Identification of Tools to Measure Changes in Musculoskeletal Symptoms and Physical Functioning in Women With Breast Cancer Receiving Aromatase Inhibitors

Karen K. Swenson, PhD, RN, AOCN®, Mary Jo Nissen, PhD, MPH, Susan J. Henly, PhD, RN, Laura Maybon, RN, Jean Pupkes, RN, ACNS-BC, AOCN®, Karen Zwicky, BS, Michaela L. Tsai, MD, and Alice C. Shapiro, PhD, RD, LN

Purpose/Objectives: To estimate and compare responsiveness of standardized self-reported measures of musculoskeletal symptoms (MSSs) and physical functioning (PF) during treatment with aromatase inhibitors (AIs).

Design: Prospective, longitudinal study.

Setting: Park Nicollet Institute and North Memorial Cancer Center, both in Minneapolis, MN.

Sample: 122 postmenopausal women with hormone receptor-positive breast cancer.

Methods: MSSs and PF were assessed before starting AIs and at one, three, and six months using six self-reported MSSs measures and two PF tests.

Main Research Variables: MSSs and PF changes from baseline to six months.

Findings: Using the Breast Cancer Prevention Trial–Musculoskeletal Symptom (BCPT-MS) subscale, 54% of participants reported MSSs by six months. Scores from the BCPT-MS subscale and the physical function subscales of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) and Western Ontario and McMaster Osteoarthritis Index (WOMAC) were most responsive to changes over six months.

Conclusions: BCPT-MS, AUSCAN, and WOMAC were the most responsive instruments for measuring AI-associated MSSs.

Implications for Nursing: Assessment and management of MSSs are important aspects of oncology care because MSSs can affect functional ability and AI adherence.

Knowledge Translation: The three measures with the greatest sensitivity were the BCPT-MS, AUSCAN, and WOMAC questionnaires. These measures will be useful when conducting research on change in MSSs associated with AI treatment in women with breast cancer.

Breast cancer is the most common cancer among women in the United States, with an estimated 232,340 women to be diagnosed in 2013 (American Cancer Society, 2013). Among postmenopausal women diagnosed with breast cancer, about 75% present with hormone receptor-positive disease, and that proportion is increasing (Anderson, Katki, & Rosenberg, 2011; Glass, Lacey, Carreon, & Hoover, 2007). Current guidelines recommend endocrine treatment with aromatase inhibitors (AIs) in postmenopausal women with hormone receptor-positive breast cancer following primary treatment with surgery or radiation therapy (Carlson et al., 2011). Five years of adjuvant AI treatment has been associated with an 18%–32% reduction in the risk of breast cancer recurrence over tamoxifen in clinical trials (Coates et al., 2007; Coombes et al., 2004).

AIs (anastrozole, letrozole, and exemestane) generally are prescribed for hormone receptor-positive disease after initial breast surgery, chemotherapy, or radiation therapy are completed (Cuzick et al., 2010). Women are given their prescription, along with instructions about the reason for treatment and a brief overview of potential side effects (Davidson, Vogel, & Wickerham, 2007; Love, 2005). Because follow-up visits are recommended every four to six months, instead of the frequent visits during radiation therapy or chemotherapy, appointment scheduling rarely permits ongoing, comprehensive face-to-face patient education regarding AI treatment, including management of side effects, from the nurse (National Comprehensive Cancer Network, 2013). Women may feel that the treatment phase is behind them at this time point. Women also may perceive that oral endocrine treatments are less important than surgery, chemotherapy, and radiotherapy (Fallowfield et al., 2006). These factors, in addition to the side effects from AI treatment, may lead to decreases in treatment adherence. However, treatment effectiveness is affected by adherence, because patients derive the most benefit from AI treatment when taken consistently at the correct dose and duration for the entire five-year period (Early Breast Cancer Trialists' Collaborative Group, 2005).

AI-associated musculoskeletal symptoms (MSSs) occur more frequently in women than previously identified in initial clinical trials (Presant et al., 2007). They are the most common adverse events reported with AI treatment, and now are estimated to affect 40%–50% of women on AI treatment regimens (Coleman et al., 2008; Crew et al., 2007; Gaillard & Sterns, 2011; Henry, Giles, & Stearns, 2008). These symptoms include bone pain, joint pain, joint stiffness, and muscle weakness. The most intense AI-related symptoms have been identified in the wrists, hands, and knees (Mao et al., 2009). MSSs lead to discontinuation of AI treatment in almost 25% of women (Henry et al., 2012). The onset of peak symptoms has been reported to manifest during the first four to eight months after initiating AI treatment (Kanematsu et al., 2011).

The Symptom Management Model (SMM) (Dodd et al., 2001) was used as the theoretical framework for the current study. The SMM incorporates three aspects—the symptom experience, symptom management strategies, and potential outcomes (Dodd et al., 2001). AIs produce a symptom cluster of MSSs that includes joint pain, tendinopathy, and joint stiffness. Those symptoms likely have a common cause related to the effect of AIs completely blocking estrogen production.

Aggressive management of AI-associated MSSs with lifestyle changes such as weight loss and exercise and short-term use of over-the-counter analgesics such as ibuprofen may help reduce pain and maintain function (Coleman et al., 2008; Henry et al., 2012; Rajotte et al., 2012). Other preliminary studies reported benefits from acupuncture (Crew et al., 2010), serotonin and norepinephrine reuptake inhibitors (Henry et al., 2011), prednisolone (Kubo et al., 2012), immunologic therapy (Zhang, Tang, & Zhao, 2010), dehydroepiandrosterone sulfate (Gallicchio, MacDonald, Wood, Rushovich, & Helzlsouer, 2011), bisphosphonates plus calcium supplements (Muslimani et al., 2009), and vitamin D supplements (Khan, Reddy, et al., 2010). However, these studies have used a variety of instruments to measure outcomes, limiting assessment of comparative efficacy and effectiveness. This gap in knowledge inhibits the ability to develop and evaluate treatments for AI-associated MSSs (Winters-Stone, Schwartz, Hayes, Fabian, & Campbell, 2012).

Many methods have been used to measure MSSs and physical functioning (PF) prospectively over time and across clinical trials. Previous studies have used single-item scales, such as a pain visual analog scale, to measure changes in symptoms (Henry et al., 2012; Kubo et al., 2012), or global measures such as the Eastern Cooperative Oncology Group (ECOG) score to measure PF (Briot, Tubiana-Hulin, Bastit, Kloos, & Roux, 2010). A gap exists in the current understanding of which standardized functional measures and instruments are clinically useful in this setting. Longitudinally validated measures of MSSs used in rheumatology and orthopedic clinics are available, but whether scores obtained using them are responsive to change is unknown in women treated with AIs. Responsiveness refers to the degree to which scale questions elicit responses reflecting change on two occasions during a specified period of time (Husted, Cook, Farewell, & Gladman, 2000; Liang, 2000). Effect size approaches to estimating responsiveness express magnitude of change in terms of some measure of variation in the scores. Effect size approaches provide standardized, unit-free measures with which to make comparisons about responsiveness across instruments. Such information is critical in the selection of instrumentation to measure change in MSSs and PF during the design phase of randomized, controlled clinical trials. To the authors' knowledge, the responsiveness of scores obtained from the various approaches used to measure MSSs and PF has not been assessed in this population. That gap limits the ability of high-quality clinical trials to assess the effects of interventions for AI-related MSSs and PF because quality-of-change estimates in the key outcomes are not known. The purpose of this study was to explore changes in self-report measures of MSSs and PF from baseline (prior to initiation of AIs) to one and six months following initiation of AI treatment. Specific aims were to (a) describe MSSs scores, (b) describe PF scores, (c) report the prevalence of clinically important symptoms at each time point, and (d) compare responsiveness. Following the analysis, the authors hoped to identify the instruments most suitable for measuring change in MSSs and PF in women during the first six months of AI treatment.

Methods

Design

The Aromatase Inhibitor Musculoskeletal Symptom (AIMS) Study was a multisite, prospective observational study to assess responsiveness in scores used to index change in MSSs and PF following initiation of adjuvant AI treatment for women with invasive breast cancer. MSSs were measured at baseline (prior to beginning AI therapy) and at one, three, and six months after starting AI therapy. Tests for PF were conducted at baseline and at three and six months after starting AI therapy. The study was approved by the Park Nicollet Institute and North Memorial Cancer Center institutional review boards prior to enrollment of research participants.

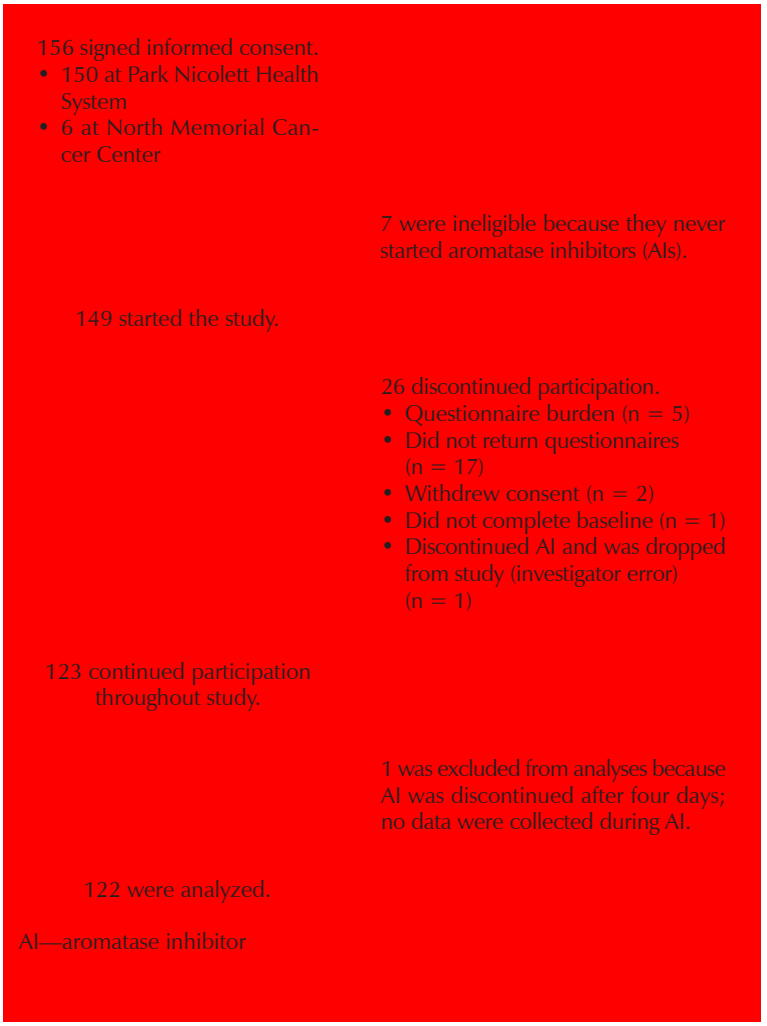
Sample

Inclusion criteria included (a) postmenopausal women with a diagnosis of stage I–IIIa hormone receptor-positive invasive breast cancer; (b) those who completed initial treatment of surgery, radiation therapy, chemotherapy, or tamoxifen therapy; (c) those prescribed AI treatment (e.g., exemestane, anastrazole, letrozole); and (d) those who signed consent for the study. Exclusion criteria were (a)

having a history of rheumatoid arthritis because of confounding symptoms associated with RA, (b) being unable to read or understand English, and (c) having a psychiatric history that could affect informed consent or study compliance.

The AIMS Study was conducted at Park Nicollet Cancer Center and North Memorial Cancer Center, both located in Minneapolis, MN. A total of 156 participants consented during a 22-month enrollment period; seven participants were ineligible because they did not start AI treatment, 26 participants withdrew from the study primarily because of questionnaire burden, and one participant discontinued AI treatment before any postbaseline assessments (see Figure 1). Analyses were conducted on 122 women.

Formal power calculations were not conducted for this study because analyses focused on the responsiveness of the instruments rather than testing a specific hypothesis. The sample size reflects the number of women available to enroll during the recruitment period.



Instruments

MSSs data were collected using six validated self-report questionnaires and two performance-based tests of PF. The literature and colleagues who conduct outcomes research in orthopedic surgery and rheumatology were consulted to identify instruments that were validated, standardized outcome measures for MSSs in the general population and for patients in rheumatology and orthopedics. The study team (oncology nurses, epidemiologist, medical oncologist, rheumatologist, and orthopedic surgeon) reviewed potential instruments and selected these self-report instruments of MSSs and performance-based tests of PF based on their face validity, previous reliability and validity testing in other populations, and ease of administration.

The **Breast Cancer Prevention Trial–Musculoskeletal Symptom (BCPT-MS) subscale** comprises three items measuring general aches and pains, joint pain, and muscle stiffness (Stanton, Bernaards, & Ganz, 2005). The BCPT-MS was derived from the original BCPT Symptom Checklist, a 42-item questionnaire validated in breast cancer survivors (Day et al., 1999; Ganz et al., 2000). The use of this subscale to assess arthralgia and myalgia pain has strong psychometric properties when used cross-sectionally. The musculoskeletal subscale represents a separate construct by both explanatory and confirmatory factor analyses, and has high reliability (Cronbach $\alpha = 0.82$). The subscale score consists of the mean of responses to three questions addressing general aches and pains, joint pain, and muscle stiffness. Scores range from 0–12, with higher scores representing worse symptoms.

The **Australian/Canadian Osteoarthritis Hand Index (AUSCAN)**, version 3.1, is a 15-item questionnaire assessing pain, stiffness, and PF in the hands, and has been tested extensively in patients with osteoarthritis of the hand. The AUSCAN is a responsive, valid, and reliable measure (Cronbach $\alpha = 0.89–0.96$) of outcomes with population-based age and gender-specific normative values (Allen, DeVellis, Renner, Kraus, & Jordan, 2007; Bellamy, Sothern, Campbell, & Buchanan, 2002). It consists of three subscales (pain, stiffness, and PF), each scored as the sum of the items on that subscale. Possible scores range from 0–20 for pain, 0–4 for stiffness, and 0–36 for PF, with higher scores indicating worse symptoms.

The **Western Ontario and McMaster Osteoarthritis Index (WOMAC)**, version 3.1, assesses pain, stiffness, and PF in the lower extremities, knees, and hips. The instrument is a 24-item questionnaire with good validity and reliability (Cronbach $\alpha = 0.93–0.96$) for which age- and gender-specific normative values are available (Bellamy, 2005). Like the AUSCAN, it consists of three subscales (pain, stiffness, and PF), each scored as the sum of the items on that subscale. It has been used extensively to evaluate symptoms of patients with osteoarthritis of the

knee and hip. Possible scores range from 0–20 for pain, 0–10 for stiffness, and 0–68 for PF, with higher scores representing worse symptoms.

The **Brief Pain Inventory (BPI)** is a 14-item questionnaire that assesses multiple aspects of pain severity, including worst pain, least pain, average pain, and present pain, as well as the interference of pain with daily activities such as sleep, activity, mood, and enjoyment of life (Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995). The BPI has established reliability (Cronbach α = 0.8–0.87 for pain severity and 0.89–0.92 for interference) and validity in patients with cancer (Serlin et al., 1995). A severity composite score is calculated as the mean of the items addressing pain severity, and an interference composite score is calculated as the mean of the items addressing interference with quality of life. Possible scores range from 0–40 for pain severity and 0–70 for interference, with higher scores representing worse symptoms.

The **Quick Disabilities of the Arm, Shoulder, and Hand (QuickDASH)** is an 11-item questionnaire measuring upper extremity MSSs and disabilities (Hudak, Amadio, & Bombardier, 1996). The instrument is a shortened version of the original 30-item DASH (Gummesson, Ward, & Atroshi, 2006). The QuickDASH has shown reliability (Cronbach α = 0.93) and content validity in a group of breast cancer survivors taking AIs (Leblanc, Mao, Stineman, Demichele, & Stricker, 2013). Possible scores ranged from 5–55, with higher scores indicating worse symptoms.

The **Patient-Reported Outcomes Measurement Information System (PROMIS) PF Short Form 1 scale** is a 10-item questionnaire to assess PF in daily activities. It has been tested for validity against other instruments in arthritis research (Fries, Cella, Rose, Krishnan, & Bruce, 2009). Test-retest reliability was very good (0.8 or greater) and known-group validity was demonstrated with large effect sizes for pain intensity, pain interference, and fatigue (Broderick, Schneider, Junghaenel, Schwartz, & Stone, 2013). A static short form was administered, consisting of five questions about how much the patient's health is limited by various symptoms and five questions evaluating the patient's ability to complete activities of daily living. The sum of the responses to the 10 items was calculated and then transformed to allow for direct comparison of the scores using a conversion table to a t score with a mean of 50 and standard deviation of 10. Possible total scores range from 0–50, with higher scores reflecting better physical functioning.

The **Hand Grip Strength Test (HGST)** is a measure based on performance that provides a validated, consistent, reproducible assessment of grip strength (Mathiowetz, Weber, Volland, & Kashman, 1984). Handgrip capacity was measured using a calibrated Jamar Hydraulic Hand Dynamometer with standardized procedures (Mathiowetz et al., 1985). The patient is asked to squeeze the dynamometer with as much force as possible, starting with the dominant hand and then alternating between dominant and nondominant hands. The mean scores of the dominant and nondominant hands were calculated. Known-group validity was established by strength measures negatively correlating with age ($r = -0.29$ to -0.41; $p < 0.01$). The HGST is measured in the pounds of force used to squeeze the dynamometer. Lower scores represent worse symptoms, and age and sex norms are given in Matiowetz et al. (1985).

The **Timed Up and Go (TUG) test** is a performance-based measure of functional mobility, physical capacities, and autonomy (Mathias, Nayak, & Isaacs, 1986; Podsiadlo

Age (years)	62.7	9.7	63	32–81
Body mass index[a]	29	5.8	28	17.7–49.1
Race				
Caucasian			119	98
African American			1	1
Multiple			1	1
Missing data			1	1
Ethnicity				
Non-Hispanic			119	98
Unknown			3	3
Employment status				
Employed full-time			41	34
Employed part-time			9	7
Not employed			69	57
Missing data			3	3
Stage of cancer				
I			72	59
II			40	33
III			9	7
Missing data			1	1
Hormone receptor				
Estrogen receptor (ER)-positive			11	9
Progestogen receptor (PR)-positive			1	1
ER- or PR-positive			109	89
Missing data			1	1
Radiation therapy				
Yes			85	70
No			36	30
Missing data			1	1
Chemotherapy				
Yes			46	38
No			76	62
Tamoxifen treatment				
Yes			27	22
No			95	78
Initial aromatase inhibitor				
Anastrozole			94	77
Letrozole			25	21
Exemestane			3	3

& Richardson, 1991). The test consists of rising from a chair, walking three meters, turning around, returning to the chair, and sitting down. Time to completion (measured in seconds) was recorded on each of the three trials and the mean of those three trials was calculated. Higher time represents worse symptoms.

BCPT-MS	1.08	0.85	1.26***	1.05	1.49***	1.04	1.7***	1.18
AUSCAN								
Pain	1.6	2.64	2.17***	3.16	2.94***	3.45	3.38***	3.92
Stiffness	0.48	0.69	0.58*	0.78	0.76***	0.83	0.92***	1.01
WOMAC								
Pain	2.37	2.9	3.27**	3.93	3.6***	3.87	4.03***	4.5
Stiffness	1.41	1.49	1.84**	1.87	2.16***	1.83	2.46***	2.04
BPI								
Severity	1.66	1.54	1.98	2.06	2.17	2.02	2.31	1.97
Interference	1.08	1.75	1.39	1.87	1.53	1.85	1.75	2.14
QuickDASH	10.44	11.05	12.62	13.46	15.29	14.75	16.42	16.09

Statistics and Data Analysis

Comparisons of demographic and clinical characteristics between women whose data were included in analyses and those who were not because of participation discontinuation (n = 26) or lack of data during AI treatment (n = 1) were analyzed using chi-square tests for categorical variables and t tests for continuous variables. Women whose baseline on that measure was completed after AI initiation (five women for BCPT-MS, AUSCAN, BPI, QuickDASH, and PROMIS; six women for WOMAC; and one woman for HGST and TUG) were not included in that particular comparison.

Means and standard deviations were calculated at baseline (before AI initiation), and at one, three, and six months. The PF tests (HGST and TUG) were measured at baseline and three and six months. Results obtained following discontinuation of all AI treatment were excluded (n = 12). Four women who switched from one AI to another but remained on the second AI were included in analyses for all time periods. Availability of data from the same participants at each time point allowed the use of paired t tests to determine whether results changed significantly from baseline. To determine the earliest time at which significant change occurred, paired t tests compared baseline to one month (on self-report measures), baseline to three months, and baseline to six months scores.

Based on previous normative data from the Breast Cancer Prevention Trial and personal communication from the authors of that trial (Stanton et al., 2005), a cut point of an average score of 1.5 on the BCPT-MS was used to identify women who were experiencing clinically significant MSSs on each occasion.

Responsiveness was indexed using standardized mean response (SMR) (Husted et al., 2000; Liang, 2000) from baseline to one month for self-report measures, and between baseline to endpoint for self-report and performance measures. For most participants, the endpoint was six months; for those who discontinued all AIs prior to six months, the endpoint was the last measure taken prior to discontinuation. SMR is the mean change in score divided by the standard deviation of changes in scores between the two time periods: $([1/n] \Sigma [x_2 - x_b])/SD_{[x_2 - x_b]}$.

The SMR, an effect size approach to estimating responsiveness (Cohen, 1977), provides a unit-free measure with which to make comparisons across instruments. Although its use as an indicator of clinically important change or absolute magnitude of change has been questioned, and other measures of responsiveness exist, the authors chose this one because of its wide use and close ties to tests of statistical significance. SMR is widely used to compare the responsiveness of scores obtained from multiple measures within an experiment (Liang, Fossel, & Larson, 1990; Terwee, Dekker, Wiersinga, Prummel, & Bossuyt, 2003). All analyses were conducted using SAS, version 9.2. All tests of significance were two-sided, with a nominal p value of less than 0.05.

Results

Demographic and Clinical Characteristics

From February 1, 2010 to December 31, 2011, a total of 156 women consented; seven participants were ineligible because they did not subsequently start AI treatment. At baseline, no significant differences existed between those who completed the study (n =

AUSCAN: Physical function subscale	3.35	4.26	4*	5.08	5.2**	5.83	6.24**	6.8
WOMAC: Physical function subscale	6.12	7.67	9.37	11.53	10.66	11.34	12.89	13.47
Hand Grip Strength Test	44.51	11.53	ND	ND	45.15	11.15	44.44	11.12
Timed Up and Go test	6.22	1.95	ND	ND	6.24	1.84	6.25	1.94
PROMIS: Physical function subscale	48.74	7.69	49.83	9.07	48.68	8.92	48.58	9.32

122) and those who dropped out or were excluded (n = 27) (see Table 1). Of those who completed the study, the majority were older Caucasian (98%) women with stage I cancer (59%). The mean body mass index was 29 kg/m^2. About 38% of participants had received previous chemotherapy, and 22% had received initial tamoxifen treatment and were switched over to AI treatment. Participants were prescribed anastrozole (77%), letrozole (21%), or exemestane (3%) as their initial AI treatment.

For all participants who started AI treatment (n = 149), 24 (16%) discontinued their initial AI treatment. AI discontinuation was significantly more frequent among individuals who dropped out of or were excluded from the study (8 of 27, 30%) than those who completed the study (16 of 122, 13%) ($p = 0.035$). Of the 16 participants who completed the study and discontinued the original AI, eight (50%) were switched to another AI, and four of those participants continued on the second AI for the duration of the study.

Musculoskeletal Symptoms and Functional Status

Musculoskeletal symptoms: As shown in Table 2, a significant difference existed in mean MSS scores from baseline to one, three, and six months for the BCPT-MS, AUSCAN, and WOMAC at all occasions. The differences were positive (e.g., pain, stiffness, severity, interferences) as measured by the various instruments, and increased on subsequent occasions compared to baseline. In addition, inspection of the mean scores between adjacent occasions showed significant increases by time point for all measures of MSSs.

Functional performance: Self-report measures of PF were significantly different from baseline when questions were included in a test battery that also asked about MSSs (see Table 3). Scores on the PROMIS PF Short Form were not different from baseline when measured on subsequent occasions. Significant changes from baseline were not found in the two PF tests (HGST and TUG).

Occurrence of clinically important symptoms: The proportion of participants who met the BCPT-MS criterion for experiencing clinically important MSSs increased over time: 28% at baseline, 37% at one month, 47% at three months, and 54% at six months. The increasing MSSs over six months corroborated the trend in average scores of self-reports of MSSs during the six months after starting AI treatment. The significant increases in MSSs on the BCPT-MS subscale scores and worsening function scores on the AUSCAN and WOMAC from baseline to one month, three months, and six months after starting AI treatment can be seen in Tables 2 and 3.

Responsiveness

SMDs taken from baseline are shown in Table 4. For MSSs self-report scores at one month, responsiveness ranged from a low of 0.206 (AUSCAN stiffness) to a high of 0.341 (AUSCAN pain). SMDs for MSSs scores were higher at six months than one month for all instruments. At six months, SMDs for MSSs measures ranged from a low of 0.282 (BPI interference) to a high of 0.62 (BCPT-MS). At one month, the WOMAC (SMD = 0.385) outperformed other self-reports of PF; at six months, the WOMAC (SMD = 0.667) was higher than all self-reported scores of PF and the performance tests. Notably, the SMDs for the PROMIS PF Short Form, HGST, and TUG all were very low, indicating that the instruments were not sensitive to changes in symptoms over time.

Discussion

Previous studies have linked AI treatment with subsequent onset of MSSs and dysfunction that can become

severe enough to prompt discontinuation of AI treatment. Despite the importance of handling this problem, consensus on how best to measure AI-associated MSSs does not exist. Using the SMDs, this study found that scores on the BCPT-MS subscale, the AUSCAN PF subscale, and the WOMAC PF subscale were most responsive to change in AI-associated MSSs. Scores from these three instruments demonstrated the greatest SMD for AI-associated MSSs. The BCPT-MS subscale has three questions on joint pains, muscle stiffness, and general aches and pain, which adequately capture AI-associated MSSs change for use in clinical trials. In addition, the sensitivity and brevity of this instrument make it useful in clinical practice as a global screening tool for measuring changes in MSSs.

Although all three subscales of the AUSCAN and WOMAC (pain, stiffness, and PF) show significant worsening over time, the PF subscales were most responsive to change. That may be a result of participants being better able to distinguish differences in functional status over time (as measured by the PF subscales), whereas pain and stiffness may fluctuate more over time and be more difficult for women to quantify and report. Self-reports of symptom severity may be more sensitive to response shifts than reports of functioning. The worst AI-related arthralgias have been reported in the wrists, hands, and knees (Mao et al., 2009). These symptoms relate to functional activities on the AUSCAN (upper extremity) and WOMAC (lower extremity) questionnaires, such as fastening buttons or jewelry and going up and down a flight of stairs.

Unlike prior research (Lintermans et al., 2011; Morales et al., 2008), the current study did not find that grip strength measured by a hand-held dynamometer was responsive to changes in AI-associated MSSs. That may be because of differences in instrumentation and measurement techniques. The initial study of grip strength (Morales et al., 2008) asked participants to squeeze a balloon of a modified sphygmomanometer that measured maximal force, which may have been a more sensitive test than the dynamometer used in the present study. The TUG test was not responsive to changes over time, and this may be attributable to a ceiling effect in the current study's patient population, which was relatively young compared to previous studies using this test (Mathias et al., 1986; Podsiadlo & Richardson, 1991); most of the women were very mobile and able to complete the test without difficulty at all time points.

The current study found that AI-associated MSSs increased over time from baseline to the six-month time point; previous studies have reported peak occurrence of MSSs at six months (Khan, O'Dea, & Sharma, 2010). Notably, 28% of women were experiencing clinically important MSSs on the BCPT-MS subscale at baseline prior to beginning AI treatment. Those baseline symptoms may be related to prior chemotherapy, comorbid conditions, or other medications; regardless, the average level of symptoms did increase over the six-month period.

The proportion of women who discontinued their initial AI treatment was relatively low (16%); no information was collected regarding reasons for discontinuing initial AI treatment. Of the women who discontinued their AI, 50% went on to try another AI treatment, and 25% of those continued the second AI treatment through the six-month time point. That is consistent with other studies that have found benefits to switching to another AI if the initial AI is poorly tolerated (Briot et al., 2010; Henry et al., 2012). Higher AI discontinuation rates related to MSSs have been previously reported, but included longer follow-up time (Henry et al., 2012).

Limitations

Limitations to the current study include the relatively small sample size with limited ethnic and racial diversity. Despite the small sample size, differences between baseline and subsequent scores were significant for all the MSSs measures. Budgetary constraints and patient burden of completing questionnaires at multiple time

BCPT-MS	0.274	0.62
AUSCAN		
Pain	0.341	0.552
Stiffness	0.206	0.575
Physical function	0.238	0.6
WOMAC		
Pain	0.284	0.476
Stiffness	0.32	0.587
Physical function	0.385	0.667
QuickDASH	0.219	0.467
Brief Pain Inventory		
Severity	0.227	0.368
Interference	0.272	0.282
PROMIS: Physical function	0.041	0.128
Hand Grip Strength Test	ND	0.047
Timed Up and Go test	ND	0.133

points limited the feasibility of collecting data beyond the first six months of AI treatment.

Implications for Nursing

AI-associated MSSs are common, affecting almost half of women on AI treatments. Scores on the BCPT-MS subscale and the AUSCAN and WOMAC PF subscales were found to be most responsive to change among the instruments included in this study. Using standardized scales responsive to change in women receiving AIs is essential in studies of AI treatment. MSSs impact important aspects of oncology care, including quality of life, functional ability, and adherence to AI treatments. This study was a first step toward standardizing the assessment of change in MSSs and PF associated with AI treatment. Standardized, validated responsive measures of AI-associated MSSs will be useful for the conduct of randomized, controlled studies (Winters-Stone et al., 2012). Additional research is needed to replicate these results and identify interventions to reduce pain and maintain functional status.

Conclusion

This study found the most useful instruments to measure AI-associated MSSs. The three measures with the greatest sensitivity to changes over time were the BCPT-MS, AUSCAN, and WOMAC questionnaires. This information will be useful for designing and conducting future research on MSSs associated with AI treatment.

The authors gratefully acknowledge Annette Stanton, PhD, for providing guidance on the use of the BCPT-MS questionnaire, John Schoesboe, MD, and Greg Brown, MD, PhD, for medical guidance for selecting research instruments, and Amanda Forbes and Maria Grau for database development and questionnaire administration.

Karen K. Swenson, PhD, RN, AOCN®, was the oncology research director of the Oncology Research Department at Park Nicollet Institute at the time the manuscript was written and currently is a manager/scientific advisor in the Virginia Piper Cancer Institute at Abbott Northwestern Hospital; Mary Jo Nissen, PhD, MPH, is a senior health services researcher in the Oncology Research Department at Park Nicollet Institute; Susan J. Henly, PhD, RN, is a professor in the School of Nursing at the University of Minnesota; Laura Maybon, RN, is a research clinician in the Oncology Research Department at Park Nicollet Institute; Jean Pupkes, RN, ACNS-BC, AOCN®, is a clinical nurse specialist at North Memorial Medical Center; Karen Zwicky, BS, is a senior regulatory specialist in the Frauenshuh Cancer Center at Park Nicollet Institute; Michaela L. Tsai, MD, is a physician at Minnesota Oncology; and Alice C. Shapiro, PhD, RD, LN, is a research scientist in the Oncology Research Department at Park Nicollet Institute, all in Minneapolis, MN. This research was supported, in part, by the 2010 ONS Foundation Breast Cancer Research Grant, which is supported by Susan G. Komen for the Cure®. Swenson can be reached at karen.swenson2@allina.com, with copy to editor at ONFEditor@ons.org. (Submitted November 2012. Accepted for publication January 23, 2013.)

Digital Object Identifier: 10.1188/13.ONF.549-557

References

Allen, K.D., DeVellis, R.F., Renner, J.B., Kraus, V.B., & Jordan, J.M. (2007). Validity and factor structure of the AUSCAN Osteoarthritis Hand Index in a community-based sample. *Osteoarthritis and Cartilage, 15,* 830–836.

American Cancer Society. (2013). *Cancer facts and figures, 2013.* Atlanta, GA: Author.

Anderson, W.F., Katki, H.A., & Rosenberg, P.S. (2011). Incidence of breast cancer in the United States: Current and future trends. *Journal of the National Cancer Institute, 103,* 1397–1402.

Bellamy, N. (2005). The WOMAC Knee and Hip Osteoarthritis Indices: Development, validation, globalization, and influence on the development of the AUSCAN Hand Osteoarthritis Indices. *Clinical and Experimental Rheumatology, 23*(5, Suppl. 39), S148–S153.

Bellamy, N., Sothern, R.B., Campbell, J., & Buchanan, W.W. (2002). Rhythmic variations in pain, stiffness, and manual dexterity in hand osteoarthritis. *Annals of the Rheumatic Diseases, 61,* 1075–1080.

Briot, K., Tubiana-Hulin, M., Bastit, L., Kloos, I., & Roux, C. (2010). Effect of a switch of aromatase inhibitors on musculoskeletal symptoms in postmenopausal women with hormone-receptor-positive breast cancer: The ATOLL (articular tolerance of letrozole) study. *Breast Cancer Research and Treatment, 120,* 127–134.

Broderick, J.E., Schneider, S., Junghaenel, D.U., Schwartz, J.E., & Stone, A.A. (2013). Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. *Arthritis Care Research, 65,* 1623–1633. doi:10.1002/acr.22025

Carlson, R.W., Allred, D.C., Anderson, B.O., Burstein, H.J., Carter, W.B., Edge, S.B., . . . Zellars, R. (2011). Invasive breast cancer. *Journal of the National Comprehensive Cancer Network, 9,* 136–222.

Coates, A., Keshaviah, A., Thurlimann, B., Mouridsen, H., Mauriac, L., Forbes, J., . . . Goldhirsch, A. (2007). Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: Update of study BIG 1–98. *Journal of Clinical Oncology, 25,* 486–492.

Cohen, J. (1977). *Statistical power analysis for the behavioral sciences* (revised ed.). New York, NY: Academic Press.

Coleman, R.E., Bolten, W.W., Lansdown, M., Dale, S., Jackisch, C., Merkel, D., . . . Hadji, P. (2008). Aromatase inhibitor-induced arthralgia: Clinical experience and treatment recommendations. *Cancer Treatment Reviews, 34,* 275–282. doi:10.1016/j.ctrv.2007.10.004

Coombes, R.C., Hall, E., Gibson, L.J., Paridaens, R., Jassem, J., Delozier, T., . . . van de Velde, C. (2004). A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *New England Journal of Medicine, 350,* 1081–1092.

Crew, K.D., Capodice, J.L., Greenlee, H., Brafman, L., Fuentes, D., Awad, D., . . . Hershman, D.L. (2010). Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *Journal of Clinical Oncology, 28,* 1154–1160.

Crew, K.D., Greenlee, H., Capodice, J., Raptis, G., Brafman, L., Fuentes, D., . . . Hershman, D.L. (2007). Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *Journal of Clinical Oncology, 25,* 3877–3883.

Cuzick, J., Sestak, I., Baum, M., Buzdar, A., Howell, A., Dowsett, M., & Forbes, J.F. (2010). Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncology, 11,* 1135–1141.

Davidson, B., Vogel, V., & Wickerham, L. (2007). Oncologist-patient discussion of adjuvant hormonal therapy in breast cancer: Results of a linguistic study focusing on adherence and persistence to therapy. *Journal of Supportive Oncology, 5,* 139–143.

Day, R., Ganz, P.A., Costantino, J.P., Cronin, W.M., Wickerham, D.L., & Fisher, B. (1999). Health-related quality of life and tamoxifen in breast cancer prevention: A report from the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *Journal of Clinical Oncology, 17,* 2659–2669.

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E.S., Humphreys, J., . . . Taylor, D. (2001). Advancing the science of symptom management. *Journal of Advanced Nursing, 33,* 668–676.

Early Breast Cancer Trialists' Collaborative Group. (2005). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet, 365,* 1687–1717. doi:10.1016/S0140-6736(05)66544-0

Fallowfield, L., Atkins, L., Catt, S., Cox, A., Coxon, C., Langridge, C., . . . Price, M. (2006). Patients' preference for administration of endocrine treatments by injection or tablets: Results from a study of women with breast cancer. *Annals of Oncology, 17,* 205–210.

Fries, J.F., Cella, D., Rose, M., Krishnan, E., & Bruce, B. (2009). Progress in assessing physical function in arthritis: PROMIS short forms and computerized adaptive testing. *Journal of Rheumatology, 36,* 2061–2066.

Gaillard, S., & Stearns, V. (2011). Aromatase inhibitor-associated bone and musculoskeletal effects: New evidence defining etiology and strategies for management. *Breast Cancer Research, 13,* 205.

Gallicchio, L., Macdonald, R., Wood, B., Rushovich, E., & Helzlsouer, K. (2011). Androgens and musculoskeletal symptoms among breast cancer patients on aromatase inhibitor therapy. *Breast Cancer Research and Treatment, 130,* 569–577. doi:10.1007/s10549-011-1611-2

Ganz, P.A., Greendale, G.A., Petersen, L., Zibecchi, L., Kahn, B., & Belin, T.R. (2000). Managing menopausal symptoms in breast cancer survivors: Results of a randomized controlled trial. *Journal of the National Cancer Institute, 92,* 1054–1064. doi:10.1093/jnci/92.13.1054

Glass, A.G., Lacey, J.V., Jr., Carreon, J.D., & Hoover, R.N. (2007). Breast cancer incidence, 1980–2006: Combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *Journal of the National Cancer Institute, 99,* 1152–1161.

Gummesson, C., Ward, M., & Atroshi, I. (2006). The shortened disabilities of the arm, shoulder and hand questionnaire (QuickDASH): Validity and reliability based on responses within the full-length DASH. *BMC Musculoskeletal Disorders, 7,* 44.

Henry, N.L., Azzouz, F., Desta, Z., Li, L., Nguyen, A.T., Lemler, S., . . . Storniolo, A.M. (2012). Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *Journal of Clinical Oncology, 30,* 936–942.

Henry, N.L., Banerjee, M., Wicha, M., Van Poznak, C., Smerage, J.B., Schott, A.F., . . . Hayes, D.F. (2011). Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. *Cancer, 117,* 5469–5475. doi:10.1002/cncr.26230

Henry, N.L., Giles, J.T., & Stearns, V. (2008). Aromatase inhibitor-associated musculoskeletal symptoms: Etiology and strategies for management. *Oncology, 22,* 1401–1408.

Hudak, P.L., Amadio, P.C., & Bombardier, C. (1996). Development of an upper extremity outcome measure: The DASH (disabilities of the arm, shoulder, and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). *American Journal of Industrial Medicine, 29,* 602–608.

Husted, J.A., Cook, R.J., Farewell, V.T., & Gladman, D.D. (2000). Methods for assessing responsiveness: A critical review and recommendations. *Journal of Clinical Epidemiology, 53,* 459–468.

Kanematsu, M., Morimoto, M., Honda, J., Nagao, T., Nakagawa, M., Takahashi, M., . . . Sasa, M. (2011). The time since last menstrual period is important as a clinical predictor for non-steroidal aromatase inhibitor-related arthralgia. *BMC Cancer, 11,* 436.

Khan, Q.J., O'Dea, A.P., & Sharma, P. (2010). Musculoskeletal adverse events associated with adjuvant aromatase inhibitors. *Journal of Oncology, 2010,* 654348. doi:10.1155/2010/654348

Khan, Q.J., Reddy, P.S., Kimler, B.F., Sharma, P., Baxa, S.E., O'Dea, A.P., . . . Fabian, C.J. (2010). Effect of vitamin D supplementation on serum 25-hydroxy vitamin D levels, joint pain, and fatigue in women starting adjuvant letrozole treatment for breast cancer. *Breast Cancer Research and Treatment, 119,* 111–118.

Kubo, M., Onishi, H., Kuroki, S., Okido, M., Shimada, K., Yokohata, K., . . . Katano, M. (2012). Short-term and low-dose prednisolone administration reduces aromatase inhibitor-induced arthralgia in patients with breast cancer. *Anticancer Research, 32,* 2331–2336.

Leblanc, M., Mao, J.J., Stineman, M. Demichele, A., & Stricker, C. (2013). Validation of QuickDASH outcome measure in breast cancer survivors for upper extremity disability. *Archives of Physical Medication and Rehabilitation.* Advance online exclusive.

Liang, M.H. (2000). Longitudinal construct validity: Establishment of clinical meaning in patient evaluative instruments. *Medical Care, 38*(9, Suppl.), II84–II90. doi:10.1097/00005650-200009002-00013

Liang, M.H., Fossel, A.H., & Larson, M.G. (1990). Comparisons of five health status instruments for orthopedic evaluation. *Medical Care, 28,* 632–642. doi:10.1097/00005650-199007000-00008

Lintermans, A., Van Calster, B., Van Hoydonck, M., Pans, S., Verhaeghe, J., Westhovens, R., . . . Neven, P. (2011). Aromatase inhibitor-induced loss of grip strength is body mass index dependent: Hypothesis-generating findings for its pathogenesis. *Annals of Oncology, 22,* 1763–1769. doi:10.1093/annonc/mdq699

Love, S.M. (2005). *Dr. Susan Love's breast cancer book* (4th ed.). Cambridge, MA: Da Capo Lifelong Press.

Mao, J.J., Stricker, C., Bruner, D., Xie, S., Bowman, M.A., Farrar, J.T., . . . DeMichele, A. (2009). Patterns and risk factors associated with aromatase inhibitor-related arthralgia among breast cancer survivors. *Cancer, 115,* 3631–3639. doi:10.1002/cncr.24419

Mathias, S., Nayak, U.S., & Isaacs, B. (1986). Balance in elderly patients: The "get up and go" test. *Archives of Physical Medicine and Rehabilitation, 67,* 387–389.

Mathiowetz, V., Kashman, N., Volland, G., Weber, K., Dowe, M., & Rogers, S. (1985). Grip and pinch strength: Normative data for adults. *Archives of Physical Medicine and Rehabilitation, 66*(2), 69–74.

Mathiowetz, V., Weber, K., Volland, G., & Kashman, N. (1984). Reliability and validity of grip and pinch strength evaluations. *Journal of Hand Surgery, 9,* 222–226.

Morales, L., Pans, S., Verschueren, K., Van Calster, B., Paridaens, R., Westhovens, R., . . . Neven, P. (2008). Prospective study to assess short-term intra-articular and tenosynovial changes in the aromatase inhibitor-associated arthralgia syndrome. *Journal of Clinical Oncology, 26,* 3147–3152. doi:10.1200/JCO.2007.15.4005

Muslimani, A.A., Spiro, T.P., Chaudhry, A.A., Taylor, H.C., Jaiyesimi, I., & Daw, H.A. (2009). Aromatase inhibitor-related musculoskeletal symptoms: Is preventing osteoporosis the key to eliminating these symptoms? *Clinical Breast Cancer, 9*(1), 34–38.

National Comprehensive Cancer Network. (2013). *NCCN Clinical Practice Guidelines in Oncology: Breast cancer* [v.3.2013]. Retrieved from www.nccn.org/professionals/physician_gls/pdf/breast.pdf

Podsiadlo, D., & Richardson, S. (1991). The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *Journal of the American Geriatrics Society, 39,* 142–148.

Presant, C.A., Bosserman, L., Young, T., Vakil, M., Horns, R., Upadhyaya, G., . . . Howard, F. (2007). Aromatase inhibitor-associated arthralgia and/or bone pain: Frequency and characterization in non-clinical trial patients. *Clinical Breast Cancer, 7,* 775–778.

Rajotte, E.J., Yi, J.C., Baker, K.S., Gregerson, L., Leiserowitz, A., & Syrjala, K.L. (2012). Community-based exercise program effectiveness and safety for cancer survivors. *Journal of Cancer Survivorship, 6,* 219–228. doi:10.1007/s11764-011-0213-7

Serlin, R.C., Mendoza, T.R., Nakamura, Y., Edwards, K.R., & Cleeland, C.S. (1995). When is cancer pain mild, moderate, or severe? Grading pain severity by its interference with function. *Pain, 61,* 277–284.

Stanton, A.L., Bernaards, C.A., & Ganz, P.A. (2005). The BCPT symptom scales: A measure of physical symptoms for women diagnosed with or at risk for breast cancer. *Journal of the National Cancer Institute, 97,* 448–456. doi:10.1093/jnci/dji069

Terwee, C.B., Dekker, F.W., Wiersinga, W.M., Prummel, M.F., & Bossuyt, P.M.M. (2003). On assessing responsiveness of health-related quality-of-life instruments: Guidelines for instrument evaluation. *Quality of Life Research, 12,* 349–362. doi:10.1023/A:1023499322593

Winters-Stone, K.M., Schwartz, A.L., Hayes, S.C., Fabian, C.J., & Campbell, K.L. (2012). A prospective model of care for breast cancer rehabilitation: Bone health and arthralgias. *Cancer, 118*(8, Suppl.), 2288–2299.

Zhang, Q., Tang, D., & Zhao, H. (2010). Immunological therapies can relieve aromatase inhibitor-related joint symptoms in breast cancer survivors. *American Journal of Clinical Oncology, 33,* 557–560.