pm SE of the mean) for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and 3, 6, 9, and 12 months follow-up with significant effect of time, but no group or interaction effects.

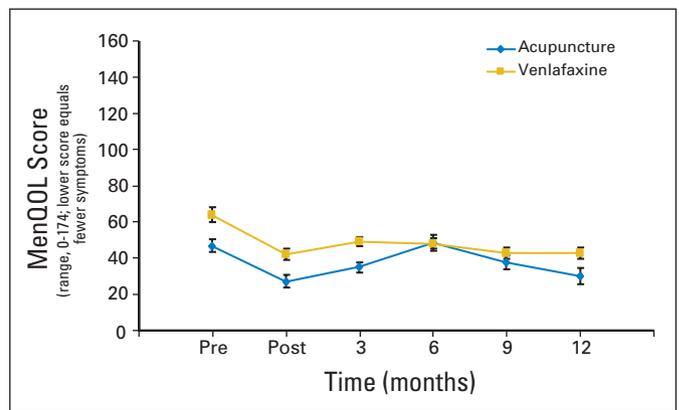


Fig 6. Menopause Specific Quality of Life (MenQOL) scores (mean \pm SE of the mean) for acupuncture and venlafaxine groups at pretreatment (Pre), post-treatment (Post), and 3, 6, 9, and 12 months follow-up with significant effect of time, but no group or interaction effects.

showed that acupuncture was as effective as venlafaxine in decreasing the number of hot flashes. Most remarkable was the duration of the acupuncture effect. Within 2 weeks of discontinuing drug therapy, venlafaxine patients experienced significant increases in the number of hot flashes compared with post-treatment levels. Although the study design did not include hot flash frequency reports for the 5- to 12-week period, a 2-month physician post-treatment follow-up visit suggested that hot flash frequency remained low between the 4-week visit and the 3-month visit for the acupuncture group. The 3-month visit was the first reported time that an increase in hot flash frequency occurred for the acupuncture group.

Acupuncture had no adverse effects, and patient reports to the physician at follow-up indicated acupuncture had the additional benefit of increased sex drive in some women (approximately 25%). Most women also reported an improvement in their energy, clarity of thought, and sense of well-being.

Given the results of this small randomized study, we feel that integrative therapies have a role in improving the quality of life of cancer patients and should be explored further as an option for treatment of cancer-related adverse effects. Acupuncture has been shown to be effective in treating nausea and pain in patients with cancer¹⁸⁻²⁰ and in gynecology to treat primary dysmenorrhea.²¹ It has also been used for analgesia during delivery,²² to induce ovulation,²³ and to correct breech presentation.²⁴

Recently, there have been four studies suggesting a benefit of acupuncture in patients with hormone-treated breast cancer. One is a small Italian pilot study²⁵ in which women were treated with acupuncture weekly for 3 months, then reduced to monthly for maintenance while taking tamoxifen. Their results indicated that acupuncture was effective in reducing hot flashes in patients with hormone-treated breast cancer, but patient group size was small ($n = 15$) and follow-up was short. Researchers noted reductions in anxiety, depression, and somatic and vasomotor symptoms, although libido was not modified.²⁵ Two studies from the United Kingdom have shown the benefit for acupuncture in patients with breast cancer who took tamoxifen. In one study,²⁶ 54 women who suffered from vasomotor symptoms were offered eight sessions of weekly traditional acupuncture. At the end of treatment, 36% of patients reported a 50% or greater improvement in symptoms, and 89% reported some improvement. Positive results were maintained after treatment ended. The author reported personal

accounts by the women who felt their energy levels had increased and their overall quality of life had improved after acupuncture. Similar findings were noted in a more recent study using ear acupuncture.²⁷

A larger RCT from Norway²⁸ compared 10 weeks of true acupuncture to sham acupuncture in 59 women who received tamoxifen after breast cancer surgery. They found true acupuncture was more effective in decreasing vasomotor symptoms than sham, both during treatment and for 12 weeks post-treatment. However, an RCT by Deng et al,²⁹ comparing 4 weeks of true acupuncture and sham acupuncture in 70 patients with tamoxifen-treated breast cancer did not confirm this finding. Although there was a significant decrease in hot flashes as a result of true acupuncture, it was not significantly different than that of sham acupuncture. However, when sham acupuncture patients were switched to true acupuncture, there appeared to be a trend toward a benefit for true acupuncture. This reduction in hot flash frequency persisted for up to 6 months post-treatment.

Although findings of the study by Deng et al²⁹ were negative, this could be because sham acupuncture may have a greater effect than an inactive placebo. Recent studies using functional magnetic resonance imaging to evaluate true versus sham acupuncture showed that sham acupuncture sometimes stimulates the anterior cingulate cortex and thalamic regions of the brain.³⁰ Although sham acupuncture may mimic some of the effects of true acupuncture, its effects do not appear to be as great or durable.³¹⁻³³ Other studies reported that rotating the needle strengthens the effects of true acupuncture only and that these points have specific neuronal activity that results in the therapeutic effect.³⁴ The study by Deng et al²⁹ also treated the patients for a shorter time than any of the positive-results studies previously cited.

Future areas of research include the mechanism of action of acupuncture and an exploration of the exact frequency and duration of treatment that may be required. Because benefits of acupuncture lasted at least 3 months post-treatment, treatment may only be needed as a boost three to four times per year. Ultimately, this could be more cost effective for insurance companies. Another area for future study may be the use of acupuncture treatment for vasomotor symptoms due to androgen deprivation therapy in prostate cancer patients.³⁵

A point that should be considered in recommending acupuncture in this setting is that tamoxifen is converted in the body to its active metabolites by the cytochrome P450 pathway. Selective serotonin reuptake inhibitors can inhibit cytochrome P450 pathways³⁶ and tamoxifen's effectiveness may be affected in breast cancer patients who take both drugs, which could result in increased recurrence rates. Therefore, acupuncture would be a good alternative for treatment of vasomotor symptoms in those patients.

In conclusion, acupuncture appears to be at least as effective as drug therapy in patients with breast cancer who experience vasomotor symptoms, and it may provide additional and longer term benefits without adverse effects. It is a safe, effective and durable treatment for vasomotor symptoms secondary to long-term antiestrogen hormone therapy in breast cancer patients. We hope this study will lead to a change in the pattern of practice of treating vasomotor symptoms in patients with breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception and design: Eleanor M. Walker, Alba I. Rodriguez, Beth Kohn, Ramon Nunez, Susan Jakary, Robert A. Levine

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Final approval of manuscript: Eleanor M. Walker, Alba I. Rodriguez, Beth Kohn, Ronald M. Ball, Jan Pegg, Jeffrey R. Pocock, Ramon Nunez, Ed Peterson, Susan Jakary, Robert A. Levine

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