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Impact of Adjuvant Breast Cancer Chemotherapy on Fatigue, Other Symptoms, and Quality of Life

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Purpose/Objectives: To identify differences in fatigue, other physical symptoms, and psychological symptoms and their relationship to quality of life (QOL) during chemotherapy and as long as one year after.

Design: Longitudinal, descriptive design embedded in a pilot intervention study.

Setting: Midwestern urban oncology clinics and patient homes.

Sample: 25 Caucasian women, aged 40–65 years (\bar{X} = 54.3), with stage I or II breast cancer receiving doxorubicin-based chemotherapy.

Methods: The Piper Fatigue Scale, Hospital Anxiety and Depression Scale, Symptom Experience Scale, and Medical Outcomes Study Short-Form General Health Survey were completed before and after each treatment; 30, 60, and 90 days after the last treatment; and one year after the first treatment.

Main Research Variables: Fatigue, physical and psychological symptoms, and QOL.

Findings: Fatigue levels were moderately intense during treatments and decreased significantly over time. Sleep disturbances and pain were the most frequent, intense, and distressing other physical symptoms. Anxiety was highest at baseline, and depression was highest during the fourth chemotherapy treatment. Fatigue was correlated with other physical and psychological symptoms at some times during treatments and consistently following treatments. Higher fatigue was associated with lower QOL in several domains.

Conclusions: Fatigue is associated with other physical and psychological symptoms that fluctuate during and after treatment. Higher fatigue compromises QOL.

Implications for Nursing: Interventions targeting primary or cluster symptoms can reduce the impact of adjuvant chemotherapy on fatigue, other symptoms, and QOL.

Key Points . . .

- ▶ Fatigue is a moderately intense symptom during adjuvant breast cancer chemotherapy that decreases, but does not return to low levels for all women, after active treatment.
- ▶ Frequent and problematic symptoms associated with fatigue are pain, sleep disturbances, nausea, concentration disturbances, anxiety, and depression.
- ▶ Higher levels of fatigue are related to lower quality of life in most domains during and after adjuvant breast cancer chemotherapy.
- ▶ Targeting primary or cluster symptoms can assist in managing fatigue.

grows of the potential for acute and long-term symptoms and decreased quality of life (QOL) among survivors whose five-year survival rate is 97% for localized disease and 80% for regional disease (American Cancer Society, 2005; Knopf, 2000). Cross-sectional studies have found that women with

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Since the 1970s, cancer has gone from being a fatal disease to a chronic illness, with approximately 64% of adults diagnosed with cancer expected to be alive five years after diagnosis (Division of Cancer Control and Population Sciences, 2005). The use of combined modality therapy has contributed to the improved outcomes and has lengthened the survival curve (Ganz et al., 2002). As more women receive adjuvant chemotherapy for breast cancer, recognition

breast cancer report fatigue, decreased stamina, depression, and poor sleep quality long after completing therapy that affects their QOL (Bower et al., 2000; Broeckel, Jacobsen, Horton, Balducci, & Lyman, 1998; Cella, Davis, Breitbart, & Curt, 2001). Despite this knowledge, healthcare providers have little understanding of the characteristics of and relationships among the symptoms and QOL and how they change over time.

The overall purpose of the current study was to describe the impact of adjuvant chemotherapy for breast cancer on fatigue, other symptoms, and QOL during and after treatment. Specific aims were to

1. Identify differences in fatigue, other physical symptoms (nausea, pain, appetite, sleep disturbances, bowel patterns, concentration, and appearance), and psychological symptoms (anxiety and depression) across four cycles of chemotherapy; at 30, 60, and 90 days after the last treatment; and one year after the first treatment.
2. Identify relationships among (a) fatigue and other physical and psychological symptoms at baseline, after selected treatments, and at selected times after the last treatment and (b) fatigue and QOL at baseline, 60 days after the last treatment, and one year after the first treatment.

Conceptual Framework

Piper's Integrated Fatigue Model, which proposes 14 factors that influence fatigue in patients with cancer, guided the study (Piper, Lindsey, & Dodd, 1987). The intervention for the pilot study attempted to positively influence the relationship illustrated in the model between sleep/wake patterns and fatigue. In prior studies, disturbances in sleep/wake patterns and increased symptoms (including difficulty sleeping) have been shown to be associated with fatigue (Berger & Farr, 1999; Berger & Higginbotham, 2000; Berger & Walker, 2001).

Literature Review

Fatigue

The most common unrelieved and distressing symptom related to cancer and chemotherapy treatment is fatigue (Patrick et al., 2004). Fatigue secondary to cancer and its treatments differs from acute fatigue because patients continue to suffer feelings of weakness and tiredness not fully relieved by rest (Cella et al., 2001).

Fatigue, like pain, is not explained by physiologic mechanisms alone; it also must be understood as a multidimensional concept that includes physical, psychological, social, and spiritual aspects. It is a perception best measured by self-report (Piper et al., 1998). Although literature focusing on fatigue has increased, researchers still have not agreed on a universal definition of fatigue. For the current study, fatigue was defined as "a subjective feeling of tiredness that is influenced by circadian rhythm and can vary in unpleasantness, duration, and intensity" (Piper et al., 1987, p. 19).

Women receiving adjuvant therapy for breast cancer have indicated that fatigue is one of the most common and distressing symptoms (de Jong, Courtens, Abu-Saad, & Schouten, 2002; Donovan et al., 2004). As many as 99% of women studied experienced some level of fatigue during the course of treatment, and more than 60% rated the level of fatigue as moderate to severe (Jacobsen et al., 1999). Fatigue has been

found to increase significantly after the first cycle of chemotherapy and remain elevated during the following three cycles of treatment (Jacobsen et al.).

Few authors have contributed to the literature on fatigue after adjuvant treatment for breast cancer, despite findings that fatigue persists in the weeks and months after completion of treatment. Breast cancer survivors 3–36 months following adjuvant chemotherapy have reported more fatigue than a comparison group with no history of cancer (Broeckel et al., 1998). About one-third of breast cancer survivors reported more severe fatigue associated with higher levels of depression, pain, and sleep disturbances (Bower et al., 2000).

Other Physical and Psychological Symptoms

A majority of women experience physical and psychological side effects associated with cancer treatment (Badger, Braden, & Mishel, 2001). In addition to fatigue, women undergoing chemotherapy report a variety of gastrointestinal, psychoneurologic, and menopausal symptoms. Until recently, research has focused on individual symptoms such as fatigue. However, researchers now are recognizing that some symptoms may be interrelated even though they may not share the same etiology (Beck, Dudley, & Barsevick, 2005; Dodd, Miaskowski, & Paul, 2001). Fatigue in women with breast cancer has been linked most frequently to pain (Eversley et al., 2005), depression (Badger et al., 2005), sleep disturbances (Berger & Farr, 1999), and menopausal symptoms (Tchen et al., 2003).

Fatigue at the time of treatment and at cycle midpoints has been best explained and predicted by levels of symptom severity (nausea, difficulty sleeping, and negative mood) (Berger & Walker, 2001). A follow-up study throughout the entire third cycle of chemotherapy confirmed that fatigue and symptom distress occur in unison at most time points during chemotherapy treatment cycles and during recovery (Berger & Higginbotham, 2000). Fatigue was significantly predicted by depression, pain, current tamoxifen use, mastectomy, and anxiety in a sample of 112 patients with breast cancer who were at a clinic for treatment or follow-up examination (Haghighat, Akbari, Holakouei, Rahimi, & Montazeri, 2003).

Adjuvant therapy has been shown to result in adverse effects that affect physical health status 5–10 years after the diagnosis of breast cancer (Ganz et al., 2002). Increased fatigue among survivors has been related to poorer sleep quality, more menopausal symptoms, greater use of catastrophizing, and presence of a psychiatric disorder (Broeckel et al., 1998). Multivariate analysis of 1,957 breast cancer survivors that were one to five years after initial diagnosis found depression and pain to be the strongest predictors of fatigue (Bower et al., 2000). Despite advances in symptom management, these persistent and late side effects remain major sources of distress for cancer survivors (Goodell & Nail, 2005; Longman, Braden, & Mishel, 1999; Pasacreta, 1997). The effectiveness of symptom management for persistent treatment-related side effects has become a QOL indicator (Longman et al.).

Quality of Life

Clinical investigators have become increasingly more aware of the importance of QOL during and after treatment. Interference with daily functioning and decreased QOL have been reported in breast cancer survivors (Bower et al., 2000; Broeckel, Jacobsen, Balducci, Horton, & Lyman, 2000).

Breast cancer survivors with no past systemic adjuvant therapy had better QOL in the domains of physical functioning, physical role function, bodily pain, social functioning, and general health than those who had received systemic adjuvant therapy (chemotherapy or tamoxifen). A multivariate analysis found past chemotherapy to be a statistically significant predictor of poorer current QOL ($p = 0.003$) (Ganz et al., 2002).

Limited information exists concerning the relationships among fatigue, other symptoms, and QOL before, during, and after chemotherapy treatments. Learning about the relationships will enhance the understanding of the problems faced by survivors. The knowledge can lead to the development of management strategies to improve long-term QOL for women living with breast cancer.

Methods

Design

The study was longitudinal and descriptive, embedded in a pilot study that tested an intervention designed to improve sleep and modify fatigue.

Sample and Setting

Eligibility criteria included women who (a) were aged 40–65 years, (b) were newly diagnosed with stage I or II breast cancer, (c) had undergone a modified radical mastectomy or lumpectomy, (d) were receiving a doxorubicin-based chemotherapy regimen, (e) spoke English and were able to complete the research tools, and (f) had a Karnofsky Performance Scale score greater than 60. Age was restricted because of the natural changes in sleep patterns that occur at about age 40 and the possibility that women older than 65 may have fatigue associated with various comorbid diseases that could threaten the validity of the results. Exclusion criteria included women with comorbidities known to be associated with fatigue (e.g., diagnosis of chronic insomnia, congestive heart failure, chronic obstructive pulmonary disease, insulin-dependent diabetes, neuromuscular disease, current steroid therapy) and jobs with rotating or permanent shifts that result in sleep at times other than at night.

Three oncology clinics were used to recruit the desired sample size for the pilot study in an efficient manner. In a period of six months, 23 participants completed the study during treatment, which included two baseline days and the first seven days after each of four chemotherapy treatments. Twenty-one participants completed the study after treatment ended, which included seven days of data collection at 30, 60, and 90 days after the last treatment and one year after the first treatment.

Measurement of Variables

The researchers tried to minimize participant burden and selected measurement tools that had established reliability and validity.

Fatigue: Three measurements of subjective fatigue were used. The first was the total **Piper Fatigue Scale (PFS)**, intended to measure peak fatigue. The second was a single **fatigue intensity (FI) item** (question 7 from the PFS), intended to capture daily fatigue. The third was the fatigue items (composed of frequency, intensity, and distress characteristics) in the **Symptom Experience Scale (SES)**, to describe symptoms during the previous week.

The PFS contains 22 items that measure four dimensions of subjective fatigue: behavioral severity (six items), sensory (five items), cognitive/mood (six items), and affective/meaning (five items). Each item is anchored by two words (e.g., strong/weak), and an individual circles a number from 0–10 that best describes the current fatigue experience. Total and subscale mean scores were obtained by summing the individual items of each subscale and dividing by the number of items in the subscale or total score. Five open-ended questions regarding the temporal dimension of fatigue, perceived cause, effect, and additional symptoms complete the PFS. Content and concurrent validity have been estimated in patients with cancer. The PFS took two to five minutes to complete at baseline, on day 3 (peak fatigue), after each treatment, and at each of the later times. Internal consistency reliability of the scale and subscales ranges from alphas of 0.92–0.98 in numerous and diverse studies (Piper et al., 1998) and was 0.94–0.98 in the current study.

The FI item (question 7 on the PFS) was used to measure midday fatigue intensity: “How would you describe the degree of intensity of the fatigue you are experiencing today?” (0–10). The FI item has been reported to be correlated with the total score on the PFS ($r = 0.86–0.95$, $p < 0.001$) (Berger & Higginbotham, 2000). Recording a number from 0–10 that reflected midday (2–6 pm) fatigue intensity took less than one minute each day. The FI score was obtained beginning two days before each treatment and for seven days after each treatment and at each of the times following treatment. The frequency, intensity, and distress characteristics of the FI were gathered as part of the SES.

Other physical symptoms: The SES measures women’s symptom experiences associated with treatment for breast cancer. The physical symptoms included in the instrument are those directly relevant to breast cancer treatment: nausea, pain, appetite, sleep disturbances, fatigue, bowel patterns, concentration, and appearance. The frequency, intensity, and distress of each of the eight symptoms over the prior seven days is rated on a five-point, descriptive Likert scale, for a total of 24 items that take approximately five minutes to complete. The scale ranges from 0 (absence of symptoms) to 4 (most negative symptom experience). A higher score indicates a more negative symptom experience. Alpha reliabilities for the eight symptoms have been reported to range from 0.86–0.95 (Samarel et al., 1996) and were 0.83–0.93 in the current study. The fatigue items were excluded from the SES for the study to avoid multicollinearity.

Psychological symptoms: The **Hospital Anxiety and Depression Scale (HADS)** is a brief, multidimensional, 14-item, self-reported scale that screens for anxiety and depression symptoms in medically ill patients (Zigmond & Snaith, 1983). The seven items on each psychological symptom are scored by intensity individually on a 0 (none) to 3 (severe) subscale for a total score ranging from 0–21. The total scores of each subscale are interpreted as normal (0–7), mild (8–10), moderate (11–14), or severe (15–21). The HADS takes less than five minutes to complete. Internal consistencies are 0.80–0.93 for anxiety and 0.81–0.90 for depression scales, and discriminant and concurrent validity have been established (Herrmann, 1997). The HADS was completed at baseline, treatment 4, 60 days after the last treatment, and one year after the first treatment. Alpha reliabilities ranged from 0.72–0.89 for anxiety scales and from 0.74–0.84 for depression scales in the current study.

Quality of life: The Medical Outcomes Study Short-Form General Health Survey (MOS SF-36-standard) measures perceived health status, physical functioning, and mental health domains of QOL. Eight scales are computed: physical, role physical, role emotional, social, bodily pain, mental, vitality, and general health. Items are scaled numerically in a Likert format. It takes less than 10 minutes to complete, and scores range from 0–100, with 100 being the most favorable score. Reliability coefficients have been reported as 0.81–0.88 (36 items). Discriminate validity was established, and the alpha coefficients ranged from 0.734–0.813 (Ware & Sherbourne, 1992). The MOS SF-36-standard was completed at baseline, 60 days after the last treatment, and one year after the first treatment. Alpha reliabilities in this study were 0.68–0.94.

Data Collection Schedule and Procedures

Following institutional review board approval, each woman who had undergone surgery for breast cancer and had scheduled an appointment to receive her first chemotherapy treatment was contacted and invited to participate in the pilot study. Further details about the pilot study and results have been reported elsewhere (Berger et al., 2002, 2003). The 89% who agreed to participate met with the researcher before or as close to the first treatment as possible, in a mutually convenient place, usually the participants' homes. After providing written consent, participants received instructions to complete the research tools on the scheduled days during treatment and after treatment ended, as shown in Table 1. Subjects received standard of care for symptoms outside of the research focus.

Data Analysis

Descriptive statistics (frequencies, means, standard deviations, and ranges) were obtained for all variables at specified times. The mean of the seven FI scores recorded daily during treatment or at times after treatment ended was calculated for analysis. Correlations were performed to determine relationships among variables. Random measurement analysis of variance (RM-ANOVA) was performed to determine the patterns of fatigue, other symptoms, and QOL over time in the pilot study. The Epi Info™ (Centers for Disease Control and Prevention, Atlanta, GA) and SPSS® Version 11.5 (SPSS Inc., Chicago, IL) statistical analysis programs were used for data management and analysis.

Results

Twenty-eight Caucasian women were contacted, and 25 (89%) agreed to participate. No minority women met the eligibility criteria. Participants were divided evenly between stage I and II disease; most were married, employed full- or part-time, postmenopausal, and high school graduates (see Table 2).

Fatigue

Participants reported moderate-intensity fatigue as measured by the PFS on day 3 after each treatment, and the level of fatigue remained relatively stable during treatment. Subjects reported reduced levels of fatigue after treatments ended, with the lowest level reported one year after the first chemotherapy treatment. Fatigue scores changed significantly over time per RM-ANOVA. Mean daily fatigue intensity scores measured by the FI item decreased from treatment 1 but rebounded at the fourth treatment before decreasing after treatment ended. FI scores per RM-ANOVA significantly changed over time in a pattern similar to PFS scores. Participants reported stable levels of fatigue distress on the SES during treatment and lower levels after treatment ended (see Table 3).

Frequency, Intensity, and Distress of Other Physical and Psychological Symptoms

Descriptive statistics were run to determine the means, ranges, and standard deviations for the frequency, intensity, and distress scores of the other physical symptoms. Seven symptoms were included (fatigue was excluded). Descriptive statistics of psychological symptoms (anxiety and depression) were run to determine the means and standard deviations.

Prior to the first chemotherapy treatment, the symptoms reported most frequently were sleep disturbances and pain. At the time of subsequent treatments, women consistently reported sleep disturbances. Gastrointestinal symptoms also occurred frequently, with nausea reported more frequently at later treatments. At all times after treatments ended, women reported that sleep disturbances and pain persisted, that nausea abated, and that difficulty concentrating occurred. Prior to the initiation of chemotherapy, the most intense symptoms reported were sleep disturbances, pain, and concentration disturbances. After treatment 1, sleep disturbances were reported as intense prior to and following later treatments. After treatment ended, sleep disturbances and pain persisted as the most intense symptoms; difficulty concentrating also was one of the most intense symptoms.

Table 1. Data Collection Timetable

Variable	Measurement	Day(s)								
		Baseline	Treatment 1	Treatment 2	Treatment 3	Treatment 4	30 Days	60 Days	90 Days	One Year
Fatigue	Piper Fatigue Scale	–2	3	3	3	3	X	X	X	X
	Fatigue intensity item	Daily x 2	1–7	1–7	1–7	1–7	X	X	X	X
Physical symptoms	Symptom Experience Scale	–2	7	7	7	7	X	X	X	X
Psychological symptoms	Hospital Anxiety and Depression Scale	–2	1	–	–	1	–	X	–	X
Quality of life	Medical Outcomes Study Short-Form General Health Survey	–2	1	–	–	–	–	X	–	X

Note. Baseline measurements were obtained before or as close to the first day of treatment as possible.

Table 2. Demographic Characteristics of the Sample

Variable	Baseline (N = 25)	One Year After Initial Treatment (N = 21)
n	n	n
Age (years)		
Baseline \bar{X} = 54.28	—	—
Baseline range = 40–65	—	—
One year after initial treatment \bar{X} = 55.33	—	—
One year after initial treatment range = 43–66	—	—
Marital status		
Single	1	—
Married	21	18
Separated	—	—
Divorced	2	2
Widowed	1	1
Employment status		
Full-time	12	9
Part-time	3	6
Homemaker	3	—
Retired	7	6
Education		
High school graduate	17	13
College graduate	7	7
No response	1	1
Ethnicity		
Caucasian	25	21
Stage		
I	11	11
II	14	10
Type of surgery		
Lumpectomy	11	9
Modified mastectomy	7	6
Modified mastectomy with reconstruction	7	6
Performance status^a		
Less than 60	—	1
70	—	—
80	8	—
90	16	15
100	1	3
Menopausal status		
Still menstruating	6	1
Last cycle more than 12 months ago	19	20
Prescription medications		
0	10	1
1	5	5
2	2	6
3	6	4
4 or more	2	5
Tamoxifen		
Yes	—	18
No	—	3
Radiation		
Yes	12	10
No	13	11

^a Missing data

Before chemotherapy started, pain and sleep disturbances were ranked as the most distressing symptoms. Following treatments 1, 3, and 4, nausea was reported as the most distressing symptom. Distress associated with concentration disturbances increased during later treatments. After treatment ended, sleep disturbances and pain were the most distressing symptoms.

The frequency, intensity, and distress scores then were combined, as instructed by the developer of the SES instrument, to create a mean score and standard deviation for each of the other physical symptoms at each time. Figure 1 illustrates the trajectory of each symptom over time. As shown in Table 3, physical symptom frequency, intensity, and distress changed significantly over time as determined by RM-ANOVA. Other physical symptom levels were mild and stable during treatment and significantly declined after treatment ended.

Mean scores for anxiety and depression were within normal limits at measured times, ranging from 1–20 for anxiety and 1–14 for depression. Women reported anxiety more frequently than depression at all times except at treatment 4. Perceived anxiety did not change significantly over time. Depression was lower at baseline, peaked at treatment 4, and then returned close to baseline after treatment ended.

Relationships of Fatigue to Other Physical and Psychological Symptoms

Pairwise correlations were performed between fatigue and the two psychological symptoms (anxiety and depression) and the seven other physical symptoms (see Table 4). At baseline, fatigue was not related to anxiety, depression, or other physical symptoms. In the seven-day periods after each chemotherapy treatment, significant relationships of fatigue to anxiety, depression, and other physical symptoms were noted at several times. The relationship of fatigue to baseline anxiety and depression was inconsistent during treatments. After treatment ended, fatigue was consistently and significantly correlated with the two psychological and the seven other physical symptoms.

Relationship Between Fatigue and Quality of Life

At baseline, the means of the six QOL domains (all except mental and general health) examined by t test analyses were significantly ($p = 0.01$) lower than the population group norms established by Ware (1993). Pearson correlations were used to examine the relationships between levels of eight QOL domains and daily FI at specific times (see Table 5). At baseline, women who were reporting higher levels of daytime fatigue experienced lower levels of QOL in four domains: physical, role emotional, mental, and vitality. At 60 days after completing chemotherapy, women experiencing higher levels of daytime fatigue reported lower QOL in seven of the eight domains (all except bodily pain). At one year after the initiation of chemotherapy, women experiencing more intense fatigue reported lower levels of QOL in all domains except physical and emotional roles.

Discussion

No previous study has provided such an in-depth description of the impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and QOL in women during and after treatment. The findings are important to researchers

Table 3. Fatigue, Other Physical Symptoms, Anxiety, and Depression Across Specified Measurement Times During and After Chemotherapy

Variable (Measure)	Baseline (SD)	Treatment				After Treatment Ended				F	p
		1 \bar{X} (SD)	2 \bar{X} (SD)	3 \bar{X} (SD)	4 \bar{X} (SD)	30 \bar{X} (SD)	60 \bar{X} (SD)	90 \bar{X} (SD)	Year \bar{X} (SD)		
Fatigue (PFS) (N = 17)	—	6.00 ^{a,h} (2.07)	5.38 ^{b,h} (1.98)	5.58 ^{c,e,f,h} (1.54)	5.86 ^{d,e,f,g,h} (1.48)	3.22 ^{c,d,e} (2.30)	3.39 ^{c,d,f} (2.77)	3.30 ^{d,g} (2.82)	2.68 ^{a,b,c,d,h} (2.08)	10.84	< 0.001
Daily Fatigue (FI) (N = 15)	—	5.50 ^{a,e} (1.81)	5.18 ^{b,e} (1.94)	4.55 ^c (1.41)	5.45 ^{d,e} (1.83)	2.88 ^{a,b,d,e} (2.05)	3.34 ^f (2.68)	3.59 ^g (2.47)	2.90 ^{a,b,d} (1.79)	8.46	< 0.001
Fatigue Distress (SES) (N = 19)	1.37 (0.50)	1.63 (0.60)	1.79 (0.79)	1.53 (0.70)	1.63 (0.60)	1.47 (0.70)	1.32 (0.82)	1.32 (0.58)	1.05 (0.52)	2.59	0.032
Anxiety (HADS) (N = 21)	6.76 (4.62)	—	—	—	6.38 (3.75)	—	5.23 (5.07)	—	4.81 (3.79)	NS	—
Depression (HADS) (N = 21)	3.62 ^{a,b} (3.09)	—	—	—	6.67 ^{a,b,c,d} (3.10)	—	3.62 ^{b,c} (3.31)	—	2.00 ^{b,d} (2.07)	11.22	< 0.001
Other symptoms (SES) (N = 18)	1.10 ^{a,i} (0.61)	1.43 ^{b,g,h,i} (0.44)	1.40 ^{c,g,h,i} (0.52)	1.31 ^{d,g,h,i} (0.41)	1.21 ^{e,g,h,i} (0.36)	0.53 ^{a,b,c,d,e,f} (34)	0.62 ^{b,c,d,e,g} (0.48)	0.60 ^{b,c,d,e,h} (0.55)	0.51 ^{a,b,c,d,e,i} (0.38)	21.26	< 0.001

FI—fatigue intensity; HADS—Hospital Anxiety and Depression Scale; PFS—Piper Fatigue Scale; SES—Symptom Experience Scale

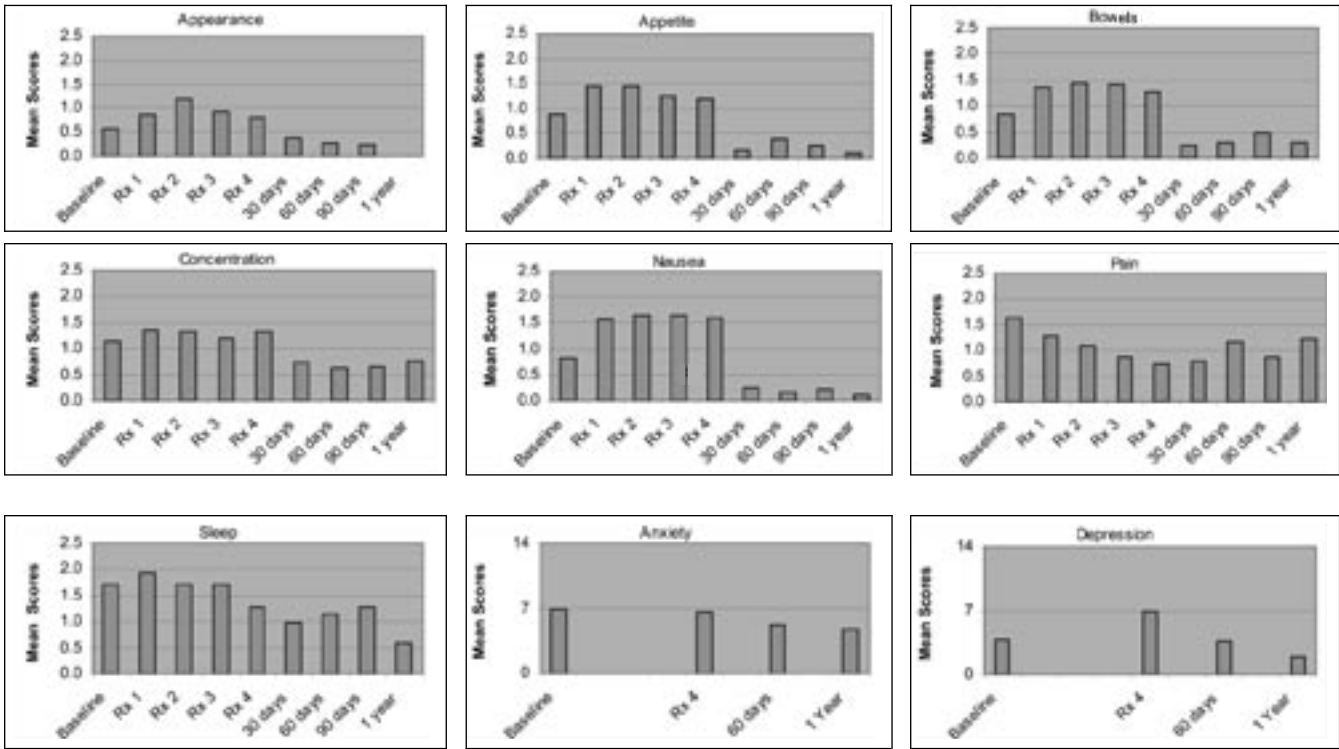
Note. Superscripts indicate significant pairwise differences at specified times (Bonferroni post hoc test).

Note. Measurement times: baseline = at first treatment; treatment 1–4 = first seven days after each chemotherapy treatment; 30, 60, and 90 days after last treatment and one year after first treatment = seven days at later times; blank = not measured

developing interventions to modify fatigue and to clinicians who support and teach patients with breast cancer.

Fatigue was found to be a moderately intense symptom during chemotherapy treatments, consistent with findings of previous studies (Berger, 1998; Boehmke, 2004; Knobf,

2000). Fatigue increased from baseline to the first treatment but did not rise with subsequent treatments, also consistent with previous findings (Berger; de Jong et al., 2002; Jacobsen et al., 1999). After completion of treatment, mean fatigue decreased but was not gone for all women. The results reinforce



Rx—treatment

Figure 1. Trajectory of Other Physical and Psychological Symptoms Over Time

Table 4. Correlations Between Fatigue^a, Anxiety^b, Depression^b, and Other Physical Symptoms^c

Fatigue	Anxiety ^b			Depression ^b			Physical Symptoms ^c		
	r	p	n	r	p	n	r	p	n
Baseline	NS	—	—	NS	—	—	NS	—	—
After treatment 1	—	—	—	—	—	—	0.573	0.003	25
After treatment 2	—	—	—	—	—	—	0.568	0.005	23
After treatment 3	—	—	—	—	—	—	0.385	0.07	23
After treatment 4	NS	—	—	0.618	0.002	22	NS	—	—
30 days after last treatment	—	—	—	—	—	—	NS	—	—
60 days after last treatment	0.620	0.004	20	0.789	< 0.001	20	0.694	< 0.001	18
90 days after last treatment	—	—	—	—	—	—	0.694	0.008	18
One year after first treatment	0.480	0.044	18	0.510	0.031	18	0.602	0.008	18

^a Fatigue as measured by the Piper Fatigue Scale

^b Anxiety and depression as measured by the Hospital Anxiety and Depression Scale

^c Recall of seven symptoms (Symptom Experience Scale excluding fatigue) for the first seven days after each chemotherapy treatment and for seven days at later times

NS—nonsignificant correlation at times when the variable was measured

previous findings that fatigue persists beyond active treatment for about one-third of breast cancer survivors (Bower et al., 2000; Cella et al., 2001).

Other frequent and problematic symptoms were pain, sleep disturbances, nausea, concentration, anxiety, and depression. The trajectories of pain, sleep, and concentration did not follow the bell curve pattern of appearance and gastrointestinal symptoms. Gastrointestinal complaints were much lower following treatment than psychoneurologic symptoms and may be related to faster recovery time for cells in the gastrointestinal tract than for the central nervous system.

Pain was one of the most problematic symptoms (Eversley et al., 2005; Given, Given, Azzouz, Kozachik, & Stommel, 2001). Various etiologies for post-treatment pain have been identified, including postsurgical pain, neuropathies, mucositis, lymphedema, metastasis, and postherpetic neuralgias (Longman et al., 1999; Shapiro & Recht, 2001). Sleep disturbances continued after completion of chemotherapy, a time when most participants were taking 20 mg tamoxifen daily and many had hot flashes. Although the majority of women treated with chemotherapy have mild or moderate nausea and vomiting, the symptoms previously have been reported as severe in about 5% of women (Shapiro & Recht). Distress related to nausea was prevalent in the women in the

current study. Cognitive disturbances increasingly have been observed to be a problem in women during and after adjuvant breast cancer chemotherapy and to be associated with fatigue and menopausal symptoms (Tchen et al., 2003). Anxiety was highest at baseline, consistent with reports that it is highest at the time of diagnosis (Williams & Schreier, 2004).

The findings also concur with previous findings that fatigue is associated with other physical and psychological symptoms during and after chemotherapy (Badger et al., 2001). Depression and fatigue at the time of the fourth treatment were linked, consistent with prior findings (Badger et al., 2001). Women who reported elevated depressive symptoms had more physical symptom distress and more impaired functioning (both $p \leq 0.001$) (Pasacrete, 1997). Findings also are consistent with literature that reported that women's higher fatigue is related to lower QOL in most domains during and after adjuvant breast cancer chemotherapy (Bower et al., 2000; Broeckel et al., 2000; Ganz et al., 2002).

Strengths of the current study are the demographic and diagnostic homogeneity of the sample, the use of well-established self-report instruments, and the longitudinal design. Measuring the level of fatigue at a set time of day and completing tools in the home setting strengthen the reliability of the findings. Limitations are the small sample size, missing data, and

Table 5. Correlations Between Quality-of-Life Domains^a and Perceived Daily Fatigue Intensity^b at Baseline and Times After Treatments

Domain	Baseline Fatigue (N = 22)	Fatigue 60 Days After Last Treatment (N = 21)	Fatigue One Year After First Treatment (N = 20)
Physical	−0.648 (p = 0.001)	−0.664 (p < 0.001)	−0.559 (p = 0.02)
Role physical	—	−0.654 (p = 0.006)	—
Role emotional	−0.516 (p = 0.014)	−0.437 (p = 0.048)	—
Social	—	−0.592 (p = 0.005)	−0.557 (p = 0.008)
Bodily pain	—	—	−0.577 (p = 0.008)
Mental	−0.416 (p = 0.054)	−0.426 (p = 0.054)	−0.447 (p = 0.048)
Vitality	−0.645 (p = 0.002)	−0.713 (p < 0.001)	−0.578 (p = 0.008)
General health	—	−0.502 (p = 0.02)	−0.594 (p = 0.006)

^a Quality-of-life domains as measured by the Medical Outcomes Study Short-Form General Health Survey

^b Fatigue intensity as measured by question 7 of the Piper Fatigue Scale

a convenience sample that included only Caucasians, which affect the generalizability of the findings. The results may not reflect the natural progression of symptoms that would have occurred without the sleep intervention. However, the intervention focused on improving sleep and did not directly address other symptoms. The participants might have reported more frequent, intense, and distressing sleep disturbances because the intervention focused on that symptom.

Care should be taken when generalizing information collected from a sample without a true baseline because surgical procedures and radiation therapy treatments were not identical for the sample. A limitation of many of the instruments is that they were used to measure fluctuating symptoms, and the time of day for completing written tools could not be controlled. A limitation of the SES is that it does not include measurement of menopausal symptoms (hot flashes and weight gain) reported by women taking tamoxifen (Boehmke, 2004).

Implications for Research and Practice

A great deal of work must be done by researchers and clinicians in regard to fatigue, other symptoms, and QOL in women receiving adjuvant therapy for breast cancer. Many variations exist in the definition and measurement of the concepts in the literature. Continued methodologic work may result in a handful of tools with established reliability and validity that can be used consistently in research studies and practice settings. Interventions must be developed and tested to modify clusters of fatigue and psychoneurologic symptoms (e.g., pain, sleep disturbances, depression, impaired cognitive functioning, menopause).

The study's findings point out the need for clinicians to routinely screen and perform further assessments of the fre-

quency, intensity, and distress of other physical and psychological symptoms and their impact on QOL in patients with breast cancer. Evidence-based antiemesis, distress, and pain guidelines and fatigue assessment and management should be integrated into practice. Aggressive management and referrals for control of the most common side effects may assist in relieving acute and chronic chemotherapy-related fatigue (Jacobsen et al., 1999).

Screening currently is not systematic or effective in practice settings for many reasons, including patient and healthcare provider issues. Patient barriers to fatigue assessment and treatment include not wanting to bother their healthcare providers, fear that their treatments may be altered if they bring up their fatigue, and the assumption that they will just have to live with it. Women experiencing fatigue, depression, pain, or sleep disturbances should be identified early, assessed frequently, and encouraged to participate in physical and psychosocial rehabilitation programs.

Interventions to reduce fatigue and other symptoms and improve QOL during and after chemotherapy are being developed and tested for effectiveness. Targeting primary or cluster symptoms and delivering effective interventions may reduce the impact of adjuvant breast cancer chemotherapy on fatigue, other symptoms, and QOL.

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References

- American Cancer Society. (2005). *Breast cancer facts and figures 2003–2004*. Atlanta, GA: Author.
- Badger, T., Segrin, C., Meek, P., Lopez, A.M., Bonham, E., & Sieger, A. (2005). Telephone interpersonal counseling with women with breast cancer: Symptom management and quality of life. *Oncology Nursing Forum*, 32, 273–279.
- Badger, T.A., Braden, C.J., & Mishel, M.H. (2001). Depression burden, self-help interventions, and side effect experience in women receiving treatment for breast cancer. *Oncology Nursing Forum*, 28, 567–574.
- Beck, S.L., Dudley, W.N., & Barsevick, A. (2005). Pain, sleep disturbance, and fatigue in patients with cancer: Using a mediation model to test a symptom cluster [Online exclusive]. *Oncology Nursing Forum*, 32, E48–E55. Retrieved November 2, 2005, from <http://www.ons.org/publications/journals/ONF/Volume32/Issue3/3203542.asp>
- Berger, A.M. (1998). Patterns of fatigue and activity and rest during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum*, 25, 51–62.
- Berger, A.M., & Farr, L. (1999). The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncology Nursing Forum*, 26, 1663–1671.
- Berger, A.M., & Higginbotham, P. (2000). Correlates of fatigue during and following adjuvant breast cancer chemotherapy: A pilot study. *Oncology Nursing Forum*, 27, 1443–1448.
- Berger, A.M., VonEssen, S., Kuhn, B.R., Piper, B.F., Agrawal, S., Lynch, J.C., et al. (2003). Adherence, sleep, and fatigue outcomes after adjuvant breast cancer chemotherapy: Results of a feasibility intervention study. *Oncology Nursing Forum*, 30, 513–522.
- Berger, A.M., VonEssen, S., Kuhn, B.R., Piper, B.F., Farr, L., Agrawal, S., et al. (2002). Feasibility of a sleep intervention during adjuvant breast cancer chemotherapy. *Oncology Nursing Forum*, 29, 1431–1441.
- Berger, A.M., & Walker, S.N. (2001). An explanatory model of fatigue in women receiving adjuvant breast cancer chemotherapy [published erratum appears in *Nursing Research*, 50(3), 164]. *Nursing Research*, 50(1), 42–52.
- Boehmke, M.M. (2004). Measurement of symptom distress in women with early-stage breast cancer. *Cancer Nursing*, 27, 144–152.
- Bower, J.E., Ganz, P.A., Desmond, K.A., Rowland, J.H., Meyerowitz, B.E., & Belin, T.R. (2000). Fatigue in breast cancer survivors: Occurrence, correlates, and impact on quality of life. *Journal of Clinical Oncology*, 18, 743–753.
- Broeckel, J.A., Jacobsen, P.B., Balducci, L., Horton, J., & Lyman, G.H. (2000). Quality of life after adjuvant chemotherapy for breast cancer. *Breast Cancer Research and Treatment*, 62, 141–150.
- Broeckel, J.A., Jacobsen, P.B., Horton, J., Balducci, L., & Lyman, G.H. (1998). Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*, 16, 1689–1696.
- Cella, D., Davis, K., Breitbart, W., & Curt, G. (2001). Cancer-related fatigue: Prevalence of proposed diagnostic criteria in a United States sample of cancer survivors. *Journal of Clinical Oncology*, 19, 3385–3391.
- de Jong, N., Courtens, A.M., Abu-Saad, H.H., & Schouten, H.C. (2002). Fatigue in patients with breast cancer receiving adjuvant chemotherapy: A review of the literature. *Cancer Nursing*, 25, 283–297.
- Division of Cancer Control and Population Sciences. (2005). *Facts about Office of Cancer Survivorship National Cancer Institute*. Retrieved May 3, 2005, from http://dcccps.nci.nih.gov/ocs/ocs_factsheet.pdf
- Dodd, M.J., Miaskowski, C., & Paul, S.M. (2001). Symptom clusters and

- their effect on the functional status of patients with cancer. *Oncology Nursing Forum*, 28, 465–470.
- Donovan, K.A., Jacobsen, P.B., Andrykowski, M.A., Winters, E.M., Balducci, L., Malik, U., et al. (2004). Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. *Journal of Pain and Symptom Management*, 28, 373–380.
- Eversley, R., Estrin, D., Dibble, S., Wardlaw, L., Pedrosa, M., & Favila-Penney, W. (2005). Post-treatment symptoms among ethnic minority breast cancer survivors. *Oncology Nursing Forum*, 32, 250–256.
- Ganz, P.A., Desmond, K.A., Leedham, B., Rowland, J.H., Meyerowitz, B.E., & Belin, T.R. (2002). Quality of life in long-term, disease-free survivors of breast cancer: A follow-up study. *Journal of the National Cancer Institute*, 94, 39–49.
- Given, C.W., Given, B., Azzouz, F., Kozachik, S., & Stommel, M. (2001). Predictors of pain and fatigue in the year following diagnosis among elderly cancer patients. *Journal of Pain and Symptom Management*, 21, 456–466.
- Goodell, T.T., & Nail, L.M. (2005). Operationalizing symptom distress in adults with cancer: A literature synthesis [Online exclusive]. *Oncology Nursing Forum*, 32, E42–E47. Retrieved November 2, 2005, from <http://www.ons.org/publications/journals/ONF/Volume32/Issue2/320242.asp>
- Haghighat, S., Akbari, M.E., Holakouei, K., Rahimi, A., & Montazeri, A. (2003). Factors predicting fatigue in breast cancer patients. *Supportive Care in Cancer*, 11, 533–538.
- Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale—A review of validation data and clinical results. *Journal of Psychosomatic Research*, 42, 17–41.
- Jacobsen, P.B., Hann, D.M., Azzarello, L.M., Horton, J., Balducci, L., & Lyman, G.H. (1999). Fatigue in women receiving adjuvant chemotherapy for breast cancer: Characteristics, course, and correlates. *Journal of Pain and Symptom Management*, 18, 233–242.
- Knobf, M. (2000). Symptom distress before, during, and after adjuvant breast cancer therapy. *Developments in Supportive Cancer Care*, 4(1), 13–17.
- Longman, A.J., Braden, C.J., & Mishel, M.H. (1999). Side-effects burden, psychological adjustment, and life quality in women with breast cancer: Pattern of association over time. *Oncology Nursing Forum*, 26, 909–915.
- Pasacreta, J.V. (1997). Depressive phenomena, physical symptom distress, and functional status among women with breast cancer. *Nursing Research*, 46, 214–221.
- Patrick, D.L., Ferketich, S.L., Frame, P.S., Harris, J.J., Hendricks, C.B., Levin, B., et al. (2004). National Institutes of Health State-of-the-Science Conference statement: Symptom management in cancer: Pain, depression, and fatigue, July 15–17, 2002. *Journal of the National Cancer Institute Monographs*, 32, 9–16.
- Piper, B.F., Dibble, S.L., Dodd, M.J., Weiss, M.C., Slaughter, R.E., & Paul, S.M. (1998). The revised Piper Fatigue Scale: Psychometric evaluation in women with breast cancer. *Oncology Nursing Forum*, 25, 677–684.
- Piper, B.F., Lindsey, A.M., & Dodd, M.J. (1987). Fatigue mechanisms in cancer patients: Developing nursing theory. *Oncology Nursing Forum*, 14(6), 17–23.
- Samarel, N., Leddy, S.K., Greco, K., Cooley, M.E., Torres, S.C., Tulman, L., et al. (1996). Development and testing of the symptom experience scale. *Journal of Pain and Symptom Management*, 12, 221–228.
- Shapiro, C.L., & Recht, A. (2001). Side effects of adjuvant treatment of breast cancer. *New England Journal of Medicine*, 344, 1997–2008.
- Tchen, N., Juffs, H.G., Downie, F.P., Yi, Q.L., Hu, H., Chemerynsky, I., et al. (2003). Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. *Journal of Clinical Oncology*, 21, 4175–4183.
- Ware, J.E. (1993). *SF-36 health survey manual and interpretation guide*. Boston: The Health Institute.
- Ware, J.E., Jr., & Sherbourne, C.D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, 30, 473–483.
- Williams, S.A., & Schreier, A.M. (2004). The effect of education in managing side effects in women receiving chemotherapy for treatment of breast cancer [Online exclusive]. *Oncology Nursing Forum*, 31, E16–E23. Retrieved November 2, 2005, from <http://www.ons.org/publications/journals/ONF/Volume31/Issue1/310143.asp>
- Zigmond, A.S., & Snaith, R.P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, 67, 361–370.