VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial to Assess the Impact of Venlafaxine and Soy Protein on Hot Flashes and Quality of Life in Men With Prostate Cancer

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Published online ahead of print at www.jco.org on September 30, 2013.

Supported by Grant No. U10 CA 081851 from the National Cancer Institute/Division of Cancer Prevention, Grant No. U10 CA 081851-06S2 from the National Center for Complementary and Alternative Medicine (NCCAM), and Physicians Pharmaceuticals. Funding for the purchase of the EffexorXR tablets and placebo pills was obtained through Grant No. U10 CA081851-06S2 from NCCAM. The soy and milk protein powders were provided free of charge by Physicians Pharmaceuticals.

Presented in part at the 47th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 3-7, 2011.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00354432.

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0732-183X/13/3132w-4092w/$20.00

DOI: 10.1200/JCO.2012.48.1432

ABSTRACT

Purpose
Hot flashes occur in approximately 80% of androgen-deprived men. Few intervention studies have been conducted to relieve hot flashes in men.

Patients and Methods
Eligible androgen-deprived men were randomly assigned to one of four daily regimens (2 × 2 factorial design) for 12 weeks: milk protein powder and placebo pill, venlafaxine and milk protein powder, soy protein powder and placebo pill, or venlafaxine and soy protein powder. The primary end point was hot flash symptom severity score (HFSSS), defined as number of hot flashes times severity. The secondary end point was quality of life (QoL), assessed by using the Functional Assessment of Cancer Therapy-Prostate.

Results
In all, 120 men age 46 to 91 years participated. Most were white (78%) and overweight or obese (83%). Toxicity was minimal. Neither venlafaxine nor soy protein alone or in combination had a significant effect on HFSSS. Soy protein, but not venlafaxine, improved measures of QoL.

Conclusion
In androgen-deprived men, neither venlafaxine nor soy proved effective in reducing hot flashes. Interventions that appear effective for decreasing hot flashes in women may not always turn out to be effective in men.

J Clin Oncol 31:4092-4098. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Hormonal manipulation is used to manage and control prostate cancer. It is useful as adjuvant therapy in early-stage disease and is the foundation for disease and symptom management in advanced disease. In late-stage prostate cancer, some men elect orchiectomy as a permanent ablative approach and others elect chemical castration using luteinizing hormone releasing hormone (LHRH) agonists.

Vasomotor symptoms (ie, hot flashes and night sweats) occur in approximately 80% of men who undergo hormone manipulation.[1] These symptoms may continue for years during long-term therapy and for months after adjuvant therapy is completed.[1] Hot flashes have been shown to negatively affect quality of life (QoL).[2,3] Management of these symptoms in men has been challenging; few studies have investigated treatment options.

Sudden withdrawal of sex steroids increases norepinephrine and serotonin release and decreases β-endorphin levels, which leads to dysregulation of the hypothalamic thermoregulatory set point resulting in downregulation of body temperature through vasodilation and sweating.[4] Selective serotonin reuptake inhibitors and serotonin-noradrenalin reuptake inhibitors have been investigated in women, yet few studies have examined their effects in men. Roth and Scher[5] reported that sertraline relieved hot flashes over a 1- to 2-month period in five case studies in men receiving hormone therapy for prostate cancer. Venlafaxine (Effexor; Pfizer, New York, NY) has been used to manage hot flashes in postmenopausal women and women with breast cancer.[6] Quella et al[7] reported that venlafaxine decreased hot flash symptom severity score (HFSSS) in men. In that single-arm pilot study, data from 16 participants revealed that venlafaxine (12.5 mg twice per day) reduced severity of hot flashes by 50% in more than half the men. However, Irani et al[8] reported that in a 12-week double-blind trial in 301 men receiving leuprorelin, venlafaxine (75 mg per day) was not as effective as medroxyprogesterone acetate or cyproterone acetate in reducing hot flashes.

Soy protein for hot flashes has been investigated in women and in one study in men.[9-17] Cross-cultural comparisons report fewer menopausal symptoms in women in countries where soy is regularly consumed compared with women in countries where soy is not consumed.[10] Isoflavones (plant substances in soy protein) are structurally similar to estradiol but have both estrogenic and antiestrogenic properties. As weak estrogen agonists, isoflavones have been used with mixed results to treat menopausal symptoms.[10-18]

Because venlafaxine and soy have an impact on different physiologic mechanisms proposed to play a role in hot flashes, these treatments could potentially provide more relief when taken together. This article reports the effects of venlafaxine and soy, separately and in combination, on hot flashes and QoL in men.

PATIENTS AND METHODS

This randomized, double-blind, placebo-controlled, 2 × 2 factorial, multicenter phase III clinical trial was conducted through the Community Clinical Oncology Program Research Base of the Comprehensive Cancer Center of Wake Forest University. Participants completed a 7-day prescreening symptom recording phase and 12 weeks of intervention. Ethical approval was obtained through institutional review boards at participating institutions; all participants signed informed consent.

Eligibility criteria included four or more moderate to severe hot flashes per day (prescreening), life expectancy ≥ 9 months, no history of hepatic dysfunction, no allergies to soy or dairy, no uncontrolled hypertension, no history of seizures, and no history of intolerance to venlafaxine. Exclusion criteria included concurrent therapy with progestational agents or other medications to alleviate hot flashes, anticipated changes in hormone regimen, current chemotherapy/radiotherapy or anticipated surgery, and recent use of venlafaxine, a monoamine oxidase inhibitor, a selective serotonin reuptake inhibitor, or a serotonin-noradrenalin reuptake inhibitor.

Participants were randomly assigned to one of four treatments: (1) placebo pill once daily in the morning plus milk powder (20 g; one packet per day), (2) venlafaxine (75 mg once daily in the morning plus milk powder (20 g; one packet per day), (3) placebo pill once daily in the morning plus soy powder (20 g with 160 mg isoflavones; one packet per day), or (4) venlafaxine 75 mg once daily in the morning plus soy powder (20 g with 160 mg isoflavones; one packet per day).

Extended release venlafaxine hydrochloride was provided in capsules. Revival soy protein powder isolate (Physicians Pharmaceuticals, Kernersville, NC) was made via water extraction to preserve the isoflavones. The placebo powder was an isocaloric milk protein powder. The soy and milk powders were each obtained from a single batch.

Clinic Visits

Once randomly assigned, participants were given a 1-month supply of powder and pills and a compliance diary; participants were required to mark on a daily basis whether they took the pill (yes/no) and consumed the powder (yes/no). They also reported number of hot flashes experienced in a 24-hour period and characterized their severity. Participants were contacted by telephone during week 2 to complete forms and assess toxicities. During weeks 4 and 8, participants were sent more powder and pills and were contacted to assess toxicities and assess protocol compliance. Participants mailed their diaries to the trial coordinator on a monthly basis.

During week 12, participants were contacted and asked to return completed QoL forms, diaries, and any leftover pills and powder. At week 13, participants taking venlafaxine were provided four pills (75 mg) and instructed to take one every other day as titration.

Measures

Participants recorded total number of hot flashes or night sweats experienced daily (24 hours) and averaged their severity (1, mild; 2, moderate; 3, severe). Daily HFSSS was calculated as the number of hot flashes times the severity ratings. A weekly mean score was calculated and used in the analyses. Higher scores reflect a greater number of and/or more intense hot flashes.

Participants completed the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire at baseline and at 12 weeks.[19,20] The FACT-P consists of the FACT-G questionnaire plus a prostate-specific subscale. Total FACT-G score is computed as the sum of the individual subscales; overall score ranges from 0 to 108. The prostate subscale comprises 12 questions specific to men with prostate cancer, and scores range from 0 to 48. The FACT-P score is the sum of the FACT-G score and the prostate-specific subscale score. Higher scores indicate better QoL.

Anthropometric measurements were taken with participants wearing light-weight clothing and without shoes. Body mass index (BMI) was

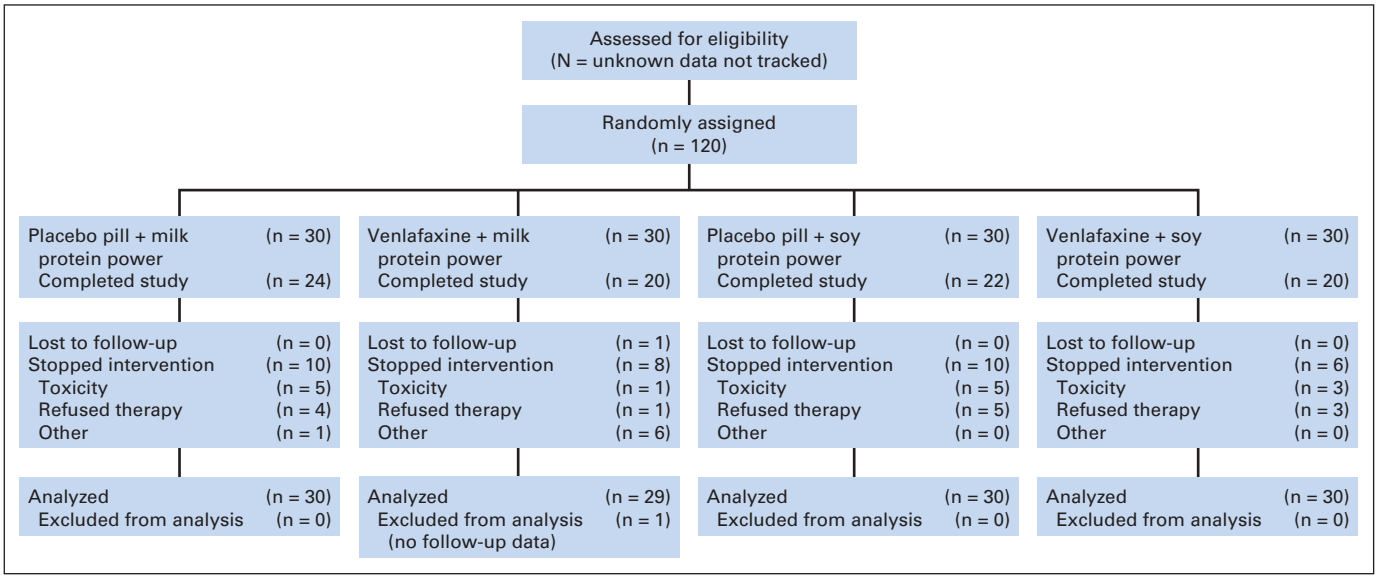

Fig 1. CONSORT diagram. Randomized trial to assess the impact of venlafaxine and soy protein on hot flashes and quality of life in men with prostate cancer.

calculated by using the following formula: (weight in kilograms)/(height in meters).[2]

Statistical Considerations

Participants were stratified by severity of disease (metastatic, nonmetastatic) and baseline severity of hot flashes (moderate *v* severe) and assigned to one of the four arms with equal probability by using variably sized permuted block randomization. The trial was powered to detect a 12.5% marginal difference in the percentage reduction in the HFSSS (between baseline and 12 weeks) between those who did and did not receive soy or between those who did and did not receive venlafaxine with 80% power at the 5% overall one-sided level of significance (using a Bonferroni correction to account for the two primary hypothesis tests). This was done assuming the standard deviation for the HFSSS reduction would be 25%, each treatment given alone would increase the reduction by 15%, the combination would increase the reduction by 25%, one interim evaluation would be conducted, and 25% of the participants would drop out early. The total sample size required was 176 patients.

Kruskal-Wallis and χ^2 tests were used to assess baseline group differences in continuous and categorical variables, respectively. Analysis of variance was used to assess differences in intervention compliance among the four arms. Fisher's exact tests were used to compare toxicity levels. Repeated measures analysis of covariance was used to assess treatment differences in number and severity of hot flashes in addition to HFSSS. All models included baseline score and strata as covariates. Models were first run by using all four arms and then by using indicator variables for soy and venlafaxine. A Toeplitz covariance structure was used to model within patient correlation across multiple visits. A linear contrast was used to assess the treatment effect at 12 weeks. Note that *P* values for these analyses are one-sided, as specified in the trial design. Additional models that included baseline participant characteristics of age, BMI, race, insurance status, and treatment (LHRH, antiandrogen, radiation) as covariates were also run. Least squares means and SEs for outcomes and percent of baseline were calculated from the model estimates at mean levels of the covariates. Additional supporting analyses were performed that included only participants with at least 80% compliance.

Analysis of covariance models were used to assess differences in QoL outcomes. The models were adjusted for baseline level of the outcome and strata. Separate models also included participant characteristics as covariates. These models included indicator variables for soy and venlafaxine. The interaction between soy and venlafaxine was assessed initially and removed when nonsignificant.

Table 1. Demographic and Health Characteristics of Participants

Characteristic	Placebo + Milk Protein		Venlafaxine + Milk Protein		Placebo + Soy Protein		Venlafaxine + Soy Protein		*P*
	No.	%	No.	%	No.	%	No.	%	
Total No. of patients	30	100	30	100	30	100	30	100	
Age, years									.459
Median	67		67		71		69		
Range	47-81		47-82		54-85		46-91		
BMI (CDC criteria)									.549
Underweight (< 18.5 kg/m^2)	0	0	0	0	0	0	1	3	
Normal (18.5-25 kg/m^2)	6	20	6	20	6	20	2	7	
Overweight (25-30 kg/m^2)	8	27	11	37	13	43	13	43	
Obese (≥ 30 kg/m^2)	16	53	13	43	11	37	14	47	
Strata									—
1 (metastatic, moderate hot flashes)	6	20	6	20	8	27	7	23	
2 (metastatic, severe hot flashes)	3	10	3	10	1	3	2	7	
3 (nonmetastatic, moderate hot flashes)	15	50	17	57	16	53	16	53	
4 (nonmetastatic, severe hot flashes)	6	20	4	13	5	17	5	17	
Race/ethnicity									.755
African American	3	10	6	20	7	23	6	20	
White	25	83	23	77	22	73	24	80	
Hispanic	1	3	1	3	1	3	0	0	
Other/unknown	1	3	0	0	0	0	0	0	
Performance status									.180
0	26	87	25	83	21	70	29	97	
1	4	13	4	13	5	17	0	0	
2	0	0	0	0	1	3	0	0	
Unknown	0	0	1	3	3	10	1	3	
Insurance/care									
VA	3	10	2	7	1	3	3	10	.724
Medicare	18	60	15	50	17	57	20	67	.619
Medicaid	0	0	2	7	0	0	0	0	.107
Private	18	60	19	63	17	57	16	53	.877
None	2	7	1	3	2	7	2	7	.929
Treatments									
Orchiectomy	2	17	2	7	1	3	2	7	.929
LHRH	26	87	23	77	23	77	25	83	.693
Antiandrogen	12	40	15	50	12	40	15	50	.750
Radiation	16	53	16	53	17	57	12	40	.579

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; LHRH, luteinizing hormone releasing hormone; VA, Veterans Administration.

Table 2. Reported Number and Severity of Hot Flashes and Hot Flash Severity Score Over Time by Group

Outcome	Week	Placebo + Milk Protein			Venlafaxine + Milk Protein			Placebo + Soy Protein			Venlafaxine + Soy Protein		
		No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
No. of hot flashes	0	30	8.6	4.4	30	8.9	5.2	29	10.0	4.2	30	9.8	8.0
	4	26	6.7	4.7	19	5.6	3.4	24	7.5	4.8	22	6.7	4.9
	8	23	5.4	3.6	20	4.9	2.6	21	7.3	5.5	20	5.9	5.2
	12	21	4.1	3.1	19	4.8	2.7	19	5.9	5.1	17	5.5	5.0
Hot flash severity	0	30	2.4	0.5	30	2.3	0.5	29	2.3	0.5	30	2.1	0.4
	4	26	2.1	0.7	19	1.8	0.6	24	2.1	0.6	22	1.7	0.8
	8	23	1.9	0.8	20	1.7	0.7	20	1.9	0.9	20	1.6	0.6
	12	21	1.8	0.8	19	1.7	0.7	19	1.8	0.9	17	1.6	1.0
Hot flash severity score	0	30	21.3	11.8	30	21.3	16.4	29	22.9	9.8	30	22.4	23.0
	4	26	16.6	15.0	19	11.4	8.7	24	16.9	12.3	22	12.6	11.9
	8	23	12.6	10.9	20	9.4	7.2	20	16.6	16.4	20	11.1	11.3
	12	21	9.3	8.5	19	9.2	7.2	19	13.6	15.3	17	11.2	10.9

Abbreviation: SD, standard deviation.

RESULTS

Participant Characteristics

A total of 120 men were accrued between April 2007 and May 2010, 30 to each arm (Fig 1). Baseline demographic and health characteristics, including disease status and treatment, are summarized in Table 1. Ages ranged from 46 to 91 years (median, 69 years), the majority were overweight or obese and white, and most had a performance status of 0 to 1. There were no significant differences among the four arms in these characteristics.

Table 2 provides descriptive statistics for the number and severity of hot flashes, as well as HFSSS over time, by treatment arm. In general, there was a fairly consistent decline in number, severity, and HFSSS over time. This is evident in the placebo as well as the intervention arms of the trial.

Hot Flash Count and Severity

The number of vasomotor symptoms decreased significantly in all arms ($P < .001$). There were no significant differences among treatment arms at any time. There were no significant differences between the soy and placebo arms at any time, and although participants in the venlafaxine arm tended to have fewer hot flashes during the initial 2 weeks, this early difference had disappeared by 12 weeks.

Hot flash severity also decreased significantly in each arm ($P < .001$). There were no significant differences in the comparison of soy and placebo at any time. The venlafaxine arm tended to have lower hot flash severity values at weeks 1, 2, 3, and 4. This difference was not significant at 12 weeks, and the interaction between venlafaxine and visit was not significant.

Hot Flash Symptom Severity Score

The HFSSS decreased significantly over time in each arm ($P < .001$; Fig 2). Although the placebo group did poorly initially, by 12 weeks there were no significant differences among the treatment arms. It is interesting to note that the placebo group reported the greatest percentage of decline from baseline to 12 weeks, and the trial was stopped early by the Data Safety Monitoring Board because of lack of effect. The marginal effects of venlafaxine and soy were then assessed. The interaction between venlafaxine and visit was significant

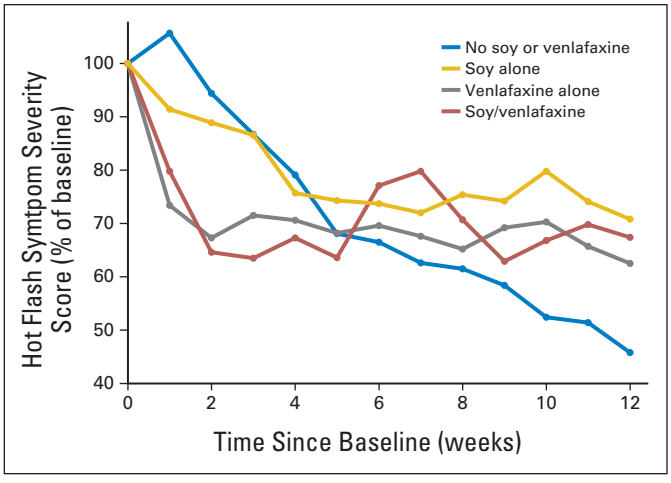

Fig 2. Hot Flash Symptom Severity Score over time in all four treatment groups.

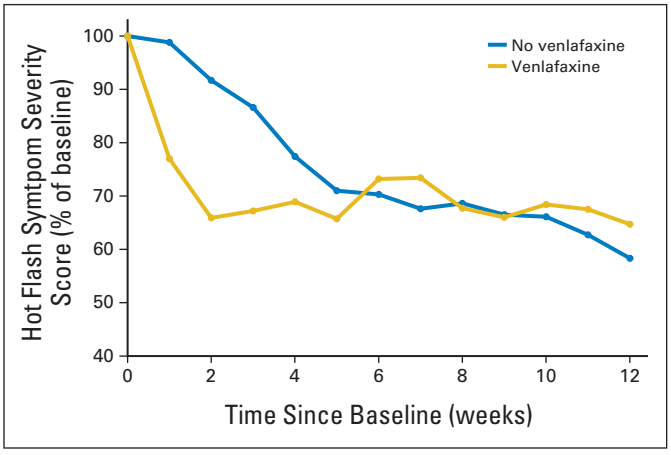

Fig 3. Hot Flash Symptom Severity Score over time in participants receiving venlafaxine and participants not receiving venlafaxine.

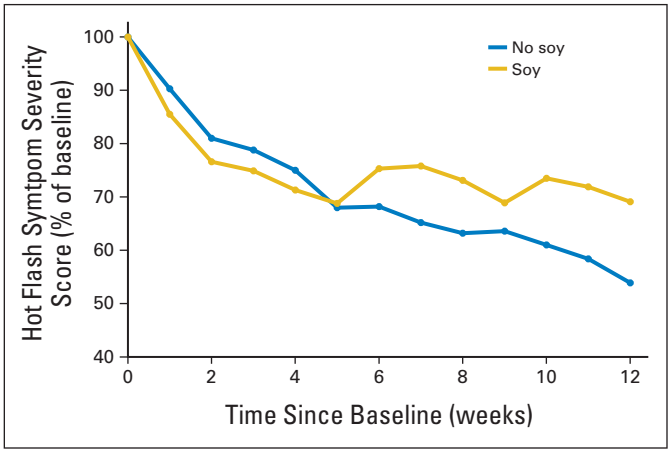

Fig 4. Hot Flash Symptom Severity Score over time in participants receiving soy and participants not receiving soy.

($P = .014$); there was an initial effect of venlafaxine that was lost over time (Fig 3). For example, at week 2, hot flash severity score decreased by 28% for participants given venlafaxine compared with 2% for those not receiving venlafaxine ($P = .005$). However, by week 12, the decrease was 29% for participants on venlafaxine compared with 36% for participants not receiving venlafaxine ($P = .723$). Similar results were found with the addition of baseline characteristics as covariates in the models, as well as models limited to participants with at least 80% compliance. Least squares estimates for changes as a percentage of baseline for those who did and did not receive soy are shown in Figure 4. There was no effect of soy at any time. In addition, there was no significant interaction between soy and visit.

Health-Related QoL

Table 3 includes the QoL results for those who did and did not receive venlafaxine and for those who did and did not receive soy. There was no significant effect of venlafaxine on the subscales, FACT-G, or FACT-P. Baseline characteristics such as age, BMI, race, insurance status, and treatment (LHRH, antiandrogen, radiation) were subsequently included in the analysis of covariance models, and venlafaxine still had no significant effect. When assessing the effects of soy, participants receiving soy had higher scores for the emotional subscale, but these differences were not statistically significant. However, there were statistically significant improvements in the soy arm in emotional and functional subscales and in FACT-G and FACT-P total scores.

Participants' self-reported compliance to taking pills and powder was evaluated. The first compliance measure assessed percentage of pills/powder taken while participants were on the trial on the basis of information in the diaries. The second measure assessed percentage of the ideal number of pills/powder taken, assuming that no pills or powder were taken on days missing information. Overall, 92% of pills and powder were taken on the basis of completed diaries. This measure of compliance did not differ significantly among arms ($P = .524$). Overall, 77% of ideal pills and powder in the placebo, 72% in the soy, 54% in the venlafaxine, and 60% in the venlafaxine plus soy ($P = .031$) arms was taken. This measure of compliance did not differ significantly between those who did and did not receive soy ($P = .945$), but was significantly lower for those who received venlafaxine compared with those who did not ($P = .009$).

Toxicity

Nineteen adverse events were reported, six in the placebo, three in the soy, eight in the venlafaxine, and two in the venlafaxine plus soy arm. None were definitely related to treatment, two were probably related, and two were possibly related. Only one grade 4 toxicity of pain was reported but was deemed unrelated to treatment. The majority of toxicities were severity grade 0 to 1. Toxicities did not differ significantly among groups. Interestingly, the majority of these conditions were experienced by the participants at baseline. Most did not worsen during treatment.

DISCUSSION

This trial was conducted to evaluate the impact of single and combined therapies that have been previously investigated, mainly in women, for their ability to decrease the occurrence and severity of hot flashes. Although neither treatment was found to be as effective as hormone therapy, the risk profile associated with hormone use in men suggests the need to identify and test alternative approaches. Unfortunately, neither venlafaxine nor soy, alone or in combination, had a significant effect on HFSSS. At week 12, there was a 28% decrease in HFSSS in the venlafaxine plus soy arm, a 35% decrease in the venlafaxine arm, a 31% decrease in the soy arm, and a 55% decrease in the placebo arm. The a priori hypothesis that venlafaxine plus soy would show the greatest reduction in HFSSS was not substantiated.

Table 3. Twelve-Week Estimates of Quality of Life Adjusted for Baseline Characteristics

	Venlafaxine		No Venlafaxine			Soy Protein		No Soy Protein		
Quality of Life Measure	No.	Mean ± SE	No.	Mean ± SE	*P*	No.	Mean ± SE	No.	Mean ± SE	*P*
Social	36	20.5 ± 1.2	42	20.8 ± 1.2	.777	39	21.3 ± 1.2	39	20.1 ± 1.2	.171
Emotional	36	20.0 ± 1.3	42	20.1 ± 1.3	.890	39	21.1 ± 1.3	39	19.0 ± 1.4	.029
Physical	36	22.0 ± 1.6	42	20.8 ± 1.5	.287	39	21.7 ± 1.5	39	21.0 ± 1.6	.566
Functional	35	15.3 ± 1.9	42	14.7 ± 1.8	.695	38	16.4 ± 1.8	39	13.6 ± 1.9	.041
FACT-G	34	79.3 ± 4.5	42	77.4 ± 4.3	.557	37	81.9 ± 4.3	39	74.7 ± 4.5	.025
Prostate	36	30.0 ± 2.1	42	29.6 ± 2.1	.792	39	30.6 ± 2.0	39	29.1 ± 2.1	.314
FACT-P	34	109.3 ± 6.2	42	107.0 ± 5.9	.607	37	112.5 ± 6.0	39	103.8 ± 6.2	.048

NOTE. Treatment group consists of two of the individual cells (eg, venlafaxine group includes data from participants taking venlafaxine with soy and venlafaxine without soy).
Abbreviations: FACT-G, Functional Assessment of Cancer Therapy-General; FACT-P, FACT-prostate.

At week 4, there was a 37% decrease in HFSSS in the venlafaxine plus soy arm and a 25% decrease in the venlafaxine arm. In a single-arm pilot study, Quella et al[7] reported a 54% decrease in HFSSS in men receiving a lower dose of venlafaxine (12.5 mg twice per day) than used in this trial. They reported that 10 (63%) of 16 evaluable men had a decrease in hot flash score greater than 50% after 4 weeks of treatment. This suggests that perhaps a lower dose of venlafaxine may be a more effective intervention. One could speculate that a lower dose of venlafaxine may confer fewer and/or milder adverse effects and result in better compliance. Compliance data show that participants taking venlafaxine were less compliant than those in the other trial arms, suggesting venlafaxine had adverse effects that some participants were not willing to tolerate.

These findings highlight the need for longer-term evaluation of treatments for hot flashes because the results were quite different at week 4 compared with those at week 12. There was benefit for venlafaxine at week 4 and perhaps reversal of the initial benefit during the second 2 months of treatment. It is unclear why the effect of venlafaxine did not continue past week 4.

Venlafaxine has been shown to be effective in women for relief of hot flashes.[21] Positive trials in women provided a starting dose of 37.5 mg per day during the first week. In this trial, participants started at 75 mg, which may have attributed to lower compliance and, therefore, to less benefit. The negative findings of this trial also suggest that the pathophysiology of hot flashes may differ in men and women. Currently, sex differences in the brain's serotonin system are under investigation.

Men assigned to venlafaxine did not report improved QoL when comparing baseline with week 12. Rather, moderate improvements in FACT scores were found for participants taking soy, although improvements were expected in participants receiving venlafaxine. Soy isoflavones have been reported to interact with estrogen receptors, particularly in the nervous system through inhibition of tyrosine kinases.[22] Additional trials evaluating soy consumption on QoL in men may be warranted since findings from this trial and from Sharma et al[9] are mixed.

Irani et al[8] reported that when comparing baseline with week 4 and baseline with week 8, participants receiving venlafaxine had significantly improved emotional functioning subscale scores. However, at week 12, the difference was no longer significant, findings similar to those reported here. This raises important questions regarding the efficacy of venlafaxine use beyond 8 weeks in men, not only for treating hot flashes but also for improving QoL.

A limitation of this study is that biomarkers of treatment compliance were not collected. Participants would have needed to return to the clinic throughout the trial and the burden was not justifiable. Participants did, however, record daily pill- and powder-taking behaviors and were encouraged to report this information accurately.

In this randomized, placebo-controlled trial testing venlafaxine and soy in men experiencing hot flashes, there was improvement in the number and severity of vasometer symptoms in all treatment groups. This could be regression to the mean. This could also be due to a placebo effect related to participating in a double-blind trial. Both illustrate the necessity of including a control condition when testing therapies for hot flashes.

In conclusion, neither soy protein nor venlafaxine were effective in treating hot flashes in men over a 12-week period, highlighting the need for additional investigations to identify treatments for hot flash management in men.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** Mara Z. Vitolins, Soy Connection (C) **Stock Ownership:** None **Honoraria:** None **Research Funding:** None **Expert Testimony:** None **Patents:** None **Other Remuneration:** None

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Collection and assembly of data: All authors
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Manuscript writing: All authors
Final approval of manuscript: All authors

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Acknowledgment

We thank the following for their participation in this clinical trial: Robin Rosdhall, RN; Lisa Autry; Gina Enevold, NP; June Fletcher-Steede, BS, RT; Rhonda Kimball; Cissy Yates; Carle Community Clinical Oncology Program (CCOP); Central Illinois CCOP; Christiana Care Health Services CCOP; Coastal Carolina Radiation Oncology; Greenville CCOP; Northern Indiana Cancer Research Consortium CCOP; Ochsner CCOP; Oklahoma CCOP; Ozarks Regional CCOP; Sioux Community Cancer Consortium CCOP; St Louis-Cape Girardeau CCOP; St Vincent Regional Cancer Center CCOP; and Stroger Hospital of Cook County Minority-Based CCOP.