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Does Venlafaxine (Effexor) Decrease the Frequency of Hot Flashes in Women with Breast Cancer?

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ABSTRACT

Objective: The objective of this systematic review is to determine whether or not "Does venlafaxine (Effexor) decrease the frequency of hot flashes in women with breast cancer?"

Study Design: Review of three English primary studies published between 2007 and 2009.

Data Sources: Randomized, controlled, double-blind clinical studies comparing venlafaxine to clonidine or to a placebo were found using OVID, PubMed, and Cochrane databases.

Outcomes Measured: Each of the studies measured outcomes based on the frequency of hot flashes prior to and following treatment with venlafaxine. Patients used questionnaires, event markers, and/or diaries to record frequency of hot flashes. In one study, physiological hot flashes were also recorded using 24-hour ambulatory skin conductance monitors.

Results: In the Buijs et al study there was no significant difference found between reported reductions of hot flashes with treatment of venlafaxine versus clonidine. However there was clinical evidence that venlafaxine reduced hot flashes when compared to baseline. In the study by Loibl et al, a significant difference was found in the reduction of hot flashes using venlafaxine compared to clonidine with venlafaxine being the superior treatment method. In the cross-over study by Carpenter et al, when comparing both low and high doses of venlafaxine to a placebo, there was significant reduction of hot flashes in both treatment groups as compared to the placebo. In addition, there were several common adverse effects reported in both the Buijs et al and Loibl et al studies, though no significant increase from baseline was noted, nor between the two groups.

Conclusion: The results of two of the reviewed RCT's and randomized cross-over study demonstrated that venlafaxine is an effective medication in decreasing the frequency of hot flashes in women with breast cancer as compared to clonidine. In the Buijs et al study there was no significant difference between the two treatments, though there was clinical reduction of hot flashes with the treatment of venlafaxine as compared to baseline. Continued research with venlafaxine is needed to determine the optimal dosing and regimen for reducing adverse effects and maximizing efficacy.

Key Words: Venlafaxine, Effexor, Breast Cancer, Hot Flashes

INTRODUCTION

Hot flashes are a common and bothersome complaint of many postmenopausal women. Due to chemotherapy, surgery, or hormone analogues, induced menopause is a common result in the treatment of breast cancer for women of all ages. Unfortunately, many premenopausal women are treated for breast cancer, and due to aggressive treatment measures many of these women undergo the changes of menopause.

Approximately 2/3 of breast cancer patients with induced menopause experience significant impairments in their quality of life due to hot flashes.[1] Of this large number of reported hot flashes, 59% rated the hot flashes as severe, and 44% rated the symptoms as "extremely bothersome."[2] It has also been documented that with the newer treatment methods of adjuvant therapy including tamoxifen or aromatase inhibitors, there is an association with vasomotor instability, leading to an increase in prevalence of hot flashes following adjuvant therapy.[3] These untreated hot flashes in breast cancer patients have been associated with negative affect, fatigue, sleep difficulties, sexual activity, and overall quality of life.[4,2] In fact, some studies indicate that women treated for breast cancer report more frequent and severe hot flashes compared to healthy women.[3]

Due to the increasing number of patients surviving breast cancer as well as being treated with adjuvant therapies, the need for a safe and effective treatment of hot flashes has become increasingly more important in healthy postmenopausal women. Currently, estrogen replacement therapy is a safe and effective method for treating hot flashes; however, treatment with estrogens is avoided in breast cancer patients due to the hormone's effects on tumor growth as well as cardiovascular events.[4] New remedies for this agonizing symptom has been sought, and recently attempted therapies targeted for

breast cancer patients include black cohosh, soy, and red clover as herbal supplementations.[5] On the pharmaceutical market, one of the most commonly used treatments for the reduction of hot flashes in breast cancer patients has been with clonidine. While it has been proven to decrease hot flashes to a moderate degree, it has been reported to also have several toxic effects.[6] Therefore, in a search for a better treatment, studies have begun to compare the use of clonidine with other drugs, namely venlafaxine.

Venlafaxine is a combined serotonin and norepinephrine reuptake inhibitor (SNRI) widely used on the pharmaceutical market as a treatment for depression and/or anxiety. More recently, venlafaxine has been tested as an effective treatment of hot flashes in breast cancer patients. Overall, venlafaxine is better tolerated long-term than hormonal replacements, and may result in improved quality of life in these individuals by decreasing the frequency of hot flashes.

OBJETIVE

The objective of this systematic review is to determine whether or not "Venlafaxine (Effexor) decreases the frequency of hot flashes in patients with breast cancer?" Recent studies have begun to test the efficacy of venlafaxine for the reduction of hot flashes, but its overall success rate compared clonidine is not widely known.

METHODS

All three studies selected met the criteria for subjects who were female breast cancer patients between the ages of 18-60 with frequent reported hot flashes. Two of the studies used were double-blind, randomized cross-over studies; one comparing treatment with venlafaxine at a low and high dose to a placebo[2], the other comparing high dose

venlafaxine to clonidine.[4] The third study used was a double-blind, randomized study comparing treatment with low dose venlafaxine BID to clonidine.[6] In the Buijs et al study,[4] the treatment group receiving 75mg daily venlafaxine was compared to a control group receiving 0.05mg BID of clonidine. Similarly, the Loibl et al[6] study compared 37.5mg BID of venlafaxine with the control group receiving 0.075mg BID of clonidine. In the crossover study by Carpenter et al[2], venlafaxine was compared at low and high doses, 37.5mg and 75mg daily respectively.

A detailed search for the studies used the key words "Effexor," "venlafaxine," "breast cancer," and "hot flashes," and was completed using OVID, PubMed, and Cochrane databases. Only English language articles published in peer-reviewed journals were selected. Articles were then narrowed down based on relevance and whether the outcomes mattered to patients (POEMS). Inclusion criteria for the selection of articles were that they were randomized, controlled, published after 2006, and had patient-oriented outcomes (POEMS). The only exclusion criteria were if they were published before 2006, due to a previous meta-analysis published at that time. The statistics reported included p-values with a value <0.05 being statistically significant, relative benefit increase (RBI), absolute benefit increase (ABI), and numbers needed to treat (NNT).

Table 1—Characteristics of studies included for analysis of venlafaxine for treatment of hot flashes

Study	Type	# of pts	Age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Buijs, 2008	RCT, double-blind, placebo controlled crossover	60	≤ 60yo	≥ 14 hot flashes per week	Previous use of venlafaxine or clonidine; received other Tx for hot flashes in previous month, took B blocker, sedatives, or antidepressants	20	Patients randomized into 2 groups, given venlafaxine or clonidine for 8wks followed by 2 wk wash-out, then 8wk treatment with the other drug
Carpenter, 2007	RCT, double-blind, placebo controlled crossover	77	≥ 18yo	≥18 with Hx breast CA, no other CA, disease-free and independently functional, no local therapy in past 1mo, ≥1 hot flash/day, no other current Tx, Taking OCP or postmenopausal, 60mi radius from study center, Dx no depressed	On tamoxifen or aromatase inhibitor for < 6wks, on antidepressants, receiving hot flash treatment in prior 1 mo	17	Patients randomized into low-dose (37.5mg) or high-dose (75mg) group receiving venlafaxine for 6wks preceded by 2wk baseline data with a 6wk placebo controlled-crossover
Loibl, 2007	Double-blind RCT	80	≥18yo	≥18 with primary breast CA, ≥14 hot flashes/wk or seeking help for them, hot flashes present for >4wks, on tamoxifen or ARI's for >1mo, Eastern Oncology Cooperative Group performance status 0-1	Previous Tx with venlafaxine, clonidine, estrogens, progestogens, or androgens for hot flashes, current non-hormonal Tx for hot flashes, current Tx with hypertensive or antidepressant agents, Dx of metastatic disease, HTN, hypotension, CVD or PVD	16	Pts randomized into two groups receiving either Venlafaxine BID or Clonidine BID for 4 wks

OUTCOMES MEASURED

Outcomes were measured by the frequency of hot flashes as reported by the patient prior to and after treatment with either venlafaxine or clonidine. Patients used questionnaires, electronic event markers, and/or diaries to record frequency of hot flashes. In one study, by Carpenter et al,[2] the frequency of physiological hot flashes was measured using 24-hour ambulatory skin conductance monitors.

RESULTS

The results assessing the efficacy pertaining to the primary outcome were presented as dichotomous data in the Buijs et al[4] and Loibl et al[6] studies, but presented as continuous data for the double-blind cross-over trial in the Carpenter et al[2] study.

The Buijs et al[4] study used a cross-over study to compare number of hot flashes at baseline with an 8 week treatment of venlafaxine versus with an 8 week treatment with clonidine following a 2 week wash-out period. For both the venlafaxine treatment group and the clonidine group, the number of hot flashes was reduced compared to baseline. There was a median score of 49% reduction for venlafaxine and 55% for clonidine after the 8 weeks. However, there was no significant difference in the reduction of venlafaxine as compared to clonidine ($p=0.55$). The control event rate (CER) was determined as those patients who had improvement, or a decrease in hot flashes in the control group treated with clonidine. The CER was calculated to be 46.8%. The experimental event rate (EER) was determined as the number of patients who had a decrease in hot flashes with venlafaxine treatment. The EER was calculated to be 51.2%. With these values, the relative benefit increase (RBI) was calculated to be 9.4% and the absolute benefit increase (ABI) was calculated to be 4.4%, with a numbers needed to treat (NNT) of 23 (Table 2).

The second study with dichotomous data was the Loibl et al[6] study again comparing the treatment of venlafaxine with that of clonidine for 4 weeks. The study began with 40 patients in each of the two groups, with only 31 finishing in the venlafaxine group and 33 in the clonidine group. For the venlafaxine group, the frequency of hot flashes significantly decreased compared to baseline by 57%. This was compared to the clonidine group with a decrease of 37%, and showed a significant decrease in hot flashes with the venlafaxine treatment as compared to the clonidine ($p = 0.025$). The CER was calculated to be 12% and the EER calculated to be 29%. The RBI was calculated to be 142% and the ABI calculated at 17% with the NNT being 6 (Table 2).

Table 2—Efficacy of venlafaxine in reduction of hot flashes compared to clonidine

Study	**Venlafaxine %reduction**	**Clonidine %reduction**	**p-value**	**CER**	**EER**	**RBI**	**ABI**	**NNT**
Buijs et al, 2009	49%	55%	p=0.55	46.8%	51.2%	9.4%	4,4%	23
Loibl et al, 2007	57%	37%	p=0.025	12%	29%	142%	17%	6

As illustrated by Table 2, there was a significant difference between venlafaxine and clonidine, with a greater decrease associated with use of venlafaxine in the Loibl et al[6] study, but no significant difference between the two in the Buijs et al[4] trial. However, this trial showed clinical decreases in hot flashes from baseline for both treatment options, but with no significant difference between the two therapies.

The third study, by Carpenter et al[2] contained only continuous data that could not be converted into dichotomous format. This study assessed the primary outcome using only venlafaxine at a low and high dose of 37.5mg and 75mg respectively. The studied measured the primary outcome using self-reports of hot flashes in addition to

physiologically documented hot flashes measured using skin conductance monitors. Both of these monitoring methods were carried out in the low-dose and high-dose groups. Effect size (ES) was measured comparing mean percent changes from baseline with the placebo and treatment groups. Physiologic hot flashes decreased 22% from baseline during low-dose treatment compared to a 0% decrease with placebo. Self-reported decreased from baseline by 42% during low-dose treatment compared to an 18% decrease with placebo. This yielded an ES of 0.16 for monitored hot flashes with and 0.22 for self-reported with low-dose treatment (Table 3, Table 4).

In the high-dose treatment group, the physiologic hot flashes decreased by 14% with a 13% increase in the placebo group. The self-reported hot flashes decreased by 25% compared to a 4% decrease with placebo. This yielded an ES of 0.22 for monitored and 0.24 for self-reported with the high-dose treatment. Paired t-tests were performed for percent change from baseline. For the low-dose group with monitored hot-flashes $p<0.001$ with confidence intervals (CI) of (0.09, 0.23). Self-reported decreases in the low-dose group had a reported $p<0.001$ with CI of (0.16, 0.29). The high-dose group had a monitored p-value of $p=0.013$ with CI of (0.05, 0.39), and a self-reported $p=0.001$ with CI of (0.10, 0.38) (Table 3, Table 4).

Table 3—Efficacy of low-dose venlafaxine (37.5mg) compared to placebo

Measurement	**Placebo**	**Low dose**	**p-value**	**ES**	**95% CI for ES**
Monitored	0% decrease	22% decrease	p<0.001	0.16	(0.09, 0.23)
Self-reported	18% decrease	42% decrease	p<0.001	0.22	(0.16, 0.29)

Table 4—Efficacy of high-dose venlafaxine(75mg) compared to placebo

Measurement	**Placebo**	**High dose**	**p-value**	**ES**	**95% CI for ES**
Monitored	13% increase	14% decrease	p=0.013	0.22	(0.05, 0.039)
Self-reported	4% decrease	25% decrease	p=0.001	0.24	(0.10, 0.38)

As illustrated in Tables 3 and 4, there were significant decreases in hot flashes both monitored and reported for both low and high dose venlafaxine treatment regimens.

In addition, there were several adverse effects reported by many of the patients throughout the study. Of the most common are nausea, dry mouth, fatigue, insomnia, and sweating.[4,5,6] (Table 5)

Table 5—Percent of patients reporting most common adverse effects at baseline and completion of treatment

	Buijs et al[4]			**Loibl et al[6]**			
Adverse Effects	Baseline	Completion Clonidine	Completion Venlafaxine	Baseline Clonidine	Completion Clonidine	Baseline Venlafaxine	Completion Venlafaxine
Nausea	12%	23%	19%	0%	2%	0%	6%
Dry Mouth	55%	47%	55%	5%	17%	6%	11%
Fatigue	88%	85%	74%	7%	14%	8%	11%
Insomnia	72%	57%	55%	9%	10%	8%	9%
Sweating	97%	94%	91%	9%	11%	9%	10%

As illustrated in the above Table 5, high percentages of patients in these two studies reported experiencing many of these symptoms at baseline, prior to beginning treatment with venlafaxine or clonidine.[4,6] In few cases highlighted in the Buijs et al[4] study, some of the symptoms were seen to improve. Prior to treatment, fatigue was reported as an experienced symptom by 88% of individuals, whereas after completing the course of venlafaxine, fatigue was reported by only 74% of patients and conversely reported by 85% receiving clonidine. Similar patterns were seen with the symptoms of insomnia and sweating. In contrast, in the Loibl et al[6] study there were only increases in percentages of reported cases of all adverse effects for the patient groups treated with venlafaxine as well as clonidine. In this same study, nausea was the only reported symptom that increased with the treatment of venlafaxine more than it increased with clonidine, rising to 6% from 0% of patients given venlafaxine, and to only 2% from 0% in those given clonidine. All

other adverse effects were reported to increase more with clonidine than with venlafaxine.[6]

DISCUSSION

Venlafaxine is one of the most commonly studied methods of therapy in the treatment of hot flashes in breast cancer patients, and recently has been compared to clonidine as an effective method of decreasing frequency of hot flashes in breast cancer patients. The Carpenter et al[2] study comparing low versus high doses of venlafaxine demonstrated clinical significance compared to placebo. Of the two studies comparing venlafaxine to the commonly used clonidine, the Loibl et al[6] study demonstrated venlafaxine to be significantly more beneficial at reducing the number of hot flashes, while the other showed no significant difference between the two, with a very high NNT necessary to see a positive result from treatment. Also, the limitation of duration of each study is important to note. The Loibl et al[6] study lasted only 4 weeks and showed a significant finding, while the Buijs et al[4] cross-over study lasted a total of 18 weeks with no significant finding demonstrated.

Also, while there is an extensive list of adverse effects associated with the use of venlafaxine, few are severe and frequent enough to inhibit its use for treatment. The withdrawal of patients prior to the completion of the Buijs et al[4] and Loibl et al[6] were in part to adverse effects noted after the start of treatment. However, according to the studies by Buijs et al[4] and Loibl et al,[6] many of the adverse effects were reported as experienced by patients even prior to receiving treatments with either clonidine or venlafaxine.[4,6] In the Loibl et al[6] study, only nausea was reported to increase from baseline in more patients when given venlafaxine than clonidine. All other adverse effects were reported in higher

percentages after treatment with clonidine than venlafaxine. This clinical picture demonstrates the benefits of the proposed use of venlafaxine as a treatment for hot flashes in breast cancer patients over the treatment with clonidine due to toxic effects and adverse reactions.[6]

In addition, according to pharmaceutical publications in accordance with the FDA, venlafaxine has a black box label for major depressive disorder due to an increased risk of suicide.[5] It is important for both future trials as well as healthcare professionals prescribing venlafaxine to be conscious of the increased incidence of depression in cancer patients,[2] and to use caution when prescribing or studying venlafaxine in breast cancer patients for the control of hot flashes.

CONCLUSION

Two of the studies reviewed demonstrated venlafaxine as an effective treatment for decreasing the frequency of hot flashes in women with breast cancer. The third study found no significant difference between venlafaxine versus clonidine in treating hot flashes. However, compared to the baseline data of no treatment, venlafaxine was clinically beneficial as a treatment, but not superior to clonidine.

More research is also indicated on the uses and dosages of appropriate therapy to provide the highest level of efficacy in treating the frequency of hot flashes in breast cancer patients. In addition, the current studies reviewed were limited to female patients with hot flashes, however there are studies currently being conducted to determine the use of venlafaxine in male and female cancer patients suffering from hormone deprivation.[6] Further studies are important to understand the benefits and limitations of using this medication in treating hormone-related symptoms in both female and male patients.

REFERENCES

1. Carpenter JS, Andrykowski MA, Cordova M et al. Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. Cancer 1998; 82: 1682-1691

2. Carpenter JS, Storniolo AM, Johns S, et al. Randomized, double-blind, placebo-controlled crossover trials of venlafaxine for hot flashes after breast cancer. Oncologist. 2007;12(1):124-135.

3. Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes towards estrogen replacement therapy. Journal of Clinical Oncology 1995; 13:2737-2744.

4. Buijs C, Mom CH, Willemse PH, et al. Venlafaxine versus clonidine for the treatment of hot flashes in breast cancer patients: a double-blind, randomized cross-over study. Breast Cancer Res Treat. 2009;115(3):573-580.

5. Epocrates. Website. Available at: https://online.epocrates.com

6. Loibl S, Schwedler K, von Minckwitz G, Strohmeier R, Mehta KM, Kaufmann M. Venlafaxine is superior to clonidine as treatment of hot flashes in breast cancer patients—a double-blind, randomized study. Ann Oncol. 2007;18(4):689-693.