Influence of Patient and Treatment Factors on Adherence to Adjuvant Endocrine Therapy in Breast Cancer

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Rates of adherence to oral adjuvant endocrine therapy have been reported to be as low as 25% in women with breast cancer (Partridge et al., 2008). The potential implications of nonadherence include compromised therapeutic efficacy, reduced disease-free and overall survival, higher hospitalization rates, longer lengths of stay, and increased numbers of physician visits (Moore, 2010; Osborne, 1998). Nonadherence to cancer therapy also may prompt clinicians to mistakenly assume that a patient's deteriorating clinical condition is a result of treatment failure, leading to dose reductions or cessation of therapy (Moore, 2010).

The basis for nonadherence to endocrine therapy in women with breast cancer is not clear. Patient factors (e.g., sociodemographic characteristics, socioeconomic status, cognitive function, mood, physical function, perceived treatment efficacy, social support) may individually predict nonadherence to prescribed medications. Similarly, illness- and treatment-related factors (e.g., disease stage, whether women also received chemotherapy, complexity of their medication regimen, presence of comorbidities, perceived financial hardship) also may individually predict nonadherence. However, according to Christensen's interactionist framework, the interactive effects of patient factors and illness or treatment factors may provide the dominant influence on nonadherence (Christensen, 2000; Christensen, Smith, Turner, & Cundick, 1994). Knowledge about those interactions is fundamental to inform the development of interventions to improve adherence to endocrine therapy in women with breast cancer. However, to the current authors' knowledge, no studies have comprehensively assessed the patient and illness or treatment factors that predict nonadherence to oral hormonal therapy in this population. The purpose of this preliminary study

Purpose/Objectives: To comprehensively assess the patient and illness or treatment factors that may predict nonadherence to adjuvant endocrine therapy and to explore whether an interaction occurs between these factors in women with breast cancer.

Design: Repeated-measures design.

Setting: The Outpatient Services of the Women's Cancer Program at the University of Pittsburgh Cancer Institute and participants' homes.

Sample: 91 women with early-stage breast cancer who received endocrine therapy.

Methods: Adherence was assessed continuously for the first 18 months of endocrine therapy. Patient and illness or treatment factors were assessed at four time points (Time 1 to Time 4). Time 1 (baseline) was within two weeks prior to the initiation of endocrine therapy. Times 2–4 occurred at six-month intervals, as many as 18 months after Time 1.

Main Research Variables: Adherence, patient factors, and illness or treatment factors.

Findings: Adherence to endocrine therapy declined significantly during the first 18 months of treatment in women with breast cancer. The presence of negative mood and symptoms before starting treatment predicted nonadherence to endocrine therapy over time. Perceptions of financial hardship, symptoms, disease stage, and more complex medication regimens intensified the effect of negative mood on adherence over time.

Conclusions: Women with breast cancer may be at risk for nonadherence to prescribed endocrine therapy if they experience depression or anxiety and symptoms prior to initiating therapy.

Implications for Nursing: Oncology nurses should be alert to women with breast cancer who are depressed or anxious or who are experiencing symptoms. Management of negative mood and symptoms may result in better adherence.

Key Words: breast cancer; adherence; symptoms; mood; financial hardship

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was to comprehensively assess the patient and illness or treatment factors that may predict nonadherence to adjuvant endocrine therapy and explore whether an interaction occurs between these factors in women with breast cancer receiving oral endocrine therapy. Specifically, the authors described the pattern of nonadherence to endocrine therapy and explored the patient and illness or treatment factors that predicted nonadherence. The authors hypothesized that adherence to endocrine therapy would decrease over time. In addition, the authors explored possible moderation effects of illness or treatment factors on the relationship between patient factors and nonadherence to endocrine therapies.

Background

About 80% of breast cancers express hormone receptors (Konecny et al., 2003). Hormone receptor status is an important prognostic indicator in breast cancer. "Positive" hormone receptor status is associated with a better prognosis, and adjuvant endocrine therapy is prescribed for women whose breast cancer is hormone receptor-positive. Two main types of endocrine therapy for breast cancer exist. Selective estrogen receptor modulators, such as tamoxifen, primarily are prescribed for premenopausal women with breast cancer and function by competitively binding with the estrogen receptor. Aromatase inhibitors, such as anastrozole, letrozole, and exemestane, are prescribed for postmenopausal women with breast cancer and function by inhibiting aromatization, the conversion of androgens to estrogen in extragonadal tissues, the predominant source of estrogen in postmenopausal women. As a consequence, plasma estrogen levels are significantly reduced (Downs-Holmes & Silverman, 2011; Sainsbury, 2013).

Endocrine therapies substantially improve the disease-free and overall survival of women with early breast cancer (Andreetta & Smith, 2007). However, rates of adherence to oral endocrine therapy for breast cancer have ranged from 25%–96%. Partridge et al. (2008) found that the proportion of women with breast cancer who were nonadherent to anastrozole increased from 22%–31% in year one of therapy to 32%–50% in year three. The clinical significance of nonadherence to endocrine therapy is not entirely clear. However, Thompson, Dewar, Fahey, and McCowan (2007) found that women who took less than 70% of their prescribed hormonal therapy had a higher mortality rate. In addition, nonadherence may be associated with the development of resistance to endocrine therapy (Osborne, 1998).

Patient Factors

Investigators have examined the influence of patient factors on nonadherence to endocrine therapy in women with breast cancer. Evidence suggested that both depression and anxiety are related to nonadherence for prescribed endocrine chemoprevention in women at risk for breast cancer (Cohen, 2002) and for endocrine therapy in women with the disease (Demissie, Silliman, & Lash, 2001; Lebovits et al., 1990). Evidence also suggested that women with breast cancer who hold negative beliefs about the value of endocrine therapy are more likely to discontinue therapy (Lash, Fox, Westrup, Fink, & Silliman, 2006; Silliman et al., 2002) and are at increased risk for nonadherence (Fink, Gurwitz, Rakowski, Guadagnoli, & Silliman, 2004). In addition, other studies indicated that "forgetting" was the most common reason women cited for not taking their hormonal therapy (Bender et al., 2010; Murthy, Bharia, & Sarin, 2002).

Evidence conflicts about the role of other patient factors in predicting nonadherence to endocrine therapy. For example, the relationship between demographic characteristics, such as age and race, and nonadherence is not clear (Atkins & Fallowfield, 2006; Demissie et al., 2001; Kahn, Schneider, Malin, Adams, & Epstein, 2007; Murthy et al., 2002; Owusu et al., 2008; Sedjo & Devine, 2011; Partridge, Wang, Winer, & Avorn, 2003; Wu et al., 2012). In addition, whether having poor physical functioning is related to nonadherence in this population is not clear (Demissie et al., 2001; Lebovits et al., 1990). Finally, Kahn et al. (2007) reported that women's perceptions of less social support from healthcare providers were related with nonadherence to endocrine therapy. To the current authors' knowledge, the association between nonadherence and social support beyond what is derived from healthcare providers has not been examined in this population.

Illness or Treatment Factors

Several illness or treatment factors also may influence nonadherence to endocrine therapy. The presence of greater number of comorbidities (Owusu et al., 2008; Sedjo & Devine, 2011) and concomitant medications (Fink, 2004; Grunfeld, Hunter, Sikka, & Mittal, 2005; Lash et al., 2006) have been associated with nonadherence to endocrine therapy. Women with lower disease stage (Lebovits et al., 1990; Wickersham, Sereika, & Bender, 2013) and who did not receive chemotherapy before endocrine therapy (Fink et al., 2004) were more likely to discontinue therapy; however, women who had breast-conserving surgery (Owusu et al., 2008) and changed endocrine therapy agents (Sedjo & Devine, 2011) were more likely to be nonadherent to therapy. One of the most common reasons for a prescribed change in endocrine therapy agents was the presence and severity of disease- and treatment-related symptoms. Most investigators have found that disease- and treatment-related symptoms are associated with nonadherence to endocrine therapy in women with breast cancer (Demissie

Attention		
Digit Vigilance Test	Seconds to complete	0+
Digit Symbol Substitution	Number correct in two minutes	0–133
Executive function		
Verbal Fluency Test (F, A, and S)	Total score in one minute each	0+
	Total repetition errors	0+
Color Word Interference Test	Composite score	2–38
Verbal learning and memory		
Rivermead Memory Test: Immediate	Total score in five minutes	0–21
Rivermead Memory Test: Delayed	Total score in five minutes	0–21
Visuospatial ability		
Complex Figure Test: Copy	Points awarded according to the accuracy of the copy	1–36
Visual learning and memory		
Complex Figure Test: Immediate	Points awarded to scoring criteria	1–36
Complex Figure Test: Delayed	Points awarded to scoring criteria	1–36

et al., 2001; Fink et al., 2004; Grunfeld et al., 2005; Kahn et al., 2007; Wickersham et al., 2013). Ziller et al. (2009) found no relationship between disease- and treatment-related symptoms and nonadherence; however, adherence was measured via self-report and symptoms were documented by medical record review.

Although greater out-of-pocket costs related to endocrine therapy have been associated with nonadherence, few studies have examined the role of economic status and financial hardship on nonadherence to endocrine therapy (Sedjo & Devine, 2011). Studies that examined the influence of patient and illness or treatment factors on nonadherence to endocrine therapy in women with breast cancer have produced conflicting results (Chlebowski & Geller, 2006; Owusu et al., 2008; Wickersham et al., 2013). The basis of these conflicting results is likely, in part, because of differences in the approaches of conceptualizing and measuring adherence. Some investigators examined nonpersistence (discontinuation) rates while approaches to measuring adherence range from self-report to pharmacy refill rates. Similarly, differences in the measurement of predictors of nonadherence may also contribute to conflicting results.

A comprehensive evaluation of the patient and illness or treatment factors that may predict nonadherence to endocrine therapy in women with breast cancer has not been conducted. In addition, whether illness or treatment factors moderate the relationship between patient factors and nonadherence also has not been explored. Guided by Christensen's (2000) interactionist framework, the current authors comprehensively evaluated these factors in women who received endocrine therapy for breast cancer and explored possible moderation effects between patient and illness or treatment factors in predicting nonadherence.

Methods

Participants were recruited through the Comprehensive Breast Program of the University of Pittsburgh Cancer Institute from December 2008 to March 2010. Eligible women were diagnosed with hormone receptor-positive stage I, II, or IIIa breast cancer, aged 18–75 years, had completed a minimum of eight years of education, and could speak and read English. Women were excluded if they had clinical evidence of metastases, history of invasive cancer or neurologic illness, or hospitalization for psychiatric illness within the last two years.

Adherence to adjuvant endocrine therapy was continuously assessed during the first 18 months of therapy. Patient and illness or treatment factors were assessed in person by a trained nurse research associate at four time points. The first assessment took place after primary surgery and chemotherapy (if applicable) but before the initiation of adjuvant endocrine therapy. The three follow-up assessments were conducted at 6, 12, and 18 months after hormonal therapy was initiated. Study procedures were reviewed and approved by the University of Pittsburgh Institutional Review Board, and written consent was obtained from all participants.

Age (years)	56.7	9.7
Years of education	14.9	2.6
Race		
Caucasian		88
Other		3
Marital status		
Married or living as married		68
Other		23
Stage		
I		54
II or III		37
Treatment		
Use of chemotherapy		21
No chemotherapy		70

Measures

Adherence to hormonal therapy: Adherence to endocrine therapy was monitored using the AARDEX microelectronic monitoring system (MEMS™) cap. The MEMS cap is a medication bottle cap that fits on a standard medication vial and electronically records the time and date of every opening and closing (i.e., dose events). Electronic monitoring has been used in other clinical studies measuring adherence to oral anticancer therapies (Ruddy, Mayer, & Partridge, 2009). Dosing history data were transferred from the cap to a personal computer at the time of each participant's follow-up assessment via Powerview software and a communicator. Data were summarized monthly in terms of the percentage of days with correct intake.

Patient and illness or treatment factors: Except where noted, patient and illness and treatment factors were assessed at all four time points. Patient factors included sociodemographic information, cognitive function, mood, physical functioning, perceived treatment efficacy, and social support. Sociodemographic information was collected only during the baseline assessment and included age, years of education, intelligence, race, and marital status.

Cognitive function was evaluated with a battery of measures to assess attention, learning and memory, executive function, mental flexibility, and visuospatial ability domains of cognitive function (see Table 1). Verbal intelligence was estimated with the **National Adult Reading Test–Revised** (Nelson, 1981). Cognitive measures were selected based on demonstrated sensitivity to changes in cognitive function in women with breast cancer and the availability of alternate, equivalent versions administered at follow-up testing to minimize practice effects.

Depression was assessed with the **Beck Depression Inventory–II (BDI-II)**, a 21-item, self-report measure of depressive symptoms and attitudes. Each item is rated on a four-point Likert-type scale, and the total score is the sum of responses for items (Beck, Steer, & Brown, 1996). The Cronbach alpha for the 91 women in this study was 0.84. The BDI-II correlated strongly with the major depression episode component of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV Axis I Disorders (0.83) (Sprinkle et al., 2002; Stukenberg, Dura, & Kiecolt-Glaser, 1990) and the Revised Hamilton Rating Scale for Depression (0.71) (Beck et al., 1996; Spreen & Strauss, 1998).

Anxiety was assessed with the **Profile of Mood States (POMS) tension-anxiety subscale**, a nine-item, self-report subscale in which adjectives are rated on a five-point Likert-type scale (McNair, Lorr, & Droppleman, 1992), and the total score is the sum of responses for items. The Cronbach alpha for the current study's sample was 0.89. The POMS is sensitive to changes in anxiety levels in patients with cancer (Cassileth et al., 1992).

Attention		
Digit Vigilance Test (time in seconds)	373.6	78.7
Digit Symbol Substitution	73.6	14.5
Comorbidities		
Number of self-reported comorbidities	6	3.4
Number of symptoms or side effects	4.5	3.7
Symptom or side-effect severity	0.45	0.28
Complexity of medication regimen		
Number of medications	5.2	3.4
Maximum daily frequency of dosing	2.3	0.93
Executive function		
Verbal Fluency Test: Total correct responses	40	10.3
Verbal Fluency Test: Total repetition errors	0.71	1.1
Color Word Interference Test: Composition Scaled Score	11.2	2
Financial hardship		
Modified Collection of Indirect and Nonmedical Direct Costs	307.5	734.2
Measure of Economic Hardship		
• Financial strain	2.3	0.99
• Inability to make ends meet	6.9	0.98
• Not enough money for necessities	12.8	5.5
• Economic cutbacks and adjustments	17.4	0.95
Intelligence		
National Adult Reading Test–Revised	108.8	7.2
Side effects of hormonal therapy		
Breast Cancer Prevention Trial		
• Total score	17.8	12.2
• Cognitive problems subscale	2	2.1
• Musculoskeletal problems subscale	3.2	3.1
• Vasomotor subscale	1.9	2.2
• Gastrointestinal subscale	0.19	0.6
• Dyspareunia subscale	1.3	1.8
• Bladder control subscale	0.57	1.2
• Weight problems subscale	0.34	0.76
• Gynecologic subscale	0.43	1
Social support		
Interpersonal Support Evaluation List		
• Appraisal subscale	26.6	4.4
• Belonging subscale	25.4	4.2
• Tangible subscale	26.3	4.3
• Self-esteem subscale	23.5	3.6
• Overall	101.9	13.9
Verbal learning and memory		
Rivermead Behavioral Memory Test Story Recall: Immediate	7.7	2.7
Rivermead Behavioral Memory Test Story Recall: Delayed	5.9	2.5
Visual learning and memory		
Complex Figure Test: Immediate recall	22.8	5.1
Complex Figure Test: Delayed recall	21.5	5.5
Beck Depression Inventory–II	5.7	5
Profile of Mood States Tension-Anxiety subscale	6	5.4
SF-36 physical function subscale	78.1	21.1
Beliefs About Medicines Questionnaire		
• Specific necessity subscale	14.8	3.2
• Specific concerns subscale	17	3.9
Visuospatial ability		
Complex Figure Test: Copy	33.1	2.5

Physical function was assessed with the 10-item physical function subscale of the **SF-36®** (Ownby, 2006; Rosen et al., 2003). Participants indicated their level of limitation in activities of daily living and instrumental activities of daily living on a scale from 1 (not limited at all) to 3 (limited a lot); an overall score was calculated by summing individual items, with higher scores indicating more limitations in physical function. The Cronbach alpha for the current study's sample was 0.91. This subscale was related to nonpersistence in women with breast cancer receiving endocrine therapy (Demissie et al., 2001).

Perceived treatment efficacy was evaluated with the 10-item **Beliefs About Medicines Questionnaire (BMQ)–specific subscale** (Horne, Weinman, & Hankins, 1999). The BMQ-specific assesses representations of medication prescribed and evaluates the perceived necessity of taking medications to remain healthy (specific necessity subscale) and the concerns about adverse effects of taking medications (specific concerns subscale). All items are rated on a five-point Likert-type scale ranging from 1 (strongly agree) to 5 (strongly disagree). Subscale scores are the sum of responses for items, with higher scores indicating stronger beliefs in the concepts represented by the scale. Scores range from 5–25 with a midpoint of 15. For the current study's sample, Cronbach alpha for the specific necessity subscale was 0.85 and for the specific concerns subscale was 0.83. The BMQ-specific is sensitive to perceived treatment efficacy in women with breast cancer receiving endocrine therapy (Grunfeld et al., 2005).

Attention				
Digit Vigilance Test: Time in seconds	–0.00947	0.01316	0.01216	0.008018
Digit Symbol Substitution	–0.0724	0.07106	–0.02826	0.04658
Executive function				
Verbal Fluency Test: Correct responses	–0.2529*	0.09874*	–0.1146	0.05959
CWIT Composition Scaled Score	0.2824	0.5174	–0.4447	0.2958
Verbal learning and memory				
Rivermead Story Recall: Immediate	–0.1607	0.3835	–0.2356	0.2349
Rivermead Story Recall: Delayed	0.192	0.4215	–0.1678	0.2467
Visual learning and memory				
Complex Figure Test–Immediate	–0.1041	0.2042	0.08484	0.1057
Complex Figure Test–Delayed	–0.07746	0.188	0.09142	0.1059
Visuospatial ability				
Complex Figure Test: Copy	0.3276	0.3998	0.2036	0.2182
Beck Depression Inventory	–0.8845***	0.1852***	–0.3106*	0.1207*
POMS tension-anxiety subscale	–0.6682**	0.1850**	0.01362	0.127
Disease and stage				
Chemotherapy	0.8005	2.4756	–	–
Stage 1 versus else	–2.4463	2.0761	–	–
Comorbidities				
Number of symptoms	–0.2649	0.2997	–0.2193	0.1185
Mean symptom severity	–5.6839	3.755	–3.1085	1.6928
Complexity of medication regimen				
Number of medications	–0.1053	0.3157	–0.1772	0.2139
Maximum dosing frequency	0.9133	1.1296	1.6905*	0.6789*
Physical functioning				
SF-36 physical function subscale	0.09915*	0.04929*	0.01058	0.02296
Perceived treatment efficacy				
BMQ Specific Necessity	–0.1135	0.3373	–0.187	0.1422
BMQ Specific Concerns	–0.3238	0.2791	–0.2362	0.1226
Side effects of hormonal therapy				
Breast Cancer Prevention Trial				
• Bladder control	0.2405	0.9085	–0.2217	0.4271
• Cognitive symptoms	–0.3148	0.5323	–0.4759*	0.2255*
• Dyspareunia	0.3953	0.6188	0.4675	0.2657
• Gastrointestinal symptoms	0.2982	1.7199	0.03649	0.7318
• Gynecologic symptoms	–3.3106**	0.984**	–0.8715	0.4554
• Musculoskeletal pain	–0.7048*	0.337*	–0.1756	0.1475
• Vasomotor symptoms	0.4681	0.471	–0.1112	0.2106
• Weight concerns	–3.6039**	1.3392**	0.2928	0.5493
• Total	–0.1402	0.08723	–0.07555	0.03919
Interpersonal Support Evaluation List				
Appraisal	3.9048	2.3498	1.9433	1.17
Belonging	–1.1303	2.5865	0.4007	1.2016
Tangible	1.4137	2.4602	1.5757	1.1337
Self-esteem	0.2206	2.9849	–1.2998	1.3121
Total	1.8129	3.0736	1.0619	1.4113

(Continued on the next page)

Age	0.1124	0.1049	–	–
Caucasian versus else	3.9762	6.867	–	–
Years of formal education	0.1046	0.3919	–	–
Married or partnered versus else	1.6486	2.338	–	–
NART Verbal IQ	–0.00736	0.005494	–	–
Financial hardship				
Measure of Economic Hardship				
• Financial strain	0.7955	1.073	0.3364	0.4996
• Inability to make ends meet	–0.4955	1.1279	–0.484	0.4952
• Not enough money for necessities	0.06332	0.1945	0.02494	0.09084
• Economic adjustments or cutbacks	–0.8508	1.1323	–0.1502	0.3141
Modified COIN: Monthly OOP costs	–0.00219	0.001786	–0.00002	0.00106

Social support was assessed using the **Interpersonal Support Evaluation List ([ISEL], general population form)** (Cohen, Mermelstein, Kamarak, & Hoberman, 1985). This 40-item, self-administered measure assesses four aspects of perceived social support, the availability of people to talk to, material aid, positive comparison, and people to do things with. Responses ranged from 0 (definitely false) to 3 (definitely true). Subscale scores are the sum of responses for items in each subscale. For the current study's sample, the Cronbach alpha for the total ISEL was 0.94, and for the ISEL subscales, the Cronbach alpha ranged from 0.8–0.86. Test-retest correlations were 0.87 for two days, 0.7 for six weeks, and 0.74 for six months (Cohen et al., 1985). The ISEL is sensitive to change in social support in women with breast cancer (Fogel, Albert, Schnabel, Ditkoff, & Neugut, 2003).

Illness and treatment factors: Illness and treatment factors included use of chemotherapy, stage of disease, complexity of medication regimen, comorbidities, disease- and treatment-related symptoms, and financial hardship. Participants' stage of disease and chemotherapy (if applicable) were abstracted from their medical record.

Complexity of the medication regimen was assessed with the **Concomitant Medication Form**, which records prescription and nonprescription (over-the-counter) medications taken by participants, including the medication name, dose, timing, and route of administration. Comorbidities were assessed with the **Brief Comorbidity Questionnaire,** which measures the presence or absence of 47 comorbid conditions.

Disease- and treatment-related symptoms were assessed with the **Breast Cancer Prevention Trial (BCPT) Symptom Checklist**, a self-report measure of the degree to which women are bothered by 43 hormone therapy- and menopausal-related symptoms in the month prior (Ganz et al., 2000; Stanton, Bernaards, & Ganz, 2005). The measure is comprised of seven subscales, including hot flashes, nausea, bladder control, vaginal problems, musculoskeletal problems, cognitive problems, and weight problems. Participants rate symptoms on a five-point Likert-type scale ranging from 0 (not at all) to 4 (extremely). Subscale scores are the average score in each subscale, and the total score is the average score of all items. For the current study's sample, Cronbach alpha for subscale scores ranged from 0.58–0.92, and Cronbach alpha for the BCPT total was 0.94.

Financial hardship was assessed using out-of-pocket costs and the **Measure of Economic Hardship** (Cohen, 2002). Out-of-pocket costs were measured by the **Modified Collection of Indirect and Nonmedical Direct Costs (COIN)**. The COIN captures expenses stemming from indirect and out-of-pocket costs associated with cancer care throughout the previous month (Rubin, 2005). Out-of-pocket costs include visits to healthcare professionals and other expenses associated with health care (e.g., visiting nurses, home health care, part-time or overtime, transportation, parking, medications). Participants were asked to estimate out-of-pocket costs in each of the 13 categories, and a summary score was produced.

The Measure of Economic Hardship is a 20-item measure that assesses financial hardship in four different domains: financial strain, inability to make ends meet, not enough money for necessities, as well as economic cutbacks and adjustments. The financial strain, inability to make ends meet, and not enough money for necessities in the last month are rated on a five-point Likert-type scale and mean subscale scores are created. Economic adjustments and cutbacks are assessed with nine items such as added job, received government assistance, and sold possessions because money was needed. This subscale score is the total number of events that occurred ranging from 0–9. For the current study, the Cronbach alpha for the domains ranged from 0.6–0.95.

Breast Cancer Prevention Trial							
Total	TD	–0.05757	0.0015	NS	NS	NS	NS
Bladder control symptoms	Baseline	0.5887	0.0016	NS	NS	NS	NS
Dyspareunia symptoms	Baseline	–0.5282	0.0002	–0.3709	0.007	NS	NS
Gynecologic symptoms	Baseline	–0.8638	< 0.0001	NS	NS	NS	NS
Musculoskeletal pain	Baseline	–0.2687	< 0.0001	–0.138	0.0094	NS	NS
Vasomotor symptoms	TD	0.1969	0.0054	NS	NS	NS	NS
Weight concerns	Baseline	–1.4688	< 0.0001	–0.6648	0.0006	0.1998	< 0.0001
Weight concerns	TD	NS	NS	NS	NS	NS	NS
Mean symptom or side-effect severity	Baseline	–2.4323	0.0018	NS	NS	NS	NS
	TD	NS	NS	NS	NS	NS	NS
Monthly out-of-pocket costs	Baseline	–0.00286	< 0.0001	–0.00211	< 0.0001	0.000706	< 0.0001
Number of medications	TD	–0.1134	0.0007	–0.1012	0.0104	0.03726	0.0015
Number of self-reported comorbidities	Baseline	NS	NS	NS	NS	NS	NS
Number of symptoms or side effects	Baseline	0.2001	0.0008	NS	NS	NS	NS
	TD	0.0671	0.0056	NS	NS	NS	NS
Stage (Stage 1 versus else)	Baseline	–1.1769	0.0015	NS	NS	NS	NS

Analysis

SAS®, version 9.3, was used for analysis. For hypothesis testing, the level of significance was set at 0.01 (two-tailed) to control for inflation of type 1 error from multiple testing. A detailed descriptive analysis of the data was performed. Random coefficients modeling was used to estimate individual trajectories and the average trajectory for the sample.

To explore what patient and illness or treatment factors predict medication adherence, the analyses initially were performed considering the effects of patient and treatment or illness factors individually and then jointly using t statistics (the ratio of the estimated parameter to its standard error). Model assessment was conducted following model fitting and parameter estimation to identify sources of model misspecification and influential cases.

The current authors explored possible moderation effects of the illness or treatment factors on the relationship between patient factors and adherence using conditional regression models by focusing on patient factors demonstrating a level of significance ($p < 0.01$). Two-way interaction terms, computed as the product of individual patient factors with treatment or illness factors, were added hierarchically to the regression model following inclusion of the main effects for the patient and treatment or illness factors to yield parameter estimates of the interaction effect.

Results

A total of 91 women were enrolled in the study (see Table 2). Most women had stage I disease and 23% received chemotherapy prior to beginning endocrine therapy. Adherence levels for the first month of endocrine therapy were 99% for the percentage of prescribed doses taken and 96% for the percentage of days with the correct intake of endocrine therapy. The rate of adherence declined linearly over the first 18 months of therapy ($\beta = 0.6$, $p = 0.0009$).

Patient Factors

Participants scored within normal ranges on cognitive tests (see Table 3). Participants reported low depressive symptoms ($\bar{X} = 5.7$, SD = 5), low levels of anxiety ($\bar{X} = 6$, SD = 5.4), and relatively high physical functioning ($\bar{X} = 78.1$, SD = 21.1). Participants' scores regarding their perceptions of the necessity of oral endocrine therapy fell at the midpoint of the scale ($\bar{X} = 14.8$, SD = 3.2), whereas

concerns about endocrine therapy were slightly higher ($\bar{X}$ = 17, SD = 3.9). Women also reported high levels of overall social support ($\bar{X}$ = 101.9, SD = 13.9).

Higher pretherapy levels of depressive symptoms and anxiety, as well as poorer pretherapy physical functioning, were associated with lower adherence as indicated by the percentage of prescribed doses taken and the percentage of days with the correct intake of endocrine therapy (see Table 4). Better performance on the verbal fluency test (Lezak, Howieson, & Loring, 2004), a measure of executive function, also was associated with nonadherence as assessed by the percentage of prescribed doses taken and the percentage of days with the correct intake of endocrine therapy.

Disease and Treatment Factors

On average, women reported taking five medications per day and reported taking medications twice per day. Participants reported an average of six comorbidities and five symptoms or side effects. Overall and subscale scores on the BCPT Symptom Checklist were all below midpoint. The average out-of-pocket cost for medical expenses during the previous month was $308. In general, women in this study were not experiencing financial hardship. Nonadherence to endocrine therapy was associated with greater perceived bother from cognitive symptoms ($p < 0.05$), musculoskeletal pain ($p < 0.05$), weight concerns ($p < 0.01$), and gynecologic symptoms ($p < 0.01$).

Interactions

The potential for illness or treatment factors to modify the effect of patient factors on nonadherence to therapy was examined. Because this work was exploratory, the authors limited these interaction analyses to situations where significant main effects were observed between patient illness factors and nonadherence as indicated by the percentage of days with the correct intake. In addition, the authors only reported interactions with a high level of significance ($p < 0.01$) (see Table 5).

The main effects between patient factors and nonadherence modified most frequently by illness or treatment factors were the associations between nonadherence and depressive symptoms and anxiety. Significant interaction effects were predominantly observed at baseline. The most common illness or treatment factors that modified the associations between patient factors and nonadherence were greater bother associated with symptoms and greater out-of-pocket costs associated with breast cancer therapy. The significant association of higher levels of depressive symptoms and nonadherence at baseline was intensified by the number and severity of symptoms; for example, more participants reported more bother associated with musculoskeletal, gynecologic, and dyspareunia symptoms, as well as weight concerns as measured by the BCPT. The relationship also was intensified by disease stage, number of medications taken, and out-of-pocket costs as measured by the COIN. Greater concerns about bladder control weakened the negative effect of depressive symptoms on nonadherence. Having a higher number of symptoms weakened the association between depressive symptoms and nonadherence over time.

The significant association of higher anxiety and poorer adherence at baseline also was amplified by greater bother related to musculoskeletal and dyspareunia symptoms, weight concerns, and greater out-of-pocket costs. Over time, the relationship between higher anxiety and poorer adherence was intensified by a greater number of concomitant medications but weakened by greater concerns about bladder control.

Discussion

The authors conducted a comprehensive assessment of factors that may influence nonadherence to endocrine therapy in women with breast cancer and explored whether illness and treatment factors modified the effect of patient factors on nonadherence. As hypothesized by the authors, and similar to the results of other investigators (Partridge et al., 2008), adherence to endocrine therapy declined significantly during the first 18 months of therapy in women with breast cancer.

Patient Factors

When exploring the influence of patient factors on adherence to endocrine therapy, the current study's authors found that greater pretherapy levels of depressive symptomatology and anxiety predicted poorer endocrine therapy adherence. Conflicting results related to the influence of mood (depression and anxiety) on nonadherence to endocrine therapy have been reported. Demissie et al. (2001) reported significantly higher tamoxifen nonpersistence in women who reported problems with mood (36%) versus women who reported no mood problems (12%). Lebovits et al. (1990) found that women who discontinued self-administered chemotherapy had significantly higher depressive symptom disturbances compared to women who did not discontinue therapy ($p < 0.05$). Differences in the approach to the assessment of mood may partially explain these differences in findings. In addition, Demissie et al. (2001) and Lebovits et al. (1990) examined therapy discontinuation rates whereas the current study assessed adherence continuously using the MEMS cap. More research is needed to clearly understand the influence of mood on nonadherence to endocrine therapy.

Poorer physical functioning also predicted nonadherence. Demisse et al. (2001) found that women's reports

Knowledge Translation

Women who experience negative mood and symptoms prior to the initiation of adjuvant endocrine therapy for breast cancer may be at greater risk for nonadherence to therapy.

The influence of negative mood on nonadherence to endocrine therapy may be exacerbated by symptoms experienced during therapy, perceived financial hardship, greater disease stage, and greater complexity in their medication regimen.

Management of negative mood and symptoms before women with breast cancer begin adjuvant endocrine therapy may result in better adherence to therapy.

of better physical function were related to tamoxifen nonpersistence, differing from Lebovits et al. (1990) who found no relationship between physical function and nonpersistence. The basis for these conflicting results may be because of differing measurement approaches. Lebovits et al. (1990) assessed physical function with the Karnofsky Performance Scale (Mor, Laliberte, Morris, & Wiemann, 1984), an approach in which healthcare providers ascribe a functional rating to the patient. Similar to Demissie et al. (2001), the current authors assessed physical functioning with the SF-36 physical function subscale, a self-report measure. In addition, both Demissie et al. (2001) and Lebovits et al. (1990) assessed discontinuation rates rather than adherence to therapy.

The current study explored the potential influence of cognitive function on nonadherence using a battery of objective measures designed to assess multiple domains of cognition and unexpectedly found that better performance on the verbal fluency test (Lezak et al., 2004), a measure of executive function, was associated with poorer adherence to therapy. In previous studies, the authors found that the most common reason women indicated for not taking their endocrine therapy was that they forgot and later remembered, followed by forgetting and not realizing that they had not taken the dose (Bender et al., 2010). Murthy et al. (2002) also reported that forgetting was the most common reason women cited for not taking their tamoxifen. Self-reported cognitive problems are different from objectively measured cognitive function in that they are more commonly associated with mood and symptoms such as fatigue (Bender et al., 2008). To the authors' knowledge, the current study is the first to comprehensively assess cognitive function and explore the role of cognition in nonadherence to endocrine therapy. Sample size may have been a factor in the results related to cognitive function; however, more research is needed to clarify the role of objectively and subjectively measured cognitive function in adherence to endocrine therapy.

Illness or Treatment Factors

The presence and perceived bother associated with multiple symptoms was the only illness or treatment factor related to nonadherence. The symptoms that predicted nonadherence to endocrine therapy were self-reported cognitive symptoms ($p < 0.05$), musculoskeletal pain ($p < 0.05$), weight concerns ($p < 0.01$), and gynecologic symptoms ($p < 0.01$). Several studies stated that self-reported symptoms were related to nonadherence (Wickersham et al., 2013) and higher endocrine therapy discontinuation rates (Demissie et al., 2001; Fink et al., 2004; Grunfeld et al., 2005; Kahn et al., 2007). Grunfeld et al. (2005) reported that 46% of women who discontinued tamoxifen therapy did so because of the symptoms experienced. Ziller et al. (2009) found no relationship between disease- and treatment-related symptoms and nonadherence; however, adherence was measured via self-report and symptoms were assessed by medical record review.

Interactions

To the authors' knowledge, the current study is the first to explore whether factors related to breast cancer diagnosis and treatment modify the influence of patient factors on nonadherence to endocrine therapy. The presence and severity of symptoms were the most common illness or treatment factors to modify the relationship between patient factors and nonadherence.

Greater number and severity of symptoms at pretherapy intensified the negative influence of depressive symptoms on nonadherence in the first 18 months of therapy. In addition, greater reported bother associated with pretherapy symptoms intensified the relationship between depressive symptoms and nonadherence, as well as strengthened the relationship between anxiety and nonadherence.

Less evident were the moderating effects of symptoms experienced over time on the relationship between patient factors and nonadherence. In fact, greater perceived bother with more symptoms and greater bother associated with bladder symptoms weakened the relationships over time between nonadherence and depression and nonadherence and anxiety, respectively.

Greater out-of-pocket costs intensified the relationship between nonadherence and depressive symptoms and anxiety in the current study. Widespread agreement exists that the cost of anticancer drugs has an impact on the ability of many individuals to continue treatment (Experts in Chronic Myeloid Leukemia, 2013). Although the potential negative impact of financial hardship related to disease management on nonadherence has been explored (Griffith, 1990; Morris & Schulz, 1992; Vermeire, Hearnshaw, Van Royen, & Denekens, 2001), little is known about the role of financial hardship on

nonadherence. Sedjo & Devine (2011) found that women who reported greater out-of-pocket costs related to endocrine therapy were less likely to be adherent. Lower income also was associated with greater likelihood of chemotherapy discontinuation (Lebovits et al., 1990), and women residing in high-poverty areas were less likely to receive guideline-concordant endocrine therapy (Wu et al., 2012). The current results suggest that the impact of financial hardship related to cancer and cancer therapy may extend beyond a direct effect on adherence and instead magnify the effect of negative mood on nonadherence to endocrine therapy.

Finally, greater stage of disease and a greater number of medications taken, indicating greater regimen complexity, intensified the negative impact of depressive symptoms on nonadherence. Greater regimen complexity over time also magnified the impact of anxiety on nonadherence. Other studies have investigated the relationship between number of regimen complexity and nonadherence to endocrine therapy (Fink et al., 2004; Grunfeld et al., 2005; Lash et al., 2006). Lash et al. (2006) found that women with breast cancer who were taking four or more medications when initiating tamoxifen were less likely to discontinue the drug; however, if women began taking additional medications after initiating tamoxifen, they were more likely to stop taking tamoxifen (Lash et al., 2006).

Limitations

Because of the limitations of this research, results must be interpreted with caution. Based on this small sample, the exploration of interaction effects was restricted to situations where significant main effects between patient factors and adherence were observed and significance levels for interaction effects were set at less than 0.01. In addition, the sample for this study was limited to women with early-stage breast cancer and was comprised almost entirely of women who were Caucasian and relatively well-educated, limiting the generalizability of the findings of this study. Additional research is needed to explicate the rates of adherence to endocrine therapy and the predictors of nonadherence in a more diverse population and in women with later stage breast cancer.

The current study also limited assessment of adherence to the first 18 months of endocrine therapy. Endocrine therapy is generally prescribed for a minimum of five years in women with hormone receptor-positive, early-stage breast cancer. Rates of adherence to the full, five-year trajectory of adjuvant endocrine therapy are not clear. In addition, the patient and illness or treatment factors that may influence long-term adherence to adjuvant endocrine therapy are not known. Additional research is needed to determine the full, five-year trajectory of adherence to adjuvant endocrine therapy and the clinical implications of nonadherence to therapy in this population. Identifying patient and illness or treatment factors that influence nonadherence for the full length of endocrine therapy in this population also is critical.

Conclusions and Implications for Nursing

The current results indicate that adherence to endocrine therapy declines over time. Negative mood prior to the initiation of endocrine therapy and greater perceived bother associated with multiple symptoms were major predictors of nonadherence to hormonal therapy. Disease- and treatment-related symptoms also played a dominant role in intensifying the relationship between negative mood and nonadherence to therapy. Greater out-of-pocket costs intensified the relationship between nonadherence and both depressive symptoms and anxiety. Other illness or treatment factors, such as greater disease stage and medication complexity, also moderated the relationship between negative mood and nonadherence. Although these findings are not conclusive, they provide clear direction for examination in future adherence studies. This work is critical to the development of effective interventions to improve adherence to endocrine therapy in women with breast cancer.

Nurses caring for women who will receive endocrine therapy for breast cancer should identify those who may be at greater risk for being nonadherent. Women who are depressed or anxious, experiencing disease- and treatment-related symptoms, or confronting concerns about financial hardship at pretherapy may be more likely to become nonadherent to endocrine therapy over time. Therefore, nurses should assess women to determine whether they are experiencing depression or anxiety during pretherapy and throughout the course of therapy. Nurses also should assess women to determine whether they are experiencing symptoms related to their breast cancer or its treatment. Effective management of problems with mood and symptoms experienced at pretherapy and throughout therapy may help women with breast cancer maintain better adherence to endocrine therapy over time.

Women also may experience concerns about their ability to afford adjuvant endocrine therapy. These concerns may even exist in women who have health insurance that covers the cost of their endocrine therapy. Increasing evidence points to hidden costs associated with cancer and its treatment. These hidden costs can be in the form of out-of-pocket expenses and in various sacrifices patients and families make to afford cancer care (Barrera, Caples, & Tein, 2001). Together, these concerns may lead women to experience financial hardships associated with cancer care. The current results suggest that financial hardships

perceived by women with breast cancer predict nonadherence to therapy. Therefore, nurses need to assess whether women are experiencing financial hardships related to the cancer and its treatment and provide appropriate information and referrals so that women receive the resources they need to complete the full, prescribed course of adjuvant endocrine therapy.

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