

Early report

Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial

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Summary

Background Hot flashes can be troublesome, especially when hormonal therapy is contraindicated. Preliminary data have suggested that newer antidepressants, such as venlafaxine, can diminish hot flashes. We undertook a double-blind, placebo-controlled, randomised trial to assess the efficacy of venlafaxine in women with a history of breast cancer or reluctance to take hormonal treatment because of fear of breast cancer.

Methods Participants were assigned placebo (n=56) or venlafaxine 37.5 mg daily (n=56), 75 mg daily (n=55), or 150 mg daily (n=54). After a baseline assessment week, patients took the study medication for 4 weeks. All venlafaxine treatment started at 37.5 mg daily and gradually increased in the 75 mg and 150 mg groups. Patients completed daily hot-flash questionnaire diaries. The primary endpoint was average daily hot-flash activity (number of flashes and a score combining number and severity). Analyses were based on the women who provided data throughout the baseline and study weeks.

Findings 191 patients had evaluable data for the whole study period (50 placebo, 49 venlafaxine 37.5 mg, 43 venlafaxine 75 mg, 49 venlafaxine 150 mg). After week 4 of treatment, median hot flash scores were reduced from baseline by 27% (95% CI 11–34), 37% (26–54), 61% (50–68), and 61% (48–75) in the four groups. Frequencies of some side-effects (mouth dryness, decreased appetite, nausea, and constipation) were significantly higher in the venlafaxine 75 mg and 150 mg groups than in the placebo group.

Interpretation Venlafaxine is an effective non-hormonal treatment for hot flashes, though the efficacy must be balanced against the drug's side-effects. Confirmation of the results of this 4-week study awaits the completion of three ongoing randomised studies to assess the effects of other related antidepressants for the treatment of hot flashes.

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Introduction

Hot flashes are a substantial problem in menopausal women. Oestrogen therapy is the mainstay of treatment for this symptom and generally controls hot flashes well.

Hot flashes may be more troublesome in women who have survived breast cancer^{1,2} than in other women for several reasons. First, many women treated for breast cancer when premenopausal undergo premature menopause from chemotherapy. Second, many survivors of breast cancer are given tamoxifen, the most prevalent side-effect of which is hot flashes. Third, women with a history of breast cancer have generally been denied oestrogen therapy, at least in North America, because of concerns about potentiating recurrence of breast cancer.

Many agents have been investigated as potential means for alleviating hot flashes in survivors of breast cancer. The best-described non-oestrogenic treatments for hot flashes are progestagens. For example, low doses of megestrol acetate result in a reduction of about 80% in hot flashes, compared with a decrease of about 20% with placebo.³ At present, there are no convincing data that megestrol acetate has any substantial positive or negative effect on breast-cancer morbidity or mortality. Therefore, this therapy can reasonably be used after a thorough discussion of potential risks and benefits with the patient. Nonetheless, some patients and physicians are concerned about the use of any hormone in survivors of breast cancer. Thus, non-hormonal means to alleviate hot flashes in these patients are needed. Various non-hormonal therapies, including vitamin E, clonidine, Bellergal (phenobarbital, ergotamine, and levorotatory alkaloids of belladonna), and methyldopa, have been examined⁴⁻⁷ but have limited efficacy or adverse side-effects.

On the basis of positive anecdotal experience, we undertook a pilot study of the antidepressant venlafaxine in cancer patients with hot flashes. The results supported the anecdotal experience.^{8,9}

We undertook this study to assess more definitively the efficacy and toxicity of various doses of venlafaxine for the treatment of hot flashes in survivors of breast cancer. The hypothesis was that venlafaxine would be effective in alleviating hot-flash activity. Planned subgroup analyses included an investigation into whether there was a dose-response relation, with control for potential confounding (mood change and quality of life).

Methods

Patients

Patients eligible for this trial were women who had a history of breast cancer or who were concerned about taking oestrogen for fear of breast cancer. Inclusion criteria were: troublesome hot flashes, occurring at least 14 times per week; flashes severe enough for the patient to desire therapeutic intervention, and present for at least a month before study entry; age older than 18 years; life expectancy at least 6 months; and performance status of 0–1 on the Eastern Cooperative Oncology Group scale.

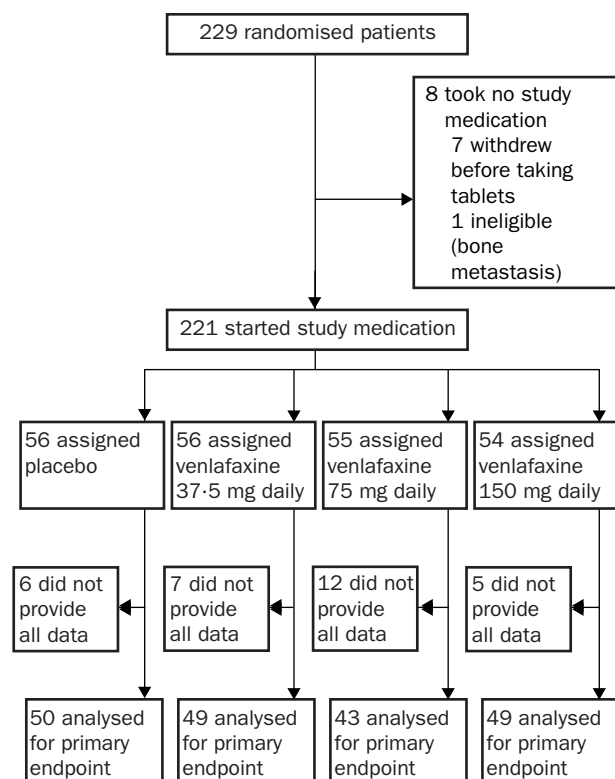


Figure 1: Trial profile

Anti-oestrogens (tamoxifen and raloxifene) and aromatase inhibitors were allowed if they had been started 4 weeks before the beginning of the study and were scheduled to continue for the next 5 weeks. Concomitant therapies not allowed were: antineoplastic chemotherapy, androgens, oestrogens, progestagens, antidepressants, clonidine, and Bellergal. Exclusion criteria were use of venlafaxine in the past; any antidepressant treatment within the preceding 2 years; pregnancy; breastfeeding; use of other medications to treat hot flashes within the previous 2 weeks; and uncontrolled hypertension (persistent diastolic blood pressure >95 mm Hg, systolic blood pressure >160 mm Hg, or both). Women with childbearing potential had to use adequate contraceptive measures. All patients were required to give written informed consent as dictated by US federal guidelines.

Design and procedures

Individual patients were stratified according to age (<50 vs ≥50 years), current tamoxifen use, duration of hot-flash symptoms (<9 vs ≥9 months), and the average frequency of hot flashes per day (2–3 vs 4–9 vs ≥10). Stratification was achieved by a method of dynamic allocation that balances the marginal distributions.¹⁰ Patients were then randomly assigned one of four treatments: extended-release venlafaxine 37.5 mg daily for 28 days; extended-release venlafaxine 37.5 mg daily for 7 days, then 75 mg daily for 21 days; extended-release venlafaxine 37.5 mg daily for 7 days, 75 mg daily for 7 days, then 150 mg daily for 14 days; or placebo for 28 days.

To ensure that treatment allocation was concealed from patients and medical professionals, and to ensure that patients received the right medication dose on each day, blister packs were issued, with three tablets each day for all patients. The tablets consisted of 37.5 mg extended-release venlafaxine, 75 mg extended-release venlafaxine, or placebo of identical appearance (tablets provided by Wyeth-Ayerst Laboratories, Philadelphia, PA, USA). Only the North

Central Cancer Treatment Group randomisation office and study statisticians had access to individual treatment assignments during the course of the study.

After randomisation, but before starting the assigned medication, each patient was asked to complete a daily diary hot-flash questionnaire for one baseline week. This questionnaire was then completed daily for the 4 weeks the patient received study medication or placebo. This questionnaire was similar to those shown to be reliable and valid in previous clinical trials involving more than 950 patients.^{3–5,8,9,11}

Patients were also asked to complete two single-item global quality-of-life questions¹² and a Beck depression inventory¹³ at the end of each of the 5 study weeks. Blood pressure was measured weekly during the study period. A study nurse contacted each patient once a week to encourage appropriate protocol participation, to inquire about hot flashes, and to assess side-effects.

If the diastolic blood pressure rose above 95 mm Hg (confirmed on more than one reading), the patient was withdrawn. The study code was broken, and the patient was allowed to taper the drug dose. 6-monthly toxicity (unmasked) and efficacy (masked) statistical summary reports were reviewed by the North Central Cancer Treatment Group external data-monitoring committee.

The weekly questionnaires inquired about potential side-effects of venlafaxine: loss of appetite, sleepiness, nausea, dizziness, tiredness (fatigue), mouth dryness, abnormal sweating, constipation, insomnia, nervousness, and mood changes.

The daily hot-flash questionnaire asked about the numbers of mild, moderate, severe, and very severe hot flashes per day (24 h period). Descriptions of hot-flash definitions from women who had taken part in previous studies were provided to each patient in the questionnaire booklet.¹⁴

Statistics

Methods used to analyse the data were similar to those used for our previous hot-flash studies.^{3–5,11} The primary endpoint was a bivariate construct of average daily hot-flash activity: the number of hot flashes and a score combining the number and severity of hot flashes. Comparisons of hot-flash activity between treatment groups used two-sided testing. Comparisons between treatment weeks that involved dose escalation used average within-patient differences. Secondary endpoints, compared by the same

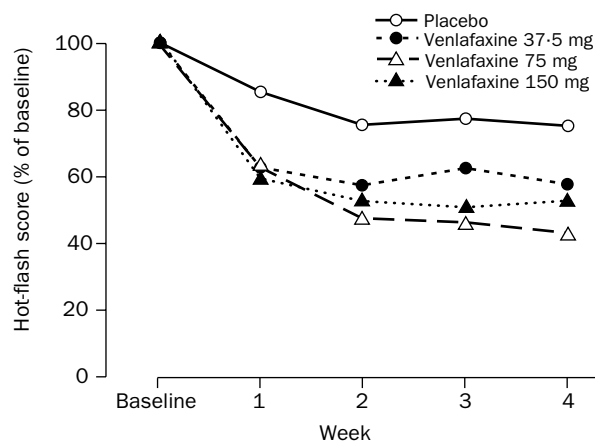


Figure 2: Mean decreases in hot-flash scores

For whole period: placebo vs 75 mg and 150 mg, $p < 0.0001$; placebo vs 37.5 mg, $p = 0.008$; 75 mg vs 37.5 mg, $p = 0.03$; 150 mg vs 37.5 mg, $p = 0.13$. Note that doses increased gradually in the 75 mg and 150 mg groups.

Measure	Median decrease (%) from baseline to week 4 (95% CI)			
	Placebo (n=50)	Venlafaxine		
		37.5 mg (n=49)	75 mg (n=43)	150 mg (n=49)
Frequency	19 (14–28)	30 (22–53)*	46 (36–63)*	58 (42–67)*
Score	27 (11–34)	37 (26–54)*	61 (50–68)*	61 (48–75)*

*p<0.001 for comparison with placebo.

Table 1: Median decrease in hot-flash frequencies and scores from baseline to treatment week 4

Score as % of baseline	Number of patients			
	Placebo (n=50)	Venlafaxine		
		37.5 mg (n=49)	75 mg (n=43)	150 mg (n=49)
0–24	5 (10%)	8 (16%)	13 (30%)	16 (33%)
25–49	5 (10%)	14 (29%)	14 (33%)	11 (22%)
50–74	16 (32%)	12 (24%)	11 (26%)	13 (27%)
75–100	12 (24%)	12 (24%)	4 (9%)	4 (8%)
>100	12 (24%)	3 (6%)	1 (2%)	5 (10%)

Table 2: Patients with hot-flash scores of various percentages of baseline during treatment week 4

methods, included changes in mood (Beck depression inventory) and quality of life from baseline to end of treatment. The proportion of patients who withdrew prematurely was compared by χ^2 test. Correlation between covariates (mood change, quality of life) was assessed with Spearman correlation coefficients. Repeated-measures ANOVA/GEE (generalised estimating equations) procedures were used to carry out a conditional analysis of the treatment effect (on the primary endpoint) in the presence of covariates.

Missing data were handled in several ways as a sensitivity analysis of the robustness of results in relation to missing data. Less than 10% of possible data were missing, and the results were consistent across a series of analyses by various imputation methods.

Daily hot-flash scores were calculated by assigning a number (1 to 4) to each severity: mild, moderate, severe, and very severe. These numbers were multiplied by the daily frequencies of each type of flash and the four products were added together to give the daily score.

We calculated that a sample size of 50 patients per group would provide 80% power to detect differences in average hot-flash activity of 0.6 SDs (1.2 hot flashes per day, a score of 3 units, or a 21% fall from baseline) with a type 1 error rate of 5%.

Results

229 patients joined this study between Feb 22 and July 27, 1999 (figure 1). Seven patients withdrew before taking any study medication and one patient was found to be ineligible. Hot-flash data for the baseline week were available for 207 patients (94%) and evaluable data over the whole study period for 191 (86%). The 30 patients who did not provide usable hot-flash data had stopped the study medications, did not properly complete or return the diary forms, or both.

At study entry the four groups were well balanced in terms of age, tamoxifen use (69% of patients), the duration of hot-flash symptoms, the patients' estimated frequencies of hot flashes, race, baseline uniscale quality-of-life values, and baseline Beck depression inventory scores. During the baseline week, hot-flash frequencies (average 8.0), scores (average 13.3), or both did not differ significantly among the four study groups.

Changes in hot-flash scores for the four study groups are shown in figure 2 and table 1. After 4 weeks of study treatment (when the groups assigned titrated doses had

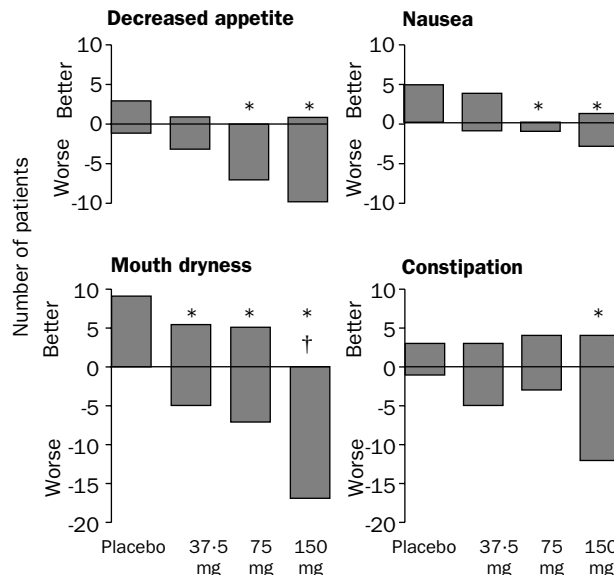


Figure 3: Toxicity comparisons during treatment week 4 compared with baseline week

Only effects with significant differences among study groups are shown. *p<0.05 for comparison with placebo group. †Significantly different from other venlafaxine groups (p=0.0006 for 37.5 mg, p=0.02 for 75 mg).

been taking the assigned maximum dose for at least 2 weeks), the median decrease in hot-flash scores was significantly greater in all three venlafaxine groups than in the placebo group (p<0.0001). Only ten of 50 (20% [95% CI 10–34]) patients in the placebo group reported a reduction of more than 50% in hot-flash activity compared with 22 of 49 (45% [31–60]), 27 of 43 (63% [47–77]), and 27 of 49 (55% [40–69]) in the three venlafaxine groups (table 2). Changes within an individual in hot-flash activity in the groups that had dose escalation mirrored the results across treatment groups, in that there were significant decreases in activity with a change from the baseline week to 37.5 mg venlafaxine (p=0.01) or from 37.5 mg to 75 mg (p=0.01), but not from 75 mg to 150 mg (p=0.74; figure 2). Efficacy was similar in patients who were and those who were not receiving tamoxifen (data not shown).

Toxicity data are best illustrated in terms of the changes in treatment week 4 compared with the baseline week because the groups assigned increasing doses had then been taking the highest dose for at least 2 weeks. There were no significant differences between groups for tiredness, dizziness, nervousness, mood changes, sweating, sleepiness, or sleeping troubles. Significant differences were seen in terms of mouth dryness, decreased appetite, nausea, and

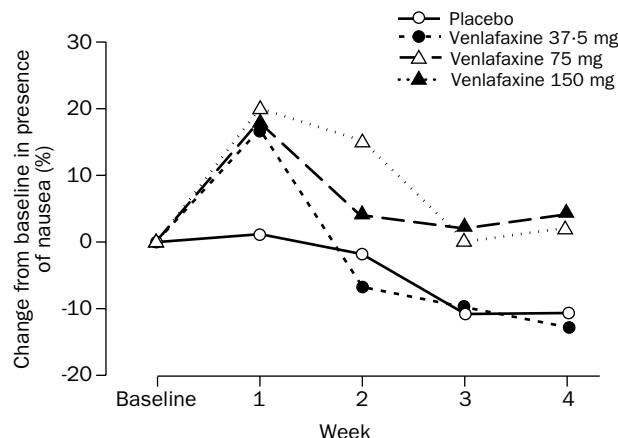


Figure 4: Changes in presence of nausea

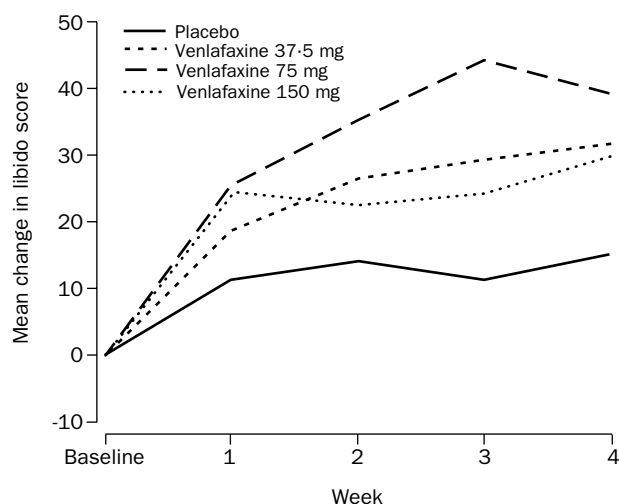


Figure 5: **Changes in libido score**
There were no significant differences between groups.

constipation (figure 3). More toxic effects occurred with the 150 mg dose than with the 75 mg dose. Nausea was temporary in most cases and largely resolved with time (figure 4).

Although we did not specifically inquire about changes in libido, item number 21 of the Beck depression inventory addresses this issue. Libido scores improved from baseline for all study groups over the 4-week study period (figure 5).

We did not observe any substantial changes in diastolic or systolic blood pressure for any of the study groups (data not shown).

Depression scores improved by an average of 1.6, 2.4, 4.8, and 3.2 points for the placebo and 37.5 mg, 75 mg, and 150 mg venlafaxine groups, respectively. Similarly, at the end of the study, 16 of the 48 (33%) patients on placebo had depression scores consistent with at least mild depression compared with 11 of 40 (23%), nine of 43 (21%), and 13 of 49 (27%) in the three venlafaxine groups ($p=0.59$). Although the trend of the depression scores paralleled the results of hot-flash activity, the relation was weak (Spearman's $\rho=0.29$, $p=0.0004$). Repeated-measures ANOVA showed that baseline depression was unrelated to the reduction in hot-flash activity ($p=0.54$).

Overall quality of life increased from baseline to treatment week 4 by an average of 3 points in the three venlafaxine groups and decreased 3 points in the placebo group ($p=0.02$). There were no significant differences in these changes among the venlafaxine groups.

Discussion

This trial suggests that venlafaxine can alleviate hot flashes and that the most appropriate dose for this indication is 75 mg daily, which was more effective than 37.5 mg daily but was as effective as, and less toxic than, the 150 mg dose. Thus, we recommend that treatment should start with a daily dose of 37.5 mg and be increased if necessary to 75 mg, but not higher. Some patients had substantial decreases in hot-flash activity with 37.5 mg venlafaxine daily. For those patients, there may not be any need to increase the dose.

With hormone treatments for hot flashes, effects may take weeks to become apparent. By contrast, the effect of venlafaxine occurred in a matter of days, in most cases. Thus, an increase in dose after a week is reasonable if greater efficacy is required.

The dose-dependent efficacy of venlafaxine may be directly related to its pharmacology. Venlafaxine affects

both serotonin reuptake (similarly to many of the other newer antidepressants) and norepinephrine reuptake (similarly to older tricyclic antidepressants).^{15,16} Venlafaxine's effects are thought to be related to the serotonin-reuptake inhibition at lower doses, but to a combination of serotonergic and noradrenergic or a predominance of noradrenergic effects at higher doses. Because hot flashes are considered to be a side-effect associated with older tricyclic antidepressants, this property of venlafaxine may explain the ceiling effect for hot flashes.

The main side-effects observed with the 75 mg daily dose of venlafaxine were mouth dryness, anorexia, and nausea. In general, these side-effects were tolerable.

Evidence on the role of antidepressants in sexual dysfunction is mixed, and the relation is further complicated by the effect of depression. Placebo-controlled studies reported in the *Physician's Desk Reference* state that the frequency of sexual dysfunction with venlafaxine is about 2%.¹⁷ An overview of these studies reported placebo-adjusted frequencies of 2% for decreased libido and 2% for unspecified female sexual dysfunction events with venlafaxine in doses of 75 to 375 mg daily.¹⁸ In one study, with doses of up to 160 mg daily, there was no mention of sexual dysfunction in the list of side-effects or the reasons for drug discontinuation.¹⁹ Another study reported nausea as the only significant adverse event with a dose of up to 182 mg daily.²⁰ Our findings confirm that venlafaxine doses of 37.5–150 mg daily did not reduce libido, at least during the first month of therapy. We hypothesise that the improvement in hot flashes may have decreased night sweats and improved sleep, thus decreasing fatigue and perhaps improving libido.

Are the methods used in this study sound? Can patient-completed questionnaires about subjective symptoms such as hot flashes provide scientifically reliable information? Psychometric studies have shown that they can.^{21,22} Patients can provide valid, reliable data about their subjective experience.^{23,24} Reports on a wide range of oncology endpoints related to quality of life have also shown the scientific integrity of these methods.^{25,26} In figure 2 of our report, the data points for the three treatment groups during the second treatment week are almost superimposed. These points represent data from 54–56 patients who were all receiving 37.5 mg daily of venlafaxine during that week. The similarity of the results shows the reproducible results of this experimental method. Further support for the method used comes from comparison of the results of one of our previous studies of clonidine for hot flashes⁵ with those from another group of investigators.²⁷ These independent studies reported remarkably similar effects of clonidine. Cross-study comparison of placebos in our hot-flash studies shows a 20–30% reduction in hot flashes over 4 weeks in groups receiving placebo. Thus, we are convinced that the method is scientific, allowing an objective measure of subjectively reported hot flashes.

The efficacy of venlafaxine against hot flashes does not seem to be specific to this single antidepressant. Preliminary results suggest that several of the other newer antidepressants can also alleviate hot flashes.^{28,29} Data from randomised trials currently investigating these drugs should better elucidate the efficacy and toxicity profiles of the different agents.

Although there was a weak correlation between the decreases in hot flashes and improved scores on the Beck depression inventory, the effect of venlafaxine on hot flashes seems to be through a mechanism other than its known effect on depression symptoms. Patients who had normal baseline depression scores had a similar reduction in hot flashes to those with high scores.

From the available information, venlafaxine can be recommended for treatment of hot flashes for patients in whom oestrogen is not desired. The drug also seems to be effective against hot flashes in men who have undergone androgen deprivation therapy for prostate cancer.⁹

Contributors

Charles Loprinzi was the principal investigator, responsible for the development and conduct of this study and the preparation of the report. John Kugler helped with study design, chaired the study group, and contributed to the report. Jeff Sloan was responsible for statistical analysis. James Mailliard, Beth LaVasseur, Shaker Dakhil, and Kate Rodger were involved in study development, accrual of patients, and review of the paper. Paul Novotny was involved with the study development, data analysis, and drafting of the report. Teresa Rummans was involved with study development and drafting of the report. Bradley Christensen was involved with study development, distribution and supply of protocol drugs, and drafting of the report.

North Central Cancer Treatment Group

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