Managing Menopausal Symptoms in Breast Cancer Survivors: Results of a Randomized Controlled Trial

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Background: Menopausal symptoms (e.g., hot flashes, vaginal dryness, and stress urinary incontinence) are very common in breast cancer survivors and cannot be managed with standard estrogen replacement therapy (ERT) in these patients. The purpose of this study was to test the efficacy of a comprehensive menopausal assessment (CMA) intervention program in achieving relief of symptoms, the improvement in quality of life (QOL), and sexual functioning in breast cancer survivors. Methods: Using a two-group, randomized controlled design, we assigned 76 postmenopausal breast cancer survivors with at least one severe target symptom either to the intervention group or to a usual-care group. Seventy-two women were evaluable at the end of the study period. The CMA intervention, delivered by a nurse practitioner, focused on symptom assessment, education, counseling and, as appropriate, specific pharmacologic and behavioral interventions for each of the three target symptoms. Psychosocial symptoms were assessed with the use of a self-report screening instrument, and distressed women were referred for counseling if needed. The intervention took place over a 4-month period. Outcomes measured were scores on a composite menopausal symptom scale, the RAND Short Form Health Survey Vitality Scale, and the Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Scale at baseline and at 4-month follow-up. All statistical tests were two-sided and were performed at the alpha = .05 significance level. Results: Patients receiving the intervention demonstrated statistically significant improvement (P = .0004) in menopausal symptoms but no significant change in vitality (P = .77). Sexual functioning was statistically significantly improved (P = .04) in the treatment group compared with the usual-care group. Conclusions: A clinical assessment and intervention program for menopausal symptom management in breast cancer survivors is feasible and acceptable to patients, leading to reduction in symptoms and improvement in sexual functioning. Measurable improvement in a general QOL measure was not demonstrated. [J Natl Cancer Inst 2000;92:1054-64]
breast cancer survivors report higher rates of hot flashes, vaginal dryness, and urinary symptoms than age-matched healthy control subjects (8, 9, 18). While the benefit-risk ratio of ERT in breast cancer survivors is being re-evaluated (19), its use in these women remains highly controversial. Therefore, these patients are often at a loss for what to do for menopause symptom management.

Several studies have evaluated the efficacy of the different behavioral (20, 21) and non-ERT pharmacologic approaches to the management of vasomotor symptoms (22–25) and urogenital atrophy (26–28). These studies provide potential strategies to address these symptoms in breast cancer survivors. In this research, our overarching goal was to develop an intervention program that would address all menopausal symptoms together with the objective of maximum symptom control and improved QOL. Modeled after the “comprehensive geriatric assessment” (CGA) (29–31), we developed an intervention program called the “comprehensive menopausal assessment” (CMA). Research in the CGA has demonstrated the benefit of targeting the intervention toward subjects who need it the most (32) and setting certain criteria for admission to the CGA protocol. If patients are too ill (i.e., near death) or too well (i.e., not in need of much improvement), it is unlikely that a CGA will serve them well. Like the geriatric approach, our CMA intervention targets a highly symptomatic group of women with the goal of reducing symptoms and improving QOL through use of education, counseling, and focused non-ERT interventions. This article describes the results of a randomized controlled trial designed to evaluate the efficacy of the CMA intervention program in breast cancer survivors.

Subjects and Methods

Subject Eligibility, Recruitment, and Procedures

Breast cancer survivors recruited for this study had to meet the following eligibility criteria at the time of recruitment: 1) a disease-free, female breast cancer patient, between 8 months and 5 years after the diagnosis of stage I or II disease (33); 2) perimenopausal or postmenopausal (defined by amenorrhea of ≥6 months); 3) all chemotherapy or radiation therapy completed at least 4 months prior to enrollment, but could be taking tamoxifen; 4) presence of at least one target symptom under investigation (hot flashes, vaginal dryness, or stress urinary incontinence) that was moderate to severe in intensity; and 5) willing to accept behavioral or pharmacologic treatment for at least one target symptom. Exclusion criteria included the following: 1) a history of other cancers, with the exception of nonmelanoma skin cancer; 2) serious chronic medical conditions that might influence the assessment of a health-related QOL; 3) an abnormal Pap smear showing dysplasia or more severe changes; 4) current symptoms of a major psychiatric illness (e.g., depression) that were not being treated or were not being controlled by medication; 5) inability to read and write in English; 6) active alcohol or substance abuse; 7) use of ERT within the past 3 months; and 8) major cognitive impairment or inability to provide informed consent.

Participants were recruited from the community by use of physician practices, paid newspaper advertisements, and notices in hospital newsletters. The Human Subject’s Protection Committee of the University of California at Los Angeles approved and monitored the study, and all subjects provided written informed consent for all phases of the research. Potential participants were sequentially screened for study eligibility through telephone and in-person evaluations. The details of the study protocol are shown in Table 1. As can be seen, there were multiple screening/eligibility tasks performed before randomization occurred. For example, we needed to exclude other causes of vaginal and urinary symptoms that would require medical treatments, before including the woman in the study. If they remained eligible for the study after completion of a brief physical and gynecologic examination, women were asked to complete daily symptom diary cards for each target symptom for 28 days and were eligible for study enrollment if they were compliant. Baseline measurements and randomization occurred at a subsequent in-person visit. Participants were stratified by age (<55 years versus >55 years) and tamoxifen use (currently used versus not used) as part of the randomization procedure.

So that we could partially control for the attention received in the CMA intervention group, women in the usual-care group were telephoned by the research assistant 2 months after the baseline visit to ask about any therapies (medications, vitamins, herbs, or psychosocial remedies) used to help manage their symptoms. Women in the usual-care group were not precluded from obtaining any medical or nonmedical management for their symptoms but were not encouraged to do so. Thus, this constitutes a genuine usual-care control group rather than a no-treatment control group. Women in the intervention group were asked to come in for a 2-month follow-up visit. One month later, all women were sent a second set of diary cards for completion prior to their final visit (to be held 4 months after the baseline visit). At the final study visit, all women completed the questionnaire battery (including report of medications or strategies to control symptoms) and had a gynecologic examination. Women in the usual-care group then received the CMA intervention, but no further outcome data were collected in this group. Women in the CMA group were thanked for their participation and were sent a letter summarizing the evaluation of their symptoms, along with treatment recommendations for their physician to consider for continuing management.

Outcome Measures

Menopausal Symptom Scale Score adapted from the Breast Cancer Prevention Trial Symptom Checklist. The Breast Cancer Prevention Trial Sympt-
tom Checklist is a 43-item list of commonly reported physical and psychologic symptoms, as well as symptoms possibly associated with the menopause and tamoxifen use (8). Respondents rated how bothered they were by each problem during the past 4 weeks, using a 5-point Likert scale of severity that ranged from 0 (not at all) to 4 (extremely). We selected seven symptoms that assessed the target menopausal symptoms being studied in this trial. The items were hot flashes and night sweats (hot flash subscale), vaginal dryness, genital itching/irritation, and pain with intercourse (vaginal subscale); and difficulty with bladder control while laughing or crying and difficulty with bladder control at other times (urinary symptoms subscale). We constructed a summary scale for all seven symptoms by summing the individual severity scores and determining the mean severity score for the seven items and termed this the “Symptom Scale Score.” The Cronbach alpha scores (34) for each subscale, respectively, were hot flash subscale = 0.76; vaginal subscale = 0.76; urinary subscale = 0.76; and the Symptom Scale Score of all symptoms = 0.50. These results show high internal consistency reliability for the individual subscales and adequate internal consistency reliability for the summary scale. One would not expect to have a high internal consistency score for the Symptom Scale Score, since it measures three distinct and only partially related symptoms.

**Vitality Scale from the RAND 36-Item Health Survey 1.0 (alternatively known as Medical Outcomes Study SF-36).** The RAND 36-Item Health Survey was administered as a generic measure of health-related QOL (35,36). The Vitality Scale, which is strongly correlated with the physical and emotional dimensions of health-related QOL, was selected as the primary QOL outcome for the trial. The Vitality Scale contains four items and is scored from 0 to 100, with 100 indicating the highest energy and 0 indicating the lowest energy or greatest fatigue. The RAND 36-Item Health Survey contains eight individual subscales: physical functioning; role limitations due to physical health problems; role limitations due to emotional problems; physical health; emotional health; vitality; emotional well-being; social functioning; pain; and general health) that are part of the three general areas of health-related QOL. Each subscale ranges from 0 to 100, with 100 being the most favorable score (36). The instrument can also be scored as two composite summary scales for physical health and mental health, whose median score is 50 and is derived from a sample of healthy women of various ages taken from the general population.

**Sexual Summary Scale from the Cancer Rehabilitation Evaluation System.** The Cancer Rehabilitation Evaluation System (CARES) is a reliable and valid, self-administered, 139-item survey instrument developed to assess the QOL and rehabilitation needs of cancer patients (37–40). There are extensive normative CARES data from breast cancer patients (4,9,41), and the CARES Sexual Summary Scale was used recently in a large study examining sexual health in breast cancer survivors (16). Scoring of the CARES generates a global score or five higher order factors (physical, psychosocial, medical interaction, marital, and sexual). The CARES Sexual Summary Scale contains eight items, and it is scored from 0 to 4, with a higher score indicating more severe problems. We also used the CARES to facilitate psychosocial screening and evaluation as part of the intervention.

**Description of the CMA Intervention**

The CMA intervention consisted of a structured, comprehensive assessment of the three target symptoms (hot flashes, vaginal dryness, and stress urinary incontinence) followed by an individualized plan of education, counseling, pharmacologic and/or behavioral interventions, psychosocial support, referrals, and follow-up tailored to each woman’s individual needs and preferences. The main goal of this intervention was to provide these symptomatic patients with the information, skills, medication, and/or the support they needed to manage their symptoms more effectively. The components of the intervention are outlined in the “Appendix” section. A full manuscript describing the intervention rationale and treatment algorithms is in preparation.

A nurse practitioner with a master’s degree in family primary care and a subspecialty in women’s health was trained by one of the study physicians (P. A. Ganz) to provide the CMA intervention. Training included systematic readings on the topics of breast cancer, its psychosocial impact, and menopause, as well as careful review of specific assessment and management strategies for the nine pilot subjects who completed the baseline assessment, six of whom were followed over the course of 4 months. The nurse practitioner, in collaboration with the study physicians, developed specific treatment algorithms (protocols) for each of the target symptoms, as well as written educational materials to accompany each medication or behavioral intervention that was recommended. The training occurred over a 6-month period of time that was constrained primarily by the limitations of the study eligibility and recruitment process. Although a family nurse practitioner provided the intervention in this study, we believe that other types of nurse practitioners (adult, women’s health, or oncology) or clinical nurse specialists in oncology could also provide the CMA intervention program in clinical practice, since they have the requisite skills to provide assessment, education, counseling, and decision support. However, depending on their specific background and expertise, some of these clinicians might need additional training in the areas of menopause and/or breast cancer.

**Data Collection and Statistical Analysis**

QOL and symptom-outcome data were collected at the baseline and follow-up visits. Data on self-initiated therapies were collected at baseline, follow-up, and once in between. For women in the CMA intervention group, data on the use of recommended therapies and related side effects were collected four times, starting with a telephone call a few days after the baseline visit. The data were entered with the use of Paradox 5.0 (Borland International, Inc., Scotts Valley, CA) and analyzed by use of SAS statistical software (Version 6.04; SAS Institute Inc., Cary, NC).

As originally conceptualized in the early 1990s, the primary trial outcomes were emotional well-being and overall QOL, with sexual functioning as a secondary outcome. With emerging data from other research studies (8,42,43), it became clear that these dimensions of health-related QOL were often quite stable over time and did not discriminate among different cancer treatments. Therefore, we chose the RAND Vitality Scale as the main QOL outcome, hypothesizing that it might be a more responsive measure of QOL. This decision was based on cross-sectional data from another study of breast cancer survivors (9). Furthermore, we concluded that a symptom measure was necessary to evaluate the efficacy of the intervention in achieving its primary goal (relief of the target menopausal symptoms). Of interest, condition-specific measures have been shown to be more appropriate for measuring outcomes in clinical trials (7,8,44). Thus, the two primary outcomes for this study were the menopause symptom scale score and the RAND Vitality Scale.

We performed a power calculation incorporating a Bonferroni adjustment to account for two primary outcomes. This suggested that a sample of 36 per group would provide in excess of 80% power to detect as significant an effect size of 0.75 standard deviations in either of the primary outcome scores (symptom scale and vitality). Such an effect size implies that approximately three quarters of the usual-care group’s outcome scores would be lower or higher than the mean outcome score in the intervention group. Given the highly symptomatic nature of the women whom we had recruited to the study, we believed that it was reasonable to expect such a large effect size in the final sample.

All statistical analyses were performed on an intent-to-treat basis (with the exception of the noncompliance analysis, described below). Univariate analyses were performed to determine the relationship of various medical, demographic, and self-report scale data (symptoms, RAND 36-Item Health Survey, and CARES) to the two main outcome variables; chi-square tests were used for categorical variables, and t tests were used for continuous variables. The research assistant checked all questionnaires for completeness after they were administered; as a result, there were no missing data. Multivariable analyses to determine the presence of a group effect (intervention or usual care) were performed on each main outcome and the secondary outcome by use of analysis of covariance (ANCOVA) models, where the dependent variables were 1) the change between a woman’s baseline and follow-up outcome score or 2) the woman’s follow-up outcome score. The models considering change in scores and follow-up scores were adjusted for age, current tamoxifen use, prior chemotherapy, ethnicity (white versus nonwhite), partnered (i.e., married or in a committed marital-like relationship [versus not partnered]), and RAND physical and mental health composite scores. For the vitality outcome, analyses were also adjusted for use of clonidine, which can cause drowsiness. (No other medications had serious side effects, so they were not considered for adjustment.) Two-sided statistical tests were used throughout.

Although intention-to-treat analyses provide unbiased estimates of the effectiveness of the intervention (i.e., the expected difference if the intervention treatment instead of the control treatment were applied in a similar population), the efficacy of the intervention (i.e., the expected difference between intervention and control among those willing to receive the intervention) can, in general, be different from the effectiveness due to noncompliance. We applied the method of Angrist et al. (45) to estimate intervention efficacy. With this method, the control arm is viewed as a mixture of individuals who would have complied with the intervention if assigned and individuals who would not have complied. Although such a distinction cannot be observed, information on compliance
behavior from the intervention arm can be used to estimate the relevant proportions in the control arm, ultimately yielding estimates of the causal effect of intervention while accounting for noncompliance. We applied this method both to unadjusted outcomes and to residuals from regression analyses that included all of the ANCOVA-model predictors except the indicator for intervention versus control.

RESULTS

Subjects

Fig. 1 shows the flow diagram of study participants from initial telephone screening, in-person screening, randomization, treatment, and completion of the study. Study recruitment began January 31, 1996, and concluded September 23, 1998. Across all phases of recruitment, the most common reasons for ineligibility were inadequate severity of target symptoms, refusal to consider a study treatment for relief of symptoms, being medically ineligible, or a variety of other reasons. Ultimately, 76 women were randomly assigned to usual care (n = 39) or to intervention (n = 37). Four dropouts occurred during the course of the follow-up (all in the intervention arm of the study), leaving 72 evaluable women. Two women dropped out because of a family member's illness and two developed metastatic disease and became medically ineligible, leaving a final sample of 39 women in the usual-care group and 33 in the intervention group. A post hoc power calculation confirmed that comparing groups of sizes 39 and 33 would provide in excess of 80% power for detecting a two-sided difference of 0.75 standard deviations in each of the primary outcomes at the 0.025 significance level (two-sided testing).

The medical and demographic characteristics of the 72 evaluable women are shown in Table 2. On average, these women were 54.5 years old and were 2.5 years since the time of their breast cancer diagnosis. They had been postmenopausal for an average of 6.9 years, and about 57% of them had taken hormone replacement therapy before their breast cancer diagnosis. About two thirds had received a lumpectomy with radiation therapy as their primary treatment, and 56% of them were on tamoxifen. The intervention and usual-care groups were balanced on all factors, with the exception of race/ethnicity, where, by chance, more of the nonwhite participants were assigned to the intervention group.

Symptoms and QOL Prior to Randomization

In Table 3, we present baseline data on the outcome measures used in this trial. Overall, these women exhibited high levels of functioning and QOL, comparable to other samples of breast cancer survivors (4,9). The scores on the RAND 36-Item Health Survey are at or above the mean for the general population of healthy women (46), also confirmed by the Composite Physical and Mental Health Scales. The two study groups scored similarly on all of the RAND scales, with the exception of the Vitality Scale, for which the usual-care group had a significantly lower baseline score (P = .05).

Relationship Between Symptoms and QOL

The women who participated in this study were highly symptomatic with respect to the target menopausal symptoms (see Fig. 2). Twenty-seven (38%) of the 72 had all three target menopausal symptoms. An additional 32 (44%) of the 72 had two of the three target menopausal symptoms. Only 18% had a single target symptom. Overall, hot flashes were the most common target symptom (97% of study participants) followed by vaginal dryness (71%) and stress urinary incontinence (51%). The mean severity score for each target symptom, as well as the menopause symptom scale score, are shown in Table 3. Hot flashes were rated as the most severe symptom (2.60 on a scale of 0–4) in both groups. Although the severity of urinary symptoms was statistically significantly worse in the usual-care group, the menopause symptom scale score was not significantly different between the two study groups.

At baseline, in spite of having moderate to severe menopausal symptoms, these breast cancer survivors reported QOL scores similar to those reported by healthy women (Table 3). Sexual functioning was the only CARES Scale to demonstrate moderate problems. The relationship between symptoms and QOL was explored by constructing a correlation matrix to examine the individual symptom subscales and the menopause symptom scale score in relationship to the RAND subscales and CARES Summary Scales. The hot flashes subscale score did not correlate significantly with any of the RAND or CARES scales. The urinary symptoms subscale score was weakly correlated with

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Fig. 1. Flow chart for recruitment of female breast cancer survivors in a randomized study to evaluate the management of menopausal symptoms.
only the Vitality Scale with $r = -0.23$ ($P = .051$). The vaginal symptoms subscale score was correlated with the CARES Global, Marital, and Sexual Summary Scales, but these correlations were weak to moderate in strength ($r$ values ranging from .29 to .51). The menopause symptom scale score (hot flashes, urinary symptoms, and vaginal symptoms) did not have a significant relationship to any of the RAND scales. However, it was modestly correlated with the CARES Global, Psychosocial, and Sexual Summary Scales ($r$ values ranging from .29 to .42).

### Assessing the Effects of the CMA Intervention Program

Table 4 presents the results of the crude and adjusted change scores in the intervention group compared with the usual-care group for the study outcomes. The change scores for the menopause symptom scale differed statistically significantly between groups ($P = .0004$), with women in the intervention group reducing the severity of their menopausal symptoms over time significantly more than the women in the usual-care group. Change in the follow-up score in each group showed a similar pattern ($P = .0001$). For the Vitality Scale outcome, both the crude and adjusted change score analyses showed no difference between groups ($P = .77$); follow-up scores, adjusted for baseline covariates, revealed the same result ($P = .27$; data not shown). Controlling for the use of the sedating drug clonidine (58% of the women in the intervention group were prescribed clonidine for at least part of the 4-month study period) did not affect the outcomes for this measure. We performed residual analysis by plotting residuals against predicted values from each of the regression models and saw no pattern that would indicate departures from model assumptions.

For sexual functioning, the crude and adjusted change scores demonstrated a statistically significant improvement in the in-
Cancer survivors with menopausal symptoms.

The study sample (n = 72) of participants in the randomized trial of female breast cancer survivors*. To better understand which aspects of sexual functioning the intervention might have influenced, we explored responses to the eight individual items of the CARES Sexual Summary Scale. In the usual-care group, only two items improved statistically significantly over the 4 months of the study (arousal and orgasm). In contrast, the women in the intervention group demonstrated statistically significant improvement in all eight items of the CARES Sexual Summary Scale (sexual attractiveness for self and partner, interest in sex for self and partner, frequency of sex, arousal, lubrication, and orgasm).

Use of Treatments in the Intervention and Usual-Care Groups

The specific treatments offered and used by the intervention participants are shown in Table 5, along with treatments used by the women in the usual-care condition. All of the women in the intervention group were provided with education about their symptoms and menopause. The self-report data on educational interventions in Table 5 suggest that women in both the intervention and usual-care groups sought out additional information about their symptoms, at about the same rate. A similar proportion of women in each group received some form of psychologic referral. The intervention-group participants used medications more frequently. However, not shown in Table 5, nine of the women in the intervention group (27%) refused medications at some point during the study. The refusal rate was highest among those being treated for hot flashes; nine (32%) of the 28 women being treated for hot flashes refused to take at least one of the medications suggested by the nurse practitioner. Only two women (6%) refused treatment for vaginal dryness, and none refused treatment for urinary incontinence. The results of the noncompliance analyses mirrored the results of the intent-to-treat analyses, both for the change-score analyses and the follow-up score analyses (data not shown).

We also examined nonmedical treatments used by the women in the usual-care group during the 4 months in the study. Of the 39 women in the usual-care group, 31% of them started vitamin therapy, 18% of them began an herbal remedy, 3% began using mind-body techniques. As can be seen, in their quest for control of symptoms, these highly symptomatic women frequently adopted these alternative remedies. In addition, six women in the usual-care group received either prescription or over-the-counter medications to address their symptoms (see Table 5).

**Discussion**

We developed and evaluated a comprehensive assessment and management program for breast cancer survivors experiencing multiple and severe menopausal symptoms. The intervention applied existing methods of education, counseling, and symptom management (behavioral and non-ERT pharmacologic therapies) tailored to the needs and preferences of the symptomatic woman. Not only was the intervention feasible, but it also resulted in substantial improvement in the target symptoms, with a secondary finding of improved sexual functioning. However, vitality—an important general dimension of health-related QOL—was not improved by the intervention.

There are a number of strengths and limitations of this study. The randomized design and detailed assessment of the baseline and follow-up status of the participants allow us to have confi-

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**Table 3. Baseline scale values (mean scores and standard deviations) for 72 female breast cancer survivors**

<table>
<thead>
<tr>
<th></th>
<th>Usual-care group (n = 39)</th>
<th>Intervention group (n = 33)</th>
<th>All women (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom scores†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flashes</td>
<td>2.63 (1.1)</td>
<td>2.57 (1.2)</td>
<td>2.60 (1.12)</td>
<td>.84</td>
</tr>
<tr>
<td>Vaginal</td>
<td>1.06 (0.9)</td>
<td>1.08 (1.1)</td>
<td>1.07 (1.01)</td>
<td>.93</td>
</tr>
<tr>
<td>Urinary</td>
<td>0.76 (1.0)</td>
<td>0.39 (0.5)</td>
<td>0.59 (0.82)</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Symptom scale score</strong></td>
<td>1.42 (0.56)</td>
<td>1.31 (0.62)</td>
<td>1.37 (0.59)</td>
<td>.44</td>
</tr>
<tr>
<td>RAND 36-item health survey‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>84.9 (14.6)</td>
<td>85.6 (18.5)</td>
<td>85.2 (16.4)</td>
<td>.85</td>
</tr>
<tr>
<td>Role limits, physical</td>
<td>85.9 (24.2)</td>
<td>83.3 (29.1)</td>
<td>84.7 (26.4)</td>
<td>.68</td>
</tr>
<tr>
<td>Role limits, emotional</td>
<td>76.9 (31.7)</td>
<td>81.8 (35.4)</td>
<td>79.2 (33.3)</td>
<td>.54</td>
</tr>
<tr>
<td><strong>Vitality</strong></td>
<td>56.7 (22.2)</td>
<td>66.5 (20.3)</td>
<td>61.2 (21.7)</td>
<td>.05</td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>76.3 (12.0)</td>
<td>79.4 (15.2)</td>
<td>77.7 (13.5)</td>
<td>.34</td>
</tr>
<tr>
<td>Social functioning</td>
<td>85.6 (16.6)</td>
<td>89.4 (19.5)</td>
<td>87.3 (17.9)</td>
<td>.37</td>
</tr>
<tr>
<td>Pain</td>
<td>81.1 (20.1)</td>
<td>80.6 (19.3)</td>
<td>80.9 (19.6)</td>
<td>.92</td>
</tr>
<tr>
<td>General health</td>
<td>77.4 (17.2)</td>
<td>80.6 (17.9)</td>
<td>78.9 (17.4)</td>
<td>.45</td>
</tr>
<tr>
<td>Composite scales§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>52.0 (6.8)</td>
<td>51.6 (7.4)</td>
<td>51.8 (7.0)</td>
<td>.83</td>
</tr>
<tr>
<td>Mental</td>
<td>49.1 (7.8)</td>
<td>52.1 (9.5)</td>
<td>50.5 (8.7)</td>
<td>.14</td>
</tr>
<tr>
<td>CARES scores∥</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>0.55 (0.32)</td>
<td>0.51 (0.40)</td>
<td>0.53 (0.36)</td>
<td>.68</td>
</tr>
<tr>
<td>Physical</td>
<td>0.40 (0.42)</td>
<td>0.41 (0.42)</td>
<td>0.40 (0.46)</td>
<td>.91</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>0.61 (0.39)</td>
<td>0.63 (0.54)</td>
<td>0.62 (0.90)</td>
<td>.86</td>
</tr>
<tr>
<td>Marital</td>
<td>0.43 (0.49)</td>
<td>0.26 (0.35)</td>
<td>0.35 (0.44)</td>
<td>.07</td>
</tr>
<tr>
<td>Sexual</td>
<td>1.36 (0.91)</td>
<td>1.26 (0.91)</td>
<td>1.32 (0.90)</td>
<td>.64</td>
</tr>
<tr>
<td>Medical intervention</td>
<td>0.33 (0.45)</td>
<td>0.18 (0.35)</td>
<td>0.26 (0.42)</td>
<td>.15</td>
</tr>
</tbody>
</table>

* Scales indicated in bold are the primary (Symptom Scale Score and Vitality Scale) and secondary (Cancer Rehabilitation Evaluation System Sexual Functioning) outcomes of the study.

† A higher score indicates greater severity of symptoms.

‡ A higher score indicates better functioning or well-being.

§ The median score for the general population of women is 50. A score of 60 is one standard deviation above the median, and a score of 40 is one standard deviation below the median.

∥ A higher score indicates more problems. CARES = Cancer Rehabilitation Evaluation System.

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**Fig. 2. Venn diagram showing distribution of individual menopausal symptoms (hot flashes, vaginal dryness, and urinary incontinence) and their overlap in the study sample (n = 72) of participants in the randomized trial of female breast cancer survivors with menopausal symptoms.**

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dence in the results. The comprehensive evaluation of medical, demographic, and QOL factors enabled us to control for relevant covariates. However, there are potential sources of bias in the design, including the lack of a placebo or attention-control condition. Another consideration is the generalizability of the results from the CMA intervention, given that only one clinician was involved in providing the intervention, potentially making it clinician dependent. The intervention tested in this study represented the standardization of the clinical approaches used by the two physicians leading the study (P. A. Ganz and G. A. Green-dale), demonstrating the feasibility of training another clinician in this approach and in measuring whether the CMA intervention could have a meaningful impact on symptoms and QOL. Although the multiple components of the CMA intervention (which make it comprehensive) also make it difficult to determine which component(s) were essential or most important in leading to the success of the program, most single-modality pharmacologic studies have demonstrated only modest benefits on symptom relief (23,24,27).

### Table 4. Crude and adjusted change score analyses for primary and secondary outcomes among 72 women receiving either usual-care or intervention treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Usual-care group (n = 39)</th>
<th>Intervention group (n = 33)</th>
<th>P for group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Symptom score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted mean change score</td>
<td>0.09 (−0.04 to 0.21)</td>
<td>0.57 (0.40–0.74)</td>
<td>.0000</td>
</tr>
<tr>
<td>Adjusted mean change score</td>
<td>0.19 (−0.06 to 0.44)</td>
<td>0.61 (0.40–0.82)</td>
<td>.0004</td>
</tr>
<tr>
<td>RAND Vitality Scale‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted mean change score</td>
<td>2.3 (−3.1 to 7.7)</td>
<td>0.8 (−6.2 to 7.6)</td>
<td>.72</td>
</tr>
<tr>
<td>Adjusted mean change score</td>
<td>4.3 (−5.2 to 13.9)</td>
<td>3.0 (−5.1 to 11.1)</td>
<td>.77</td>
</tr>
<tr>
<td>Adjusted mean change score, including clonidine use as a covariate</td>
<td>−0.5 (−11.5 to 10.4)</td>
<td>4.1 (−4.0 to 12.1)</td>
<td>.40</td>
</tr>
<tr>
<td>CARES sexual functioning scale§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted mean change score</td>
<td>0.11 (−0.16 to 0.38)</td>
<td>0.46 (0.30–0.62)</td>
<td>.03</td>
</tr>
<tr>
<td>Adjusted mean change score</td>
<td>0.015 (−0.37 to 0.40)</td>
<td>0.38 (0.05–0.71)</td>
<td>.04</td>
</tr>
</tbody>
</table>

*Adjusted for the following covariates: age, current tamoxifen use, prior chemotherapy, race (white versus other), partner status (partnered versus other), and RAND Mental and Physical Composite Scores. A positive-change score indicates improvement over time, while a negative-change score indicates worsening. CI = confidence interval.

†Seven-item symptom scale that measures how bothered a woman is by each of seven symptoms (two about vasomotor symptoms, three about vaginal dryness, and two about urinary incontinence). The scale score is a mean of the ratings on each of the seven items and ranges from 0 (not at all) to 4 (extremely).

‡The RAND Vitality Scale is scored between 0 and 100, with 0 = complete lack of energy to 100 = full of energy.

§The CARES Sexual Functioning Scale measures problems with sexual interest and sexual dysfunction. A higher score indicates more problems, with 0 = no problems and 4 = very much a problem.

![Fig. 3. Change in symptom scale score from baseline to follow-up in the intervention and usual-care groups (P = .0001) of the randomized study of breast cancer survivors. A lower score indicates a lesser severity of symptoms. Ninety-five percent confidence intervals are shown. The effect of group was also significant for an analysis adjusted for covariates (P = .001) (data not shown). Closed diamonds = usual-care group; closed squares = intervention group.](image-url)

![Fig. 4. Change in Cancer Rehabilitation Evaluation System (CARES) Sexual Functioning Summary Score from baseline to follow-up in the intervention and usual-care groups (P = .02) of the randomized study of breast cancer survivors. A lower score indicates a lesser severity of problems. Ninety-five percent confidence intervals are shown. The effect of group was also significant for an analysis adjusted for covariates (P = .01) (data not shown). Closed diamonds = usual-care group; closed squares = intervention group.](image-url)
Overall, we observed that the breast cancer survivors in this study were very reluctant to try currently recommended conventional nonestrogen alternatives for the control of their hot flashes, a finding seen in other studies (47, 48). Of interest, many of the same women who were reluctant to try conventional pharmacologic agents for the control of menopausal symptoms had tried or expressed a willingness to try alternative therapies, particularly herbal or dietary supplements. Most patients were unaware of the lack of information regarding the safety and effectiveness of these therapies.

We had anticipated that menopausal symptoms would have important effects on QOL. In particular, we had hypothesized a measurable impact on vitality. In the results of the correlation among symptoms and QOL scales summarized earlier, only vaginal dryness had any statistically significant relationship to the QOL dimensions that were measured. Furthermore, correlations among symptoms and QOL scales were significant only for several dimensions of the CARES Scale. The menopause symptom scale did not have a significant relationship with any of the RAND QOL Scales but it was modestly correlated with several CARES Scales. To some extent, the larger number of questions on the CARES explains these relationships (139 on the CARES versus 36 on the RAND), as well as the marital and sexual dimensions that are only assessed on the CARES. Nevertheless, it is possible that, while symptoms may be bothersome, they may not be substantial enough to affect the major dimensions of health-related QOL (e.g., physical or emotional well-being). In the recently completed Breast Cancer Prevention Trial (7), although participants treated with tamoxifen had significantly higher rates of hot flashes, sweats, and vaginal discharge compared with those taking placebo, there was no measurable impact on QOL as measured by the Medical Outcomes Study SF-36 (7). The failure to measure a significant improvement in QOL as assessed by the Vitality Scale undoubtedly relates to its limited correlation with symptoms. In addition, the use of clonidine as one of the treatment regimens for hot flashes could have confounded a measured benefit. Furthermore, the relatively small sample size for the study may have prevented the detection of a very small effect on this component of QOL.

We have previously studied the predictors of sexual health in two large samples of breast cancer survivors (16) and in healthy postmenopausal women (49). In both of those studies, we found that the most important and consistent predictors of sexual health were the presence or absence of vaginal dryness, emotional well-being, the quality of the partnered relationship, and whether or not the woman’s partner has sexual problems (16, 49). Vaginal dryness was one of the strongest predictors of sexual dysfunction in both breast cancer survivors and postmenopausal women. As a result of those findings, we have previously recommended the evaluation of clinical interventions targeting vaginal dryness as an important strategy for dealing with sexual dysfunction in breast cancer survivors (16). Therefore, we were encouraged to find that our CMA intervention demonstrated improvement in sexual functioning.

The symptom of vaginal dryness was targeted specifically by the CMA intervention, whether or not a woman was sexually active, and other sexual concerns were addressed by the nurse practitioner in the course of psychosocial evaluation. In particular, sexuality was addressed in the context of each woman’s unique physical, psychosocial, and partnership situation. The nurse practitioner was able to discuss how the woman felt about herself and her partner and how she communicated with her partner, as well as addressing general issues of age-related changes in sexuality. Thus, patients with sexual problems were...
managed not only with lubricants and vaginal moisturizers but also with information and referral to self-help or professional resources. Perhaps, this comprehensive approach contributed to the improvement that we saw in sexual functioning. Although the exact mechanism of improved overall sexual functioning as a result of our intervention is uncertain, one possibility is that enhanced anatomic competence (e.g., more optimal vaginal lubrication during sex) leads to several positive outcomes beyond simply improved comfort. For example, it is plausible that women perceive better arousal and stimulation owing to improved secretions during sex, which enhances sexual function in a more global manner.

Finally, it is important to ask how this intervention might be incorporated into clinical practice. Increasingly, medical practice has been focusing on women’s health issues, with counseling related to menopause being an important area of interest. Since most breast cancer survivors will be unwilling to consider ERT (47,48), existing clinical programs that counsel regarding the use of estrogen will not be appropriate. However, clinicians counseling women with a history of breast cancer can adopt the comprehensive assessment and management strategies used in this intervention. It is essential that a comprehensive assessment of the target symptoms be obtained as a prelude to the education, counseling, and specific medication or behavioral interventions, to focus on what is troubling the woman and what she wants help with. Under these circumstances, one can achieve significant symptom control and may improve sexual functioning. Since the number of breast cancer survivors is expected to increase in the coming years, this clinical problem will become more common, especially in women’s health clinics and oncology practices that care for this population. We can no longer say to these women there is nothing that can be done. It is our obligation to address their symptoms and concerns through use of a comprehensive assessment and management strategy.

APPENDIX—DESCRIPTION OF THE CMA INTERVENTION

Overview

The CMA intervention targeted three specific symptoms: hot flashes, vaginal dryness, and stress urinary incontinence. Women were required to have at least one of these symptoms and to be willing to take treatment for at least one of them.

Assessment

The structured, comprehensive assessment consisted of three components: 1) symptom diary cards to collect information on the frequency, severity, and the degree to which they were bothered by symptoms, 2) an in-depth interview by the nurse practitioner focusing on target symptoms and influencing factors, and 3) a standardized psychosocial evaluation. First, the symptom diary cards, completed by the patient during the 28 days prior to the visit, were reviewed. On each card, the woman noted the timing and duration of the target symptoms and rated the severity on a numerical scale from 1 (mild) to 4 (severe) and degree of disruption/distraction experienced, also on a numerical scale from 0 (not at all) to 4 (very much). There was a section on the card for the woman to comment on her symptoms (e.g., what she was doing or feeling when the symptoms occurred). There was also a checklist of physiologic responses associated with hot flashes, completed once on the 28th day. This process helped the nurse and the patient identify the most frequent and troublesome symptom(s) and their potential triggers.

Second, the nurse practitioner interviewed each woman regarding key aspects of her symptom experience, including her description of her symptoms, her responses to those symptoms (physiologic, psychosocial, and behavioral), and how these symptoms and/or responses bothered her or disrupted her daily functioning (50). The interview also focused on obtaining information regarding any exacerbating or ameliorating factors, including past or current symptom management strategies (e.g., lifestyle or behavioral interventions, herbal or dietary supplements, other alternative/complementary therapies, and/or prescription medications). Because of the research design and the need to determine study eligibility, brief physical and gynecologic examinations, including urinalysis if indicated, were performed at an earlier screening eligibility visit (at -1 month as shown in Table 1). In clinical practice, this should follow the assessment of symptoms and should be targeted to the specific symptom(s) that are being considered for intervention. For example, a gynecologic examination would not be necessary for women without vaginal or urinary symptoms.

The psychosocial evaluation consisted of a review of the participant’s responses to the CARES questionnaire. The CARES was used to provide a comprehensive evaluation and to provide the greatest efficiency for this assessment because it is self-administered and takes about 15 minutes to complete. The CARES was completed by the patient in the office just prior to the CMA intervention assessment but could as easily be completed at home. The CARES was not formally scored by the nurse practitioner but was reviewed for items that the woman identified as a problem. Only problems rated a 3 or greater were explored in any detail by the nurse practitioner, and any relationship to the target symptoms was noted (e.g., vaginal dryness and sexual dysfunction). These problems were then addressed as part of the education and counseling component of the intervention.

Symptom Management

On the basis of this systematic data-collection process, the nurse determined which of the three symptoms and psychosocial problems that the patient wanted help with and developed an individualized plan of care, which included education, counseling, and specific pharmacologic and/or behavioral interventions. A major component of the intervention was the provision of education and counseling related to the effective management of symptoms. The content was semistructured using adjunctive written materials. The intervention content was tailored to some degree for each woman according to her specific symptoms, psychosocial concerns, informational needs (desire for information), and preference for participation in the decision-making process (51,52). We developed specific educational materials for each of the behavioral and pharmacologic interventions that were used in the intervention (except for slow abdominal breathing), and these were provided after the specific strategy was chosen, both for education and to enhance compliance with the chosen treatment. All women received a folder containing written materials, including several available pamphlets on target symptoms and sexuality after cancer, a list of self-help books on psychologic and sexual health after breast cancer, and a brochure about a resource center for women with cancer. The specific written materials are listed as follows: “Menopause,” “Estrogen Therapy,” and “Urinary Incontinence,” from the Women’s Health Learning Series, Iris Cantor/UCLA Women’s Health Education and Resource Center, 1993, 1994; “Sexuality and Cancer: For the Woman Who Has Cancer, and Her Partner” by Leslie Schover, Ph.D., American Cancer Society, 1996; “Cancer Facts: Questions and Answers About Tamoxifen,” from the Cancer Information Service, National Cancer Institute, November 29, 1995; “Coping With Menopausal Symptoms Caused by Cancer Therapy” by Jennifer L. Akin, Patient Pointer Series, Innovations in Breast Cancer Care, Vol 1, No. 1, 1995; “Reading List on Sexuality After Breast Cancer,” compiled by the Northern California Cancer Center, 1996, 1997; “Life After Breast Cancer,” Chap. 30, from Dr. Susan Love’s Breast Book, 2nd ed., 1995 (copied with...
permission from author); and “Overview of the Program, List of Groups and Classes, List of Audiotapes,” from Rhonda Fleming Mann Resource Center for Women with Cancer at UCLA.

The table below summarizes the specific interventions that were offered for each symptom.

Table 5 in the text of the article shows the frequency with which the various specific interventions were recommended to women and utilized by intervention subjects.

Additional general information was also provided as needed about hormone replacement therapy after breast cancer, the use of alternative treatments for menopausal symptoms, and the role that other factors (developmental, psychologic, social, and cultural) have on symptoms and health-related QOL. Decision-support therapy (52) was provided as necessary.

The CMA initial assessment visit (time spent with the nurse) ranged from 45 to 90 minutes, depending on the participant’s number of target symptoms and informational needs. However, if a physical examination were to be added to this visit, we would estimate an additional 10–15 minutes.

Follow-up: Re-evaluation of Symptoms, Toxicity, and Response

Follow-up included a telephone call 2 weeks after the intervention visit to assess potential side effects and/or any problems with the recommendations. An important aspect of the CMA intervention, unlike a randomized trial testing the efficacy of a single medication or behavioral strategy, was the ability to increase or decrease the dose of medication or switch to an alternate strategy. This can be seen in Table 5, where a variety of medications were used for hot flashes, until symptom relief was achieved. As part of the study, an interim visit at 2 months and a final visit at 4 months were used to evaluate response to the individualized plan. In clinical practice, the visit intervals could be lengthened as long as interim assessments occur by telephone. In our study, we used both telephone and scheduled visits to adjust, discontinue, or add treatments as appropriate. All of these contacts were relatively brief and, to some extent, were dictated by the research study rather than the clinical needs of the participants.

REFERENCES

(28) Beisland HO, Fossberg E, Sanders S. Urethral sphincteric insufficiency in urinary incontinence Behavioral—Kegel’s pelvic floor exercises (20)
(29) Lubricant—Astroglide®
(30) Behavioral—slow abdominal breathing
(31) Transdermal clonidine
(32) Medication—Replens®
(33) Medication—Phenylpropanolamine
(34) Pharmacologic—astroglide®
(35) Pharmacologic—phenylpropanolamine
(36) Stress urinary incontinence
(37) Behavioral—Kegel’s pelvic floor exercises
(38) Medication—Replens
(39) Pharmacologic—Phenylpropanolamine
(40) Psychosocial problems
(41) Referral for counseling or group support
(42) Hot flashes
(43) Pharmacologic (17)
(44) Bellergal-S
(45) Transdermal clonidine
(46) Megestrol acetate
(47) Behavioral—slow abdominal breathing (20)
(48) Vaginal dryness
(49) Moisturizer—Replens®
(50) Lubricant—Astroglide®
(51) Stress urinary incontinence
(52) Behavioral—Kegel’s pelvic floor exercises (21)
(53) Pharmacologic
(54) Replens
(55) Phenylpropanolamine (28)


Notes

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