

## Managing menopausal symptoms in women following breast cancer treatment

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Ganz P, Greendale G, Petersen L *et al.* Managing menopausal symptoms in breast cancer survivors: results of a randomized controlled trial. *Journal of the National Cancer Institute*, 2000; 92:1054-1064.

### Objective

To test the efficacy of a comprehensive menopausal assessment intervention in reducing menopausal symptoms in breast cancer survivors.

### Study design

The study involved a two group randomized controlled design. Seventy-six women recruited from physicians' practices, advertisements and hospital newsletters were allocated to intervention or usual care conditions. Eligibility criteria included being perimenopausal or postmenopausal (defined by amenorrhoea  $\geq$  6 months), being between 8 months and five years post-diagnosis of Stage I or Stage II disease and at least 4 months post radiotherapy or chemotherapy, and presence of at least one target symptom (hot flushes, vaginal dryness, stress urinary incontinence) of moderate to severe intensity. Patients were excluded if they had received HRT within the past 3 months. Women allocated to the treatment condition received a structured comprehensive menopausal assessment (CMA) intervention. The intervention involved comprehensive assessment of menopausal symptoms, followed by development of an individualised plan comprising education, counselling, pharmacological and behavioural interventions tailored to the individual's needs. The intervention was delivered by a nurse practitioner and involved 3 clinic visits plus follow up phone calls over a four month period. The effectiveness of the intervention was assessed by comparing pre-post test differences between the

intervention and usual care group on measures of severity of menopausal symptoms, vitality (a subscale of the RAND SF-36 Quality of Life Scale), and sexual functioning (a subscale of the CARES quality of life instrument).

### Results

Women who received the CMA intervention demonstrated significantly greater reduction in severity of menopausal symptoms over time compared to women in usual care group, and a statistically significant improvement in sexual functioning compared to the usual care group. No significant differences between intervention and usual care groups were identified for scores on the vitality subscale.

### Conclusion

The CMA intervention was effective in decreasing menopausal symptoms and improving sexual functioning for women with breast cancer who were experiencing multiple and severe menopausal symptoms. However, these improvements did not result in measurable improvements in the vitality dimension of overall quality of life.

### COMMENTARY

The management of menopausal symptoms is an integral component of breast cancer care. Breast cancer commonly affects postmenopausal women, in whom diagnosis coincides with current or previous menopausal symptoms.<sup>1</sup> Moreover, current therapies for treatment of breast cancer are often aimed at suppressing or antagonising the effects of endogenous oestrogens,<sup>2</sup> thus producing treatment-related effects typically associated with menopause. These effects can include symptoms such as an increase in the frequency and severity of hot flushes, vaginal dryness, and urinary incontinence, as well as decreased libido, dyspareunia, and difficulties in achieving orgasm.

While few population-based studies have been undertaken to define the scope of the problem, available studies suggest the prevalence of menopausal symptoms in women with breast cancer is high. A 1994 British study reported that 60% of their

sample of 108 outpatients with breast cancer experienced menopausal symptoms.<sup>3</sup> Similarly, a 1995 study of 190 postmenopausal women 2 to 6 years post diagnosis of breast cancer reported 41% of their sample attributed at least one physical or mental health problem to menopause, with 50% of these women requesting treatment for their menopausal symptoms.<sup>4</sup> A more recent study of 114 postmenopausal women who were at least 3 months post completion of treatment for breast cancer reported 60% of their sample experienced at least 6 out of 13 characteristic menopausal symptoms. In addition, 54% of their sample rated at least two of these symptoms as 'quite a bit' or 'extremely' severe.<sup>5</sup> Importantly, other studies have suggested that the prevalence and impact of menopausal symptoms amongst women who have received treatment for breast cancer is greater than that experienced amongst the general population. These studies report that breast cancer survivors have higher rates of hot flushes, vaginal dryness, and urinary symptoms than age-matched healthy controls.<sup>6,7</sup>

While menopausal symptoms are often noted clinically as being bothersome for many women, the extent to which such symptoms impact on the day-to-day functioning and quality of life for women with breast cancer has not been clearly defined. Some studies suggest women with more severe menopausal symptoms experience higher rates of depressive symptoms,<sup>8</sup> lower quality of life,<sup>3,9</sup> poorer sleep quality and higher levels of fatigue.<sup>10</sup> In the present study, while statistically significant associations between menopausal symptoms and the RAND Quality of Life subscales were not identified, modest correlations were reported between menopausal symptoms and the psychosocial and sexual functioning subscales of the CARES quality of life instrument. These results suggest that menopausal symptoms are quite distressing and can negatively impact on quality of life for a notable proportion of women. Such data challenges clinicians and researchers to identify more effective strategies for managing menopausal symptoms.

Some caution is required in drawing definitive conclusions from the above data, since the symptoms attributable to menopause may also be indicative of other co-morbidities or treatment side effects. There are also limited data on the patterns and trajectory of menopausal symptoms during and following treatments, or factors associated with the prevalence and severity of menopausal symptoms to help guide intervention in this area. Nonetheless, the available studies provide sufficient evidence that the experience of menopausal symptoms by women with breast cancer is a significant problem for a sizeable proportion of women. The treatment of menopausal symptoms in women with breast cancer does, however, present some unique challenges, as the role of standard pharmacological treatments such as hormone replacement therapy remains controversial. As such, the present study makes an important contribution to this field, since it presents a fairly rigorous evaluation of non-pharmacological strategies used in combination with non-oestrogen pharmacological treatments for the management of three target symptoms: hot flushes, vaginal dryness and urinary incontinence.

Specifically, the present study evaluates the role of cognitive-behavioural interventions, combined in some cases with non-oestrogen medications, in reducing the severity and impact of menopausal symptoms. Each study participant underwent a comprehensive menopausal assessment, and an individualised plan was subsequently developed for management of specific symptoms. Treatment algorithms for the target symptoms, as well as written educational materials to accompany each medication or behavioural intervention, were used to guide and supplement the individualised plan. This type of cognitive-behavioural approach has been used for some years for the management of psychological distress experienced by people with cancer. However the role of such approaches in managing cancer-related symptoms has been less well researched. Recent evidence suggests that cognitive-behavioural strategies may be useful adjuncts to pharmacological strategies in managing cancer-related symptoms such as pain and nausea.<sup>11</sup> Their role in managing menopausal symptoms for women with breast cancer is therefore worthy of further investigation.

The fundamental premise of the comprehensive approach to symptom management trialed in the present study is that symptoms typically have multifactorial aetiologies and dimensions. As such, symptom management strategies which integrate both pharmacological and non-pharmacological interventions can potentially provide a more effective

management approach, since they focus not only on the cause, but also on the meaning as well as the outcomes of the symptom for individual persons with cancer. The present study focuses primarily on amelioration of physical symptoms. However, this type of comprehensive approach to symptom management has much potential for focusing clinicians attention on the psychological and sexual dimensions and sequelae of such symptoms as well.

A further unique feature of this study is that it addresses a combination of symptoms, rather than any one symptom in isolation. Recent studies have noted that cancer related symptoms often occur in clusters, and that it is important to understand the interactions, or synergistic effects of various symptoms in both research and practice.<sup>12</sup> As such, the approach taken in the present study, whereby a comprehensive assessment of target symptoms is a prelude to education, counselling and specific medication or behavioural intervention, potentially allows a better understanding of the relationships between various symptom experiences, and the ability to focus intervention on what is most troubling for the woman. The authors of this study draw on empirical data to support their approach, by arguing that most single modality pharmacologic studies have demonstrated only modest benefit in terms of reduction in symptomatology.

Of course, the multiple components and strategies addressed in the comprehensive assessment and intervention approach trialed in this study make it difficult to determine which, if any, components are essential or most important in reducing the severity and impact of menopausal symptoms. While both standard materials and training were employed, nurse practitioners in this study developed an individualised plan relevant to each woman's needs, and this plan was modified according to the woman's response to the intervention. Arguably, such an approach better reflects the realities of day-to-day clinical practice, and the complex and multidimensional nature of symptom experiences.

Other limitations noted by the authors should also be considered in determining the generalisability of the findings from this study. In particular, the study involved a small sample comprising a specific group of highly symptomatic women. These women were unique in that they demonstrated high scores on psychosocial functioning at the commencement of the study and were highly educated. They were also a highly motivated group who had complied with the requirement to complete symptom diaries each day for 28 days before they were considered for entry into the study. The extent to which the behavioural

approaches investigated in this study are effective for other groups of women with breast cancer requires further investigation.

This study provides evidence that a comprehensive assessment and individualised management plan using education and counselling in combination with pharmacological strategies can be useful in reducing the severity of menopausal symptoms, and the impact these symptoms have on quality of life and sexual functioning for women following treatment for breast cancer. The authors suggest that the intervention can be delivered by health professionals who have generic skills in assessment, education, counselling and decision support, and who have specific knowledge of breast cancer and menopause. The study provides evidence that targeting intervention towards those who need it most may be of some benefit, emphasising the importance of ensuring mechanisms are in place for identifying women for whom menopausal symptoms are most troublesome. The challenge for clinicians is to identify how these comprehensive approaches to managing menopausal symptoms can be incorporated into routine clinical practice.

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# Managing hot flushes in women treated for breast cancer

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Loprinzi CL, Kugler JW, Sloan JA  
*et al.* Venlafaxine in management  
of hot flushes in survivors of breast  
cancer: a randomised controlled trial.  
*Lancet* 356; 2059-2063, 2000

## Objective

To assess the efficacy and toxicity of venlafaxine for the treatment of hot flushes in survivors of breast cancer.

## Study Design

This was a randomised double blind placebo-controlled study. Patients were allocated to one of four treatments

- 1) extended release venlafaxine 37.5mg daily for 28 days
- 2) extended release venlafaxine 37.5mg daily for 7 days then 75mg daily for 21 days
- 3) extended release venlafaxine 37.5mg daily for 7 days, then 75mg daily for 7 days, then 150mg daily for 14 days
- 4) placebo for 28 days.

Patients were stratified according to age, current tamoxifen use, duration of hot flush symptoms, and the average frequency of hot flushes per day. The study was conducted between February and July 1999 by centres in the North Central Cancer Treatment Group.

## Study Population

Women were eligible to participate if they had a history of breast cancer or were concerned about taking oestrogen for fear of breast cancer. Inclusion criteria were: troublesome hot flushes occurring at least 14 times per week; hot flushes severe enough for the woman 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 0-1 on the ECOG scale. Anti-oestrogens (tamoxifen, raloxifene) and aromatase inhibitors were permitted if started 4 weeks before the beginning of the study and were to continue for the next 5 weeks.

## Outcome Measures

A run-in period occurred so that after randomisation but before starting the trial medication each patient completed a daily hot flush diary for one baseline week. This questionnaire was then completed daily for 4 subsequent weeks. It asked about the frequency of mild, moderate, severe and very severe hot flushes per day. Women also completed two global quality of life questions and the Beck Depression

Inventory. Weekly questionnaires inquired about potential toxicity of venlafaxine. The primary endpoint was the self-reported average daily hot flush activity, a score incorporating hot flush number and severity. Secondary endpoints included change in mood and quality of life.

## Results

Two hundred and twenty nine individuals participated but assessable data were not available for 30 patients. These patients had stopped the study medication or failed to return diaries, or both. The groups were well balanced in terms of age, tamoxifen use (69% were taking tamoxifen), the duration and frequency of hot flush symptoms, race, and baseline quality of life and depression scores. The hot flush frequency in participants at baseline was 8 per day. After 4 weeks, the median decrease in hot flash score was significantly greater in all 3 venlafaxine groups than in the placebo group ( $p < 0.0001$ ). The median decrease in hot flush activity was 27% for placebo, 37% for the 37.5mg venlafaxine dose and 61% for both the 75mg and 150mg doses. Efficacy was similar whether or not patients were taking tamoxifen. Toxicity data showed that the frequencies of mouth dryness, decreased appetite, nausea, and constipation were significantly higher in the venlafaxine 75mg and 150mg groups than in the placebo group. More toxic effects occurred with the 150mg dose than the 75mg dose. Nausea was temporary in most cases and largely resolved with time. Libido, as measured by one question on the Beck Depression Inventory, improved from baseline for all study groups over the 4 week period. Depression scores improved more for those women taking venlafaxine and overall quality of life was better in those taking venlafaxine compared to placebo.

## Conclusion

This trial shows that venlafaxine can alleviate hot flushes and that the most appropriate dose for this indication is 75mg daily (extended release), which was more effective than 37.5mg daily but was as effective as, and less toxic than, 150mg daily. Efficacy must be balanced against the drug's side effects.

## COMMENTARY

Menopausal symptoms are the cause of morbidity in a substantial proportion of breast cancer survivors. These women report higher rates of hot flushes, vaginal dryness and urinary symptoms than age matched healthy control subjects.<sup>1,2</sup> Breast cancer is primarily a disease of postmenopausal women in whom the

diagnosis may coincide with menopausal symptoms. At diagnosis, many women are taking hormone replacement therapy and are usually advised to stop this when breast cancer is diagnosed. Additionally, breast cancer treatments may induce menopause or its symptoms. Adjuvant chemotherapy causes ovarian failure in many premenopausal women and tamoxifen promotes vasomotor and vaginal symptoms.<sup>3,4</sup> The use of luteinizing hormone-releasing hormone agonists produces amenorrhoea in all premenopausal women, leading to a profound increase in menopausal symptoms. Although it is known that oestrogen and progesterone replacement therapy can alleviate hot flushes and other symptoms, there are continued safety concerns regarding the use of hormonal therapies in women with a history of breast cancer.

Loprinzi and colleagues have investigated a number of non-hormonal pharmacological interventions in the management of hot flushes for breast cancer survivors. They have applied the same sound methodology by using a placebo-controlled design and the application of patient based reports of hot flush activity as the primary outcome measure. These studies have shown that Clonidine has a similar degree of efficacy as vitamin E, which is a bit better than placebo.<sup>5,6</sup> Clonidine, however, comes with significant toxic effects (mouth dryness, dizziness, drowsiness, and sleep disturbance) which may limit utility and patient acceptance. Soy-derived phytoestrogens are no more effective in reducing hot flushes than placebo.<sup>7</sup> Recently, there has been interest by these investigators and others in the potential of antidepressant drugs to influence menopausal flushing, particularly in women with a history of breast cancer. Uncontrolled pilot studies have shown that treatment with serotonin-uptake inhibitors trazodone and paroxetine is associated with significant reductions in menopausal symptoms and hot flushes respectively.<sup>8,9</sup> Loprinzi *et al.* progress the issue of non-hormonal treatment of hot flushes further by evaluating the effectiveness of venlafaxine in a randomised placebo controlled trial. Venlafaxine is a drug which inhibits presynaptic reuptake of serotonin and noradrenaline and has proven efficacy in the treatment of major depressive and generalized anxiety disorders.<sup>10,11,12</sup> The place this class of drugs will have in the routine management of hot flushes is likely to be influenced by the predictability and magnitude of the response and the balance between positive

and negative effects of the drug. The positive effects seen in this study of venlafaxine include fewer hot flushes, enhanced mood and quality of life without the risks of uterine bleeding and breast cancer. The negative effects are dry mouth, constipation, nausea and reduced appetite. It remains to be seen whether the findings of this study are applicable to the wider population of post menopausal women. This will need further investigation.

What about the use of hormone replacement therapy – is it safe for breast cancer survivors? Published case series report low rates of recurrence and death in users of hormone replacement therapy after breast cancer.<sup>13,14</sup> Observational studies using matched controls have also in the main found no increased risk of breast cancer among users of hormone replacement therapy after diagnosis compared with non-users.<sup>15</sup> Most of these studies were small and/or involved relatively short periods of follow-up. Despite efforts to minimise bias in observational studies, concern remains about the residual effect of bias particularly when the exposure of interest is under control of the subjects. These results must still be considered preliminary but provide the rationale for prospective clinical trials testing the safety of hormone replacement therapy for women with a history of breast cancer. For breast cancer survivors (and their doctors) who remain uncertain about the

use of hormone replacement therapy and are unwilling to accept any potential risk, the new class of antidepressants, including venlafaxine, which reduce hot flushes by 50-60% are an option.<sup>16</sup> These agents have some associated toxic effects but are tolerated by many. Further exploration is needed to compare and contrast a variety of newer antidepressants to find the most efficacious and least toxic therapy for this clinical problem.

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**Editor's Note:** This issue of *Clinical Update* is released at a time when the risks involved in long term use of combination Hormone Replacement Therapy (HRT) are being highly publicised, as a result of the release of the Women's Health Initiative study, published in *The Journal of the American Medical Association* on 17 July 2002. Even though this study did not involve women with breast cancer, the findings should be considered in discussions with women about the management of menopausal symptoms.

### Note about the *Clinical practice guidelines for the management of early breast cancer (2nd edition)*

The second edition of the *Clinical practice guidelines for the management of early breast cancer* was released in February 2002.

One of the guideline recommendations (recommendation 10) states: *Radiotherapy after complete local excision is recommended as it significantly reduces the risk of local recurrence in the breast and the need for further surgery. It should not be omitted, even in selected patients.*

This recommendation is made because a review of current evidence found that "a group of women at sufficiently low risk of recurrence to allow breast conservation without radiotherapy has not been defined" (page 68).

It has been suggested that this recommendation appears to conflict with a statement on page 68, which reads "sometimes it may be appropriate to omit radiotherapy". The context for this statement is the woman's right to refuse radiotherapy.

It is noted throughout the guidelines that the benefits and risks of all treatment options should be discussed with the patient by the relevant specialists. Recommendation 10 emphasises the importance of ensuring all women with early breast cancer are aware of the benefits of radiotherapy. However, while radiotherapy is recommended, a woman may choose to decline it.

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