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Efficacy of nonestrogenic hot flash therapies among women stratified by breast cancer history and tamoxifen use: a pooled analysis

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Abstract

Objective—Various nonestrogenic therapies have been found to be effective in mitigating hot flashes, but it has been unclear whether the efficacy varies by whether women have had breast cancer and/or were taking tamoxifen.

Methods—This study used data from Mayo Clinic/North Central Cancer Treatment Group clinical trials that evaluated the efficacy of any nonestrogenic agent for hot flashes and had information on breast cancer history or tamoxifen use. Statistically significant changes from the fourth treatment week versus the baseline week, using individual patient data, were assessed using Student's *t* test.

Results—A total of 1,396 women from 20 hot flash studies were eligible for analysis. Overall, women without breast cancer had a similar percentage of baseline hot flash score at week 4, as did those with breast cancer (53% vs 50%, $P = 0.92$). Women who were not taking tamoxifen had a significantly lower percentage of hot flash score at week 4 as compared with those who used tamoxifen (54% vs 61%, $P = 0.01$). However, this was due to a higher reduction in hot flash scores in the placebo arms among women not receiving tamoxifen; the percentage reduction in hot flash scores at week 4 from baseline in the active therapy arms of the randomized placebo-controlled trials (ie, excluding placebo arms) was similar among the tamoxifen users and nonusers (difference in mean percentage reduction, 5.7; 95% CI, −1.76 to 13.16).

Conclusions—Some nonestrogenic therapies seem to be useful for reducing hot flashes, irrespective of the etiology of hot flashes.

Keywords

Hot flashes; Breast cancer; Tamoxifen

Hot flashes can be defined as intense episodes of heat sensation, usually over the face and upper chest, often accompanied by sympathetic symptoms such as sweating, palpitations, and anxiety.¹ They are one of the earliest and most distressing aspects of menopause.² Bothersome hot flashes are known to occur in 75% of women and can markedly impair

one's general functional ability, sleep, sexuality, self-image, ability to work, and overall quality of life.^{3,4}

Traditionally, hormone therapy has been the frontline therapy for mitigation of hot flashes.^{5–7} However, because of safety concerns, there has been considerable reluctance, especially among those with breast cancer, to use hormone therapy.^{8–11} This has led to a search for alternative non-estrogenic agents to alleviate hot flashes.

Breast cancer survivors can have more frequent and severe hot flashes than do other women, in part because of the use of aromatase inhibitors and selective estrogen-receptor modulators (SERMs), such as tamoxifen.^{12–14} Time and again, during presentations, clinical discussions, and grant reviews and in the literature, the question has been raised as to whether the efficacy of hot flash therapies is different for women with breast cancer, and/or for women taking tamoxifen, than for women with hot flashes associated with a more natural menopause.^{15,16} This question has particularly been raised regarding the use of selective serotonin reuptake inhibitors (SSRIs), such as paroxetine, or serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine.

Although rational hypotheses could posit that hot flash management might be different in breast cancer survivors versus other women and/or in women receiving SERMs versus those who are not, such should not be assumed. Rather, scientific inquiry into these questions is in order.

To examine the issue cited above, this pooled analysis was designed to evaluate whether the efficacies of hot flash therapies were different in women with breast cancer versus those without cancer. An additional goal was to evaluate whether the efficacies of hot flash therapies differed among women taking concurrent tamoxifen as compared with women not taking tamoxifen.

METHODS

Over the past two decades, investigators at Mayo Clinic and the North Central Cancer Treatment Group (NCCTG) have conducted 13 pilot trials^{17–28} as well as another 8 randomized trials evaluating the efficacy of various non-estrogenic agents for hot flashes.^{29–36} Twelve of the pilot studies^{17–28} and six of the randomized trials^{29,30,33–36} collected information on breast cancer history or tamoxifen use. All of the trials had similar study methodology, including design and measurement tools, which have been validated both theoretically and empirically.³⁷ This provides a good platform to combine the data gathered from these trials to address the question at hand. For this present project, a protocol was prepared and was then approved by the Mayo Clinic Internal Review Committee.

Eligibility criteria

All Mayo Clinic/NCCTG cancer center trials conducted by a single group of investigators for women with hot flashes were eligible for the analysis. All trials (both pilot and randomized trials) that evaluated one or more therapies for mitigation of hot flashes among women were included.

Trial description

The methodology used in these trials has been described previously.³⁷ All of the trials used an initial week without study drug to obtain baseline hot flash frequency and score data. Women were then started on study medication (active agent or placebo, when applicable). Upon study enrollment, eligible women were given a patient questionnaire booklet

containing an instruction sheet and a 5-week hot flash diary. During the entire study period, women were instructed to complete their hot flash diary questionnaires daily.

Data abstraction and statistical analysis

The relevant data from the trials were collected from the Mayo Clinic/NCCTG hot flash database. This included data about demographic characteristics, whether the woman had a history of breast cancer, and whether the woman was currently using tamoxifen. In the latter situation, the woman must have been using tamoxifen for a minimum of 1 month before study entry and must have planned to use it during the hot flash study period, without alterations.

Similarly, data about hot flash frequency and severity were also obtained from the database. Individual hot flash severities were graded from 1 to 4, as they ranged from mild to moderate to severe to very severe. Hot flash scores were computed as the daily frequency of hot flashes times the average hot flash severity. The individual data were then pooled to calculate the overall hot flash frequency and score. Treatment effectiveness was measured as the change in hot flash score and frequency from baseline to week 4. Statistically significant changes from the fourth treatment week and the baseline week were assessed using Student's *t* test. A *P* value of 0.05 was considered significant.

The analyses were done using patient level data. Forest plots were created showing the mean values and 95% confidence intervals. For the forest plots, weights were based on the relative sample size of the various studies included so that results from larger studies did not dominate the analysis. Overall effect sizes in the Forest plots were patient level results. Stepwise linear regression models for predicting week 4 score were also constructed using potential predictor variables of baseline score, tamoxifen use, breast cancer history, age, pilot study versus phase III study, placebo versus active treatment, and whether the treatment was efficacious for hot flash scores.

RESULTS

A total of 1,415 women from 20 hot flash studies were initially included for analysis.^{17–25,27–36} One trial in the database was excluded because it did not report breast cancer or tamoxifen data.²⁶ Of the women, there were 1,396 for whom the history of tamoxifen use was known (with 19 women being on a double-blinded chemoprevention trial whereby they were receiving tamoxifen vs a placebo and could not be included), and there were 1,088 women for whom the history of breast cancer was known (327 women without data available about breast cancer). The distribution of women according to history of breast cancer and tamoxifen use in the included studies is summarized in Table 1.

It should be noted that some studies did not report breast cancer data,^{21,32,33} some included women with only breast cancer (and thus did not have a non-breast cancer comparison group),^{29,30,36} and some of the individual women on the trials did not report week 4 data. These women were excluded (*n* = 203), leaving a total of 885 women for the breast cancer versus non-breast cancer analysis. Similarly, excluding individual women who did not report week 4 data (*n* = 247), a total of 1,149 women were included for the tamoxifen users versus nonusers analysis. The characteristics of the women are summarized in Table 2. In women whose data were known, there was a history of breast cancer in 80% of the women, and 53% of the women (64% of those known to have breast cancer) were using tamoxifen. There were more women with a history of breast cancer or on tamoxifen on phase III studies, and those on tamoxifen were also slightly older than women not using tamoxifen.

The efficacy of various hot flash therapies by history of breast cancer and use of tamoxifen in all the women who participated in these trials with this information available is summarized in Table 3. Overall, at week 4, women without breast cancer had a similar percentage of baseline hot flash score as did those with breast cancer (53% vs 50%, $P = 0.92$). Whereas women without breast cancer had a significantly lower mean hot flash score at week 4 (6.1 vs 7.1, $P = 0.02$) as compared with those with a history of breast cancer, they also had a significantly lower mean hot flash score at baseline (12.9 vs 14.6, $P = 0.05$) and the mean change in hot flash score from baseline to week 4 did not statistically significantly vary by history of breast cancer status.

Similarly illustrated in Table 3, women without a history of tamoxifen use had a significantly lower mean hot flash score at baseline (13.9 vs 15.2, $P = 0.03$). At week 4, women without a history of tamoxifen use had a significantly lower percentage of hot flash score as compared with those who used tamoxifen (54% vs 61%, $P = 0.01$). However, the mean change in hot flash score from baseline to week 4 did not vary significantly by the history of tamoxifen use status. The reason that the mean change in hot flash score was not significantly different, while the percent reduction was, is the difference in baseline values. The same actual reduction in hot flash numbers, when applied to a lower baseline, leads to a higher percent reduction.

Figure 1 displays the overall efficacy of various hot flash therapies by history of breast cancer and use of tamoxifen in all of the trials combined (representing a pictorial version of Table 3, except that studies with fewer than three participants per any involved arm were not illustrated in the figure because the mean number would not be meaningful). Figure 1A illustrates that the various hot flash therapies decreased hot flash scores to a similar manner in those with versus without a history of breast cancer (difference in mean percentage reduction, -1.2 ; 95% CI, -8.96 to 6.56). Figure 1B, however, suggests that the various hot flash therapies decreased hot flash scores more in women who were not concomitantly using tamoxifen (difference in mean percentage reduction, 9.0 ; 95% CI, 3.54 – 14.46). However, looking at the pilot trial arms in Fig. 1A, there was no difference in the hot flash score percent reduction from baseline among women receiving tamoxifen versus those who were not (difference in mean percentage reduction, 1.8 ; 95% CI, -9.72 to 13.32). Thus, it seemed that the overall finding of a higher reduction in hot flash scores among the non-tamoxifen users was due to the results in the randomized trials. This difference was further investigated with analyses of the randomized trials evaluating the active and placebo arms separately.

Figure 2 is a forest plot demonstrating that, in the placebo arms, there was a greater percent reduction from baseline in women not receiving tamoxifen (difference in mean percent reduction, 13.4 ; 95% CI, 0.81 – 25.99). However, in the active therapy arms of the randomized trials (excluding placebos), the percent reduction in hot flash scores at week 4 from baseline was similar among the tamoxifen users and nonusers (difference in mean percent reduction, 5.7 ; 95% CI, -1.76 to 13.16). As illustrated in Fig. 3, the percent change in hot flash score (comparing week 4 to baseline) by the nonestrogenic therapies over placebos, in the randomized trials, was found to be similar (difference in mean percent reduction, 7.2 ; 95% CI, -5.80 to 20.2), supporting the contention that the efficacy of various hot flash therapies is similar among users of tamoxifen versus those who were not using tamoxifen.

The percent reduction in hot flash scores by SSRI/SNRI therapies^{18,21,23,24,32–34} at week 4 from baseline was similar among the tamoxifen users and nonusers (difference in mean percent reduction, 4.6 ; 95% CI, -3.51 to 12.71). Similarly, the percent reduction in hot flash scores by SSRI or SNRI therapies at week 4 from baseline was similar among those with

breast cancer versus those with no cancer (difference in mean percent reduction, 0.4; 95% CI, -11.93 to 12.73).

The multivariate linear model for hot flash score at week 4 confirmed that the effectiveness of the treatment was not different by tamoxifen use or breast cancer history. When the above analyses using hot flash frequency data, as opposed to hot flash score data, were conducted, virtually identical results were seen.

DISCUSSION

This is the first study specifically dedicated to evaluate the efficacy of nonestrogenic therapies on hot flashes based on a woman's history of breast cancer and/or tamoxifen use. The current pooled analysis supports that the efficacy of non-estrogenic hot flash therapies, including SSRIs/SNRIs, is similar among women with breast cancer and/or those taking tamoxifen as compared with their counterparts.

The first report of a randomized, placebo-controlled, double-blinded clinical trial demonstrating the efficacy of a newer antidepressant for treating hot flashes was published in *Lancet* in 2000.³¹ An editorial that accompanied this article acknowledged the benefit of venlafaxine in breast cancer survivors but raised the question as to whether it would be efficacious for hot flashes in women without a history of breast cancer and in women who were not concomitantly using tamoxifen.¹⁵ This editorial presumed that there was a potential difference in response depending on whether a woman had a history of breast cancer or whether she was taking tamoxifen. At that time, there were no definitive data to ascertain that the efficacy of hot flash treatments differed based on either of these variables. However, there were also no data to support the hypothesis that efficacy would be the same.

In looking at this issue, it is noteworthy that, repetitively, individual trials that have involved women with versus without a history of breast cancer and also women who were versus were not receiving tamoxifen have failed to suggest differences between the groups in the efficacy of studied hot flash treatments.^{29,30,33–36} The one exception to this is that there is a short-term increase in hot flashes in women receiving tamoxifen who then received megestrol acetate as a treatment for the hot flashes.³¹ In this situation, the temporary increase in hot flashes lasted for only a few days. After 4 weeks' time, the efficacy of megestrol acetate for hot flashes was similar in women who were receiving tamoxifen versus those who were not. The results of this current study support the findings from these individual trials, demonstrating marked similarities between the effects of different treatments for hot flashes both in women with versus without a history of breast cancer and in women receiving versus not receiving tamoxifen.

The only other attempted evaluation of this issue was reported in an article published in *JAMA* in the recent past.¹⁶ This article was a meta-analysis involving six trials that evaluated the efficacy of newer antidepressants (paroxetine, venlafaxine, fluoxetine, and citalopram) in reducing hot flashes.¹⁶ This study reported that these interventions reduced the relative number of daily hot flashes by 1.13 (95% CI, 1.70–0.57) as compared with a placebo. The authors of this article claimed that their analysis indicated that the efficacy of SSRIs/SNRIs for hot flash reduction was significantly higher among women with breast cancer and SERM use (1.4 fewer hot flashes; 95% CI, 1.97–0.82), as compared with those without breast cancer and SERM use (mean difference, 0.17 fewer hot flashes; 95% CI, 1.41 to -1.07). However, it should be noted that the authors had analyzed individual study results based on whether any woman in the study had a history of breast cancer. For example, one study evaluating paroxetine, published in *JAMA*,³⁸ included less than 10% of women with a history of breast cancer but was analyzed as if all the women had breast cancer. The study

revealed positive results in a population that mostly did not have breast cancer, and this situation clearly affected the results of the meta-analysis.

In addition, this prior meta-analysis,¹⁶ designed to evaluate whether studied interventions changed hot flashes from baseline, included two trials^{39,40} wherein no baseline hot flash data had been collected.⁴¹ These two trials were read as being negative studies, even though it is impossible to determine whether this was true because they did not have baseline data against which to compare any changes from baseline. These two trials were included in the group that was considered to be women without a history of breast cancer. Thus, by not including a positive study in the “non-breast cancer group,” when 90% of the women in that study did not have breast cancer, and by including two trials without baseline hot flash data that were considered to be negative studies, this meta-analysis was not able to appropriately address this posed question.

A comment regarding the limitations of this current evaluation is in order. As is the nature of pooled analyses, this project was a retrospective evaluation of prospectively obtained data. Ideally, a large trial studying a single agent in women with and without a history of breast cancer and with and without the concurrent use of tamoxifen would be able to better address the question at hand. This sort of a trial, however, is not likely to be conducted given competing priorities, the available information from several smaller trials that have addressed this question,^{29,30,33–36} and the current pooled analysis. It may be that the current analysis might be the best one available to address this question for a long period of time.

CONCLUSIONS

In conclusion, it seems that the effects of nonestrogenic treatments, including SSRIs/SNRIs, on hot flashes are mostly similar, as opposed to mostly different, in women with versus without a history of breast cancer and also in women receiving versus not receiving tamoxifen.

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FIG. 1. Forest plot evaluating whether there is a difference in mean hot flash reduction from week 4 to baseline in **(A)** women with versus without a history of breast cancer and **(B)** women receiving versus not receiving concurrent tamoxifen. DHEA, dihydroepiandrosterone; MPA, medroxyprogesterone acetate; RCT, randomized controlled trial. Weight, relative contribution of each study towards meta-analysis.

FIG. 2.

Forest plot evaluating whether there is a difference in mean hot flash reduction from week 4 to baseline, in the placebo arms of studies, in women receiving versus not receiving concurrent tamoxifen. Weight, relative contribution of each study towards meta-analysis.

FIG. 3.

Forest plot evaluating whether there is a difference in mean hot flash reduction from week 4 to baseline, in the active therapy arms over the placebo arms, in women receiving versus not receiving concurrent tamoxifen. *, different doses of venlafaxine in the trial. Weight, relative contribution of each study towards meta-analysis.

TABLE 1

Distribution of women according to history of breast cancer and tamoxifen use in the included studies

Hot flash study	History of breast cancer		History of tamoxifen use	
	No (n = 243)	Yes (n = 845)	No (n = 658)	Yes (n = 738)
Pilot trials				
1. Venlafaxine ²¹	NA ^a	NA ^a	23 (88)	3 (12)
2. Nefazadone (not published)	1 (11)	8 (99)	0 (0)	9 (100)
3. Bupropion ²⁵	7 (58)	5 (42)	7 (58)	5 (42)
4. Citalopram ²³	3 (16)	15 (84)	10 (56)	8 (44)
5. Mirtazapine ²⁴	9 (41)	13 (59)	12 (55)	10 (45)
6. Gabapentin ²²	2 (10)	18 (90)	6 (30)	14 (70)
7. Desipramine ²⁰	1 (4)	23 (96)	17 (71)	7 (29)
8. DHEA ¹⁹	8 (29)	20 (71)	19 (68)	9 (32)
9. Aprepitant ¹⁷	20 (91)	2 (9)	22 (100)	0 (0)
10. Flaxseed ²⁷	18 (64)	10 (36)	18 (78)	5 (22)
11. Levetiracetam ²⁸	21 (81)	5 (19)	23 (88)	3 (12)
12. Citalopram ¹⁸	3 (12)	23 (88)	13 (50)	13 (50)
Randomized control trials				
13. Fluoxetine ³²	NA ^a	NA ^a	37 (46)	44 (54)
14. Megestrol acetate ³⁰	0 (0)	97 (100)	19 (20)	78 (80)
15. Vitamin E ²⁹	0 (0)	120 (100)	46 (38)	74 (62)
16. Soy ³⁶	0 (0)	175 (100)	56 (32)	119 (68)
17. Venlafaxine dose ^{31, b}	NA ^a	NA ^a	69 (31)	151 (69)
18. Black cohosh ³⁵	49 (37)	82 (63)	64 (53)	57 (47)
19. MPA and venlafaxine ³³	79 (36)	138 (64)	129 (59)	88 (41)
20. Gabapentin and antidepressant ³⁴	22 (19)	91 (81)	68 (62)	41 (38)

Data are presented as n (%). DHEA, dihydroepiandrosterone; MPA, medroxyprogesterone acetate.

^aNot assessed.^bThree doses of venlafaxine.

Characteristics of the women in the included studies

TABLE 2

	History of breast cancer (n = 885)		History of tamoxifen use (n = 1,149)	
	No (n = 204)	Yes (n = 681)	No (n = 538)	Yes (n = 611)
Age, mean (SD), y	55 (6.9)	55 (8.9)	54 (7.8)	55 (8.9)
White, n (%) ^a	150 (97)	566 (97)	423 (96)	533 (98)
ECOG performance status of 0, n (%) ^a	148 (97)	469 (94)	303 (96)	302 (94)
Phase III study, n (%) ^a	128 (63)	572 (84)	406 (76)	539 (88)
Tamoxifen use, n (%) ^a	8 (4)	434 (64)	0 (0)	611 (100)

ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

^a Percentages apply to known data (not including missing data). For some categories, data were missing for some patients (eg, ECOG performance status).

Efficacy of HF therapies by history of breast cancer and tamoxifen use in all of the studies that included women both with and without breast cancer and had baseline plus 4-week HF data

TABLE 3

	History of breast cancer		History of tamoxifen use	
	No (n = 204)	Yes (n = 681)	No (n = 538)	Yes (n = 611)
Baseline: HF score per day				
Mean (SD)	12.9 (9.35)	14.9 (10.37)	13.9 (10.0)	15.2 (10.6)
Median	10.6	12.6	11.1	12.7
Week 4: HF score per day				
Mean (SD)	6.1 (7.10)	7.1 (7.28)	7.4 (8.6)	8.8 (8.6)
Median	3.4	5.3	4.6	6.4
Change in score from baseline to week 4				
Mean (SD)	-6.8 (8.76)	-7.8 (9.09)	-6.5 (8.2)	-6.4 (8.7)
Median	-4.8	-5.9	-5.0	-4.4
Percentage of baseline score at week 4				
Mean (SD)	52.8 (46.86)	50.4 (40.92)	53.9 (43.2)	61.2 (49.4)
Median	40.2	40.9	45.2	54.8
>50% Reduction from baseline				
Yes	117 (57%)	200 (57%)	286 (53%)	279 (46%)

HF, hot flash.

^aFor mean change.