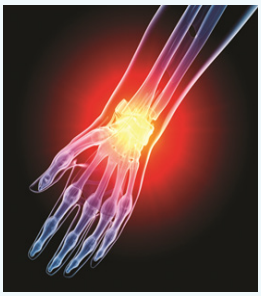
CNE Article

Etiology, Assessment, and Management of Aromatase Inhibitor-Related Musculoskeletal Symptoms

So-Hyun Park, MS, ANP-BC, M. Tish Knobf, PhD, RN, FAAN, AOCN®, and Karen M. Sutton, MD



© iStockphoto.com/David Marchal

Aromatase inhibitors (AIs) are recommended as adjuvant endocrine therapy for postmenopausal women with hormone-responsive breast cancer. With the widespread use of AI adjuvant endocrine therapy, a significant profile of musculoskeletal symptoms has emerged. Moderate to severe musculoskeletal symptoms have led some women to discontinue therapy, compromising the survival benefit. The etiology of AI-related musculoskeletal symptoms is poorly understood, which challenges development of effective management strategies. The purpose of this article is to describe AI-related musculoskeletal symptoms, review possible causes, provide assessment guidelines, and recommend management strategies based on the best available evidence. Little evidence exists for effective management strategies of AI-related musculoskeletal symptoms, and randomized clinical trials are needed to establish effective interventions. A thorough musculoskeletal assessment can help guide clinical decision making for the best individual management approach. Providers need to manage symptoms with the best available evidence to minimize symptom distress and maximize adherence to AI therapy.

So-Hyun Park, MS, ANP-BC, is a PhD student and M. Tish Knobf, PhD, RN, FAAN, AOCN®, is a professor, both in the School of Nursing, and Karen M. Sutton, MD, is an assistant professor in the Department of Orthopedic Surgery and Rehabilitation, all at Yale University in New Haven, CT. The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or editorial staff. Park can be reached at so-hyun.park@yale.edu, with copy to editor at CJONEditor@ons.org. (First submission July 2011. Revision submitted September 2011. Accepted for publication October 19, 2011.)

Digital Object Identifier: 10.1188/12.CJON.260-266

Adjuvant endocrine therapy with tamoxifen for patients with estrogen-dependent breast cancer has established benefit through significantly reduced recurrence rates and improved survival. Third generation aromatase inhibitors (AIs) (anastrozole, letrozole, and exemestane) as adjuvant endocrine therapy provide modest improvements in disease-free survival compared to tamoxifen in postmenopausal hormone-responsive breast cancer survivors (Dowsett et al., 2010; Josefsson & Leinster, 2010); however, AIs have failed to improve overall patient survival (Freedman & Winer, 2010). Despite the modest improvement in disease-free survival and similar outcomes for overall survival compared to tamoxifen, AI therapy alone for five years or given sequentially following two to three years of tamoxifen is recommended for postmenopausal women with hormone-positive breast cancer (Burstein et al., 2010). However, when the absolute benefit of one therapy versus another is small, evaluation of the safety and side-effect profile of the individual therapies is essential (Freedman & Winer, 2010).

With the widespread use of AI adjuvant endocrine therapy, a significant profile of musculoskeletal symptoms has emerged. Those symptoms are reported in 33%–50% of patients and have been associated with poor adherence, potentially leading to discontinuation of adjuvant treatment (Henry et al., 2012). However, the underlying mechanism of musculoskeletal symptoms is poorly understood and evidence is lacking to direct symptom management.

Adherence is critical in the success of therapeutic interventions, particularly with long-term treatments, such as AIs, when women are expected to take daily oral agents for at least five years. However, a significant number of patients on AI therapy discontinue their therapy because of adverse side effects (Miaskowski, Shockney, & Chlebowski, 2008). The current article will describe AI-related musculoskeletal symptoms, physiologic

evidence, and recommendations for assessment and management of symptoms.

Musculoskeletal Symptoms

The most common musculoskeletal symptoms reported are arthralgias, bone pain, and joint stiffness. New onset or worsening arthralgias had been documented in 32%–61% of patients (Crew, Greenlee, et al., 2007; Dizdar et al., 2009; Mao et al., 2009) (see Figure 1). The joints most frequently involved include hands and wrist (14%–70%), knees (11%–70%), ankles and feet (9%–52%), and, less frequently, back, hip, and spinal facets (Briot, Tubiana-Hulin, Bastit, Kloos, & Roux, 2010; Crew, Greenlee, et al., 2007; Dizdar et al., 2009; Henry et al., 2008; Mao et al., 2009). The onset of symptoms generally occurs within the first 1–3 months after treatment initiation (Henry et al., 2008; Mao et al., 2009; Presant et al., 2007) and may cause mild-to-severe symptoms (Henry et al., 2008; Morales et al., 2007). Symptoms may worsen with continued therapy. Bone and/or muscle aches were reported to increase after 12 months of AI treatment (Jones et al., 2007), and grip strength (measured by hand grip test) decreased after six months of the therapy (Morales et al., 2008). The early onset of symptoms combined with persistent or worsening symptoms has been associated with poor adherence to treatment (Briot et al., 2010).

Symptom assessment of AI-related musculoskeletal symptoms has been conducted with questionnaires, visual analog scales, Likert-type scales, and the Brief Pain Inventory. Despite differences in measurement, many women consistently rate the severity of their symptoms as moderate-to-severe (Crew, Greenlee, et al., 2007; Mao et al., 2009).

Many factors have been thought to explain or predict AI-associated symptoms. However, age, race, entry into menopause (natural versus surgical or chemical), years since menopause, type of AI, and duration of AI therapy have not been associated with AI-related joint symptoms (Crew, Greenlee, Capodice, Raptis, et al., 2007). Previous use of taxane-based chemotherapy, obesity (Crew, Greenlee, et al., 2007), vitamin D deficiency (Khan et al., 2010; Prieto-Alhambra et al., 2011; Waltman, Ott, Twiss, Gross, & Lindsey, 2009), and recent menopause (Mao et al., 2009) have been associated with AI-related musculoskeletal symptoms. The type of AI may influence symptoms. In one study, women discontinued anastrozole because their symptoms made them eligible for therapy with letrozole. Six months after beginning letrozole, 29% (n = 51) discontinued therapy because of severe joint pain; however, 72% (n = 128) continued therapy with 12%–21% reporting musculoskeletal symptoms (e.g., arthralgia, myalgia, arthritis, tendinitis) (Briot et al., 2010). Although the severity level of musculoskeletal symptoms is clinically significant, it can result in poor adherence and discontinuation of therapy. Ultimately, lack of compliance with the recommended five years of adjuvant endocrine therapy will compromise the established disease-free survival benefits. A better understanding of the underlying causes and factors and the development of effective interventions are essential.

- **Most common symptoms:** arthralgia, bone pain, and joint stiffness
- **New onset or worsening arthralgia:** 32%–61% of patients
- **Most frequently involved sites**
  - Hands and wrist: 14%–70% of patients
  - Knees: 11%–70%
  - Ankles and feet: 9%–52%
- **Onset:** 1–3 months after aromatase inhibitor treatment
- **Severity:** moderate to severe
- **Related factors:** taxane-based chemotherapy, obesity, recent menopause

FIGURE 1. Aromatase Inhibitor-Related Musculoskeletal Symptoms

Note. Based on information from Briot et al., 2010; Crew, Greenlee, et al., 2007; Dizdar et al., 2009; Henry et al., 2008; Jones et al., 2007; Khan et al., 2010; Mao et al., 2009; Morales et al., 2007; Presant et al., 2007; Prieto-Alhambra et al., 2011; Waltman et al., 2009.

Physiologic Evidence for Musculoskeletal Symptoms

A small body of research has attempted to describe the physiologic changes of those AI-related musculoskeletal symptoms from a clinical, radiologic, biologic, and genetic perspective. Clinically, patients on AI therapy who reported severe musculoskeletal pain in their hands and wrists had limited mobility, particularly limited flexion and extension of fingers or a diagnosis of trigger finger (Morales et al., 2007). Functional evaluation of joints and tendons using the hand grip test showed marked decrease of grip strength after six months of AI use (Morales et al., 2008). Markers for inflammation and autoimmune disease were explored. However, women on AI therapy had not shown elevated erythrocyte sedimentation rate, elevated C-reactive protein (Briot et al., 2010; Dizdar et al., 2009; Henry et al., 2008; Morales et al., 2007), abnormal levels of antinuclear antibodies, rheumatoid factor, antidouble-stranded DNA, or anticyclic citrullinated peptide (Dizdar et al., 2009; Henry et al., 2008).

Radiologic Assessment

Patients on AIs with musculoskeletal complaints were evaluated with ultrasound examinations. Patients taking AIs had fluid in their digital flexor tendon sheath (Morales et al., 2007) and also had overall thicker tendons compared to the control group of postmenopausal patients with breast cancer not receiving hormone treatment (Dizdar et al., 2009). Magnetic resonance imaging (MRI) was used to evaluate 12 women who reported severe musculoskeletal pain with AIs. Enhancement and thickening of the tendon sheath was found (Morales et al., 2007), which is a consistent finding with tendinopathy, tendinitis, or tenosynovitis. Of those 12 patients, some had fluid in the tendon sheaths of the digital flexor tendons (n = 11), fluid surrounding the extensor tendons (n = 4), intra-articular fluid accumulation in the metacarpal joints (n = 2), synovitis of the radiocarpal joint (n = 1), and reactive inflammatory edema in the soft tissues superficial to the tendon sheath (n = 10). Finally, compared to patients on tamoxifen with a baseline and six-month follow-up MRI, women on AIs had worsening of preexisting changes or a new onset of pathology of joints or tendons, such as greater fluid accumulation in joints and tenosynovial abnormalities (Morales et al., 2008). The radiographic findings

confirmed the clinically reported symptoms of increased joint stiffness, increased joint pain, and diminished tendon strength and range of motion.

Biologic Assessment

Estrogen has been the proposed cause of musculoskeletal problems because AIs change estrogen levels. In an attempt to explain the protective role of estrogen on joints and the lack of estrogen as a contributor to postmenopausal joint symptoms, an in vivo study of human synovial tissue was conducted from a sample of men (n = 5) and pre- (n = 8) and postmenopausal women (n = 11) (Dietrich et al., 2006). After routine orthopedic surgery, synovial tissues were obtained from the participants and examined by immunohistochemistry, western blot, and reverse transcriptase-polymerase chain reaction (RT-PCR). Estrogen receptor-β (ER-β) was detected in all the samples (N = 24) by immunohistochemistry and western blot. ER-β mRNA expression was found in 10 samples by RT-PCR. Estradiol functioned as a paracellular permeability-increasing factor on human endothelium via ER-β. Therefore, the ER-β found in synovial tissues from this study suggested a significant role of estrogen in synovial membrane function in the participants. In addition, the association between type II collagen, the main structural protein of articular cartilage, and surface cartilage erosion seen in animals with oophorectomy also supported the argument that estrogen deficiency may cause accelerated cartilage turnover and erosion (Din, Dodwell, Wakefield, & Coleman, 2010).

Joint pain may also be partly explained by lack of estrogen-mediated signaling within ER-β–positive synovial tissue; however, evidence is not consistent. Din et al.(2010) presented an alternative explanation. Increased estrogen level and elevated pain thresholds seen in pregnant women support the effects of estrogen on pain; however, women's increased tolerance of pain during the menstrual cycle, when levels of estradiol and progesterone are lowest, contradicts such effects of estrogen.

The relationship between estrogen and osteoarthritis in postmenopausal women has been studied, but the mechanism is unknown. Because estrogen acts partially through regulation of insulin-like growth factor (IGF), a study using monkeys found that when oophorectomized monkeys received estrogen replacement therapy, the result was an increase of insulin-like growth factor (IGF) -1, IGF-2, IGF binding protein (IGFBP) -1, and IGFBP-3 in the synovial fluid (Fernihough et al., 1999). IGF-1 is produced by chondrocytes, bone cells, and synovial cells, and provides stimulus for cartilage matrix synthesis. The findings of this study suggest a stimulating effect for estrogen on joint cartilage and synovium. Similar results were reported in studies using rat models. When rats with solid mammary tumors were given three different doses of the AI vorozole, a significant dose-dependent decrease of tissue IGF-1 was observed (Sugamata, Koibuchi, Iino, & Morishita, 1999). Another study with male rats also showed that the use of an AI significantly decreased serum IGF-1 level and significantly reduced bone mineral density of the femur and the four distal lumbar vertebrae (Vanderschueren et al., 1997).

To assess the effect of estrogen on osteoarthritis in postmenopausal women, the Framingham cohort study examined the effect of estrogen-replacement therapy (ERT) for the prevention of worsening radiographic knee osteoarthritis (OA) (Zhang et al., 1998). When compared to those who had never used ERT, past users of ERT had the relative risk of 0.8 (95% confidence interval [CI] [0.5,1.4]) and current users of ERT had the relative risk of 0.4 (95% CI [0.1, 3]) for incidence of radiographic knee OA. Although the results did not reach statistical significance, based on the findings and a review of the literature, Zhang et al. (1998) suggested that estrogen has a protective effect on joints.

Estrogen likely plays a substantial role in joint complaints of postmenopausal women. However, the incidence and severity of musculoskeletal symptoms in women on AIs appear uniquely worse compared to women who experience abrupt menopause (surgical- or chemotherapy-induced) or women taking tamoxifen.

A genome-wide association case control study was conducted to identify potential genetic markers of musculoskeletal symptoms (Ingle et al., 2010). Cases included women with breast cancer on AIs who experienced symptoms, and controls included women with breast cancer who did not report musculoskeletal symptoms. Four single nucleotide polymorphisms (SNPs) were identified on chromosome 14. Additional research is needed to confirm the clinical significance of these findings; however, they provide an opportunity to explore the role of pharmacogenomic profiles in managing cancer treatment-related symptoms (Offit & Robson, 2010).

Emerging evidence suggests that deficient levels of vitamin D also may be associated with AI-related musculoskeletal symptoms. A significant inverse relationship between muscle pain and serum 25-hydroxyvitamin D (25[OH]D) ($p < 0.05$) had been reported (Waltman et al., 2009) and, similarly, women on AI therapy with adequate serum vitamin D levels reported less joint pain compared to women with lower serum levels (Khan et al., 2010; Prieto-Alhambra et al., 2011). The results of those studies suggest that assessment of vitamin D is important and correction of vitamin D deficiency with supplementation is recommended. In adddition, vitamin D is critical for bone health and should be monitored in survivors who are at risk for bone loss, such as women on AI therapy.

Evidence from clinical, radiologic, biologic, and genetic perspectives on AI-related musculoskeletal symptoms either present or exclude explanations of the possible mechanism. Markers for inflammation and autoimmune disease suggest a low association among the autoimmune process and AI-related musculoskeletal symptoms. However, studies support the role of estrogen on AI-related musculoskeletal symptoms either through ER-β found in synovial issues or regulation of IGF. In addition, the identified SNPs on chromosome 14 encourage additional research in genetics for a better understanding of AI-related musculoskeletal symptoms.

Assessment of Women on Aromatase Inhibitor Therapy

As more women receive AI therapy and experience AI-related musculoskeletal symptoms, clinicians must accurately assess the musculoskeletal system. The first step is to educate women of the potential that they may develop musculoskeletal symptoms during their AI treatment. Monitor women for

symptom distress from the onset of AI prescription so that interventions can be implemented in a timely fashion. However, distinguishing preexisting musculoskeletal symptoms from AI-related musculoskeletal symptoms is important (Jones et al., 2007). Bone is one of the highly metastasized sites for breast cancer, and symptoms of bone metastasis include pain, pathologic fractures, spinal compression, and hypercalcemia (Guise, Brufsky, & Coleman, 2010). A thorough assessment of the musculoskeletal system is critical to distinguish AI-related musculoskeletal symptoms from bone metastasis so that appropriate treatment approaches can be determined.

Prior to starting treatment, evaluate the patient's body mass index, history of arthritic and musculoskeletal conditions, his or her level and type of routine physical activity, and the level of serum ionized calcium and 25(OH)D. The oncologist or oncology nurse practitioner should perform a comprehensive physical examination of the musculoskeletal system to document baseline function and any existing problems, which should include the shoulder, elbow, wrist, hands, spine, hip, knee, ankle, and feet.

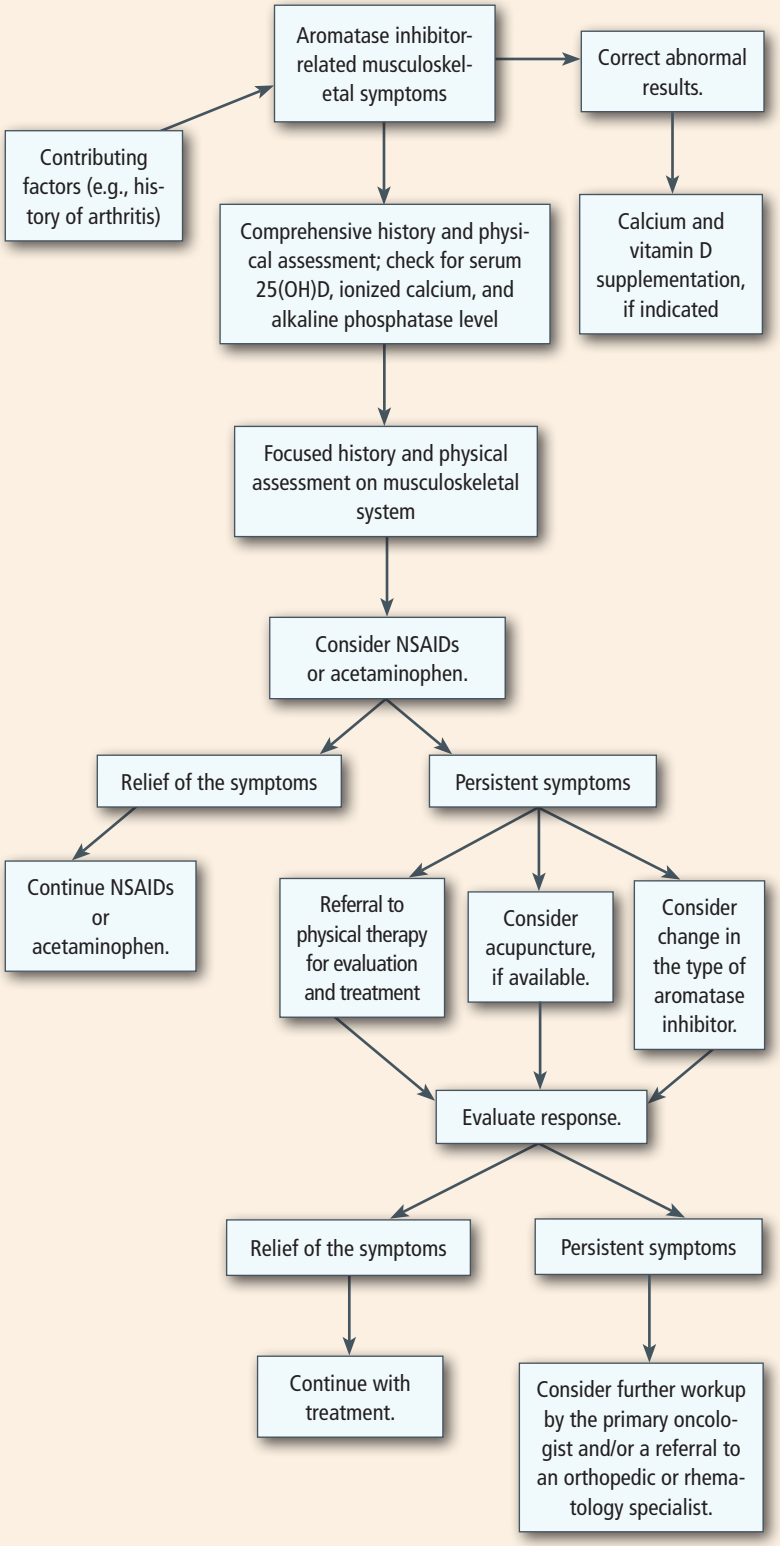
Evidence-Based Management

Although a variety of pharmacologic approaches have been evaluated clinically (Dent, Gaspo, Kissner, & Pritchard, 2011), evidence is limited for recommending a specific management strategy to women with symptomatic AI musculoskeletal complaints. The patient's level of symptom distress, degree of impairment from symptoms, and physical ability need to be integrated into potential management choices.

Preliminary evidence suggests a potential role for adequate serum level of vitamin D in AI-related musculoskeletal symptoms (Khan et al., 2010; Prieto-Alhambra et al., 2011; Waltman et al., 2009). Assessment of serum vitamin D and correction of vitamin D deficiency should be considered for all women on AIs, with or without symptoms related to bone health.

Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opiates have been used clinically (Crew, Greenlee, et al., 2007; Henry et al., 2008; Presant et al., 2007). Although the evidence fails to clearly identify the cause for inflammation in AI symptoms, the data on changes in tendons and surrounding tissues support consideration of a trial of NSAIDs or acetaminophen for symptom relief. Side effects of NSAIDs, particularly adverse gastrointestinal effects, must be considered when choosing those drugs for management. Opiates are not indicated for AI musculoskeletal symptoms, other drugs include tramadol and oral and topical diclofenac; data do not exist to indicate potential effectiveness of those drugs.

Individualized exercise programs can improve range of motion, muscle strength, pain, and balance, and, therefore, benefit women with general musculoskeletal and joint disorders (Millar, 2009). Exercise was reported by women to manage AI-related joint symptoms (Crew, Greenlee, et al., 2007); however, a



25(OH)D—25-hydroxyvitamin D; NSAIDS—nonsteroidal anti-inflammatory drugs

FIGURE 2. Evidence-Based Algorithm for Assessment and Management of Aromatase Inhibitor-Related Musculoskeletal Symptoms

specific scientific rationale for AI symptom relief with exercise or for the effectiveness of exercise in reducing AI symptoms has not been established. Despite this, exercise has multiple physiologic and psychologic benefits in women with breast cancer and referral to an exercise program or physical therapist may be beneficial for women with AI symptom distress. Many women with moderate-to-severe AI musculoskeletal symptom distress discontinue routine physical activity. Therefore, a physical therapy referral may provide the woman with a complete evaluation and an individualized plan to maximize function and potentially reduce symptom distress.

Acupuncture has been used as a nonpharmacologic intervention for various conditions, including musculoskeletal symptoms. Acupuncture has a short-term analgesic effect in musculoskeletal pain, and patients with knee osteoarthritis reported less pain when acupuncture was used as adjunctive therapy with conventional treatments (Christensen et al., 1992; Ezzo et al., 2001; Takeda & Wessel, 1994). Based on the studies in noncancer populations, the efficacy and safety of acupuncture in reducing AI-related joint symptoms were evaluated in a pilot study and a randomized clinical trial (Crew, Capodice, et al., 2007; Crew et al., 2010). Twenty-one women who experienced ongoing pain and stiffness in one or more joints after initiation of AI therapy were randomized to either acupuncture followed by observation or observation followed by acupuncture (Crew, Capodice, et al., 2007). The acupuncture intervention was designed as a 30-minute session twice a week for six weeks. Patients in the two groups who received acupuncture for six weeks reported decreased mean worst pain ($p = 0.01$), pain severity ($p = 0.02$), and pain-related interference ($p = 0.02$). Symptoms associated with OA of the knees or hips improved ($p = 0.04$), as did self-reported physical well-being ($p = 0.03$).

Subsequently, the same group of investigators conducted a randomized, sham-controlled acupuncture intervention (Crew et al., 2010). Thirty-eight women were randomly assigned to either true acupuncture ($n = 20$) or sham acupuncture group ($n = 18$). The true acupuncture group received acupuncture protocol consisting of a standardized set of acupuncture points for 30 minutes twice a week for six weeks, and the sham group received superficial needle insertion at body locations not recognized as true acupoints. Participants in the true acupuncture group had less pain ($p = 0.002$), less pain severity ($p < 0.001$), less pain-related interference ($p = 0.002$), and improved physical well-being ($p = 0.03$) compared to participants in the sham acupuncture group. Although the data suggest a role for acupuncture, the effectiveness of acupuncture in pain relief contradicts other reviews' negative, positive, and inconclusive findings (Ernst, Lee, & Choi, 2011; Hall, 2011). Adverse effects have also been documented, including infection and local trauma, which may relate to the experience and skill of the acupuncture practitioner (Ernst et al., 2011). Therefore, if acupuncture is considered, establishing the credibility of the provider is essential.

Correction of vitamin D insufficiency and a trial of NSAIDs or acetominophen is a reasonable initial management approach, followed by a physical therapy consult (see Figure 2). If a patient continues to have moderate to severe AI musculoskeletal complaints, particularly if the symptoms impair function and valued everyday life activities or risk adherence to adjuvant AI therapy, oncologists may consider switching to a different AI. AIs have comparable survival benefits (Henry & Stearns, 2010), and data suggest musculoskeletal symptoms may improve by switching to an alternate AI (Briot et al., 2010). If symptoms persist, ongoing evaluation is warranted and may include imaging studies to assess for fracture, bone metastases (axial, lower and upper extremities), progression of significant degenerative joint disease, tendon rupture, and ligament injury.

Implications for Practice

- A musculoskeletal system assessment should be performed prior to aromatase inhibitor (AI) therapy to document function and any preexisting symptoms, and should include serum calcium and vitamin D levels.
- For women who report AI-related musculoskeletal complaints, healthcare professionals should consider a trial of nonsteroidal anti-inflammatory drugs or acetaminophen as a first-line approach for symptom management.
- Physical therapy, acupuncture, change of AIs, and referral to orthopedics also may be considered depending on the symptoms and patient preferences.

Conclusion

Third generation AIs provide improved disease-free survival for postmenopausal women with hormone-responsive breast cancer; however, 33%–50% of those patients report moderate to severe musculoskeletal symptoms, which contributes to the 10%–15% of women who discontinue their therapy (Henry & Stearns, 2010). AI-related musculoskeletal symptoms also contribute to poorer quality-of-life outcomes.

A thorough musculoskeletal assessment can help guide clinical decision making for the best individual management approach. Currently, little evidence exists for effective management of AI-related musculoskeletal symptoms. Randomized clinical trials are needed to establish effective interventions for AI-related musculoskeletal symptoms. Meanwhile, providers need to manage symptoms with the best available evidence to minimize symptom distress and maximize adherence to AI therapy.

References

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.

Burstein, H.J., Prestrud, A.A., Seidenfeld, J., Anderson, H., Bulchholz, T.A., Davidson, N.E. . . . Griggs, J.J. (2010). American Society of Clinical Oncology clinical practice guideline: Update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. *Journal of Clinical Oncology, 28,* 3748–3796.

Christensen, B.V., Iuhl, I.U., Vilbek, H., Bulow, H.H., Dreijer, N.C., & Rasmussen, H.F. (1992). Acupuncture treatment of severe knee

osteoarthrosis. A long-term study. *Acta Anaesthesiologica Scandinavica, 36,* 519–525. doi:10.1111/j.1399-6576.1992.tb03511.x

Crew, K.D., Capodice, J.L., Greenlee, H., Apollo, A., Jacobson, J.S., Raptis, G., . . . Hershman, D.L. (2007). Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. *Journal of Cancer Survivorship, 1,* 283–291.

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.

Dent, S.F., Gaspo, R., Kissner, M., & Pritchard, K.I. (2011). Aromatase inhibitor therapy: Toxicities and management strategies in the treatment of postmenopausal women with hormone-sensitive early breast cancer. *Breast Cancer Research Treatment*, *126,* 295–310. doi:10.1007/s10549-011-1351-3

Dietrich, W., Haitel, A., Holzer, G., Huber, J.C., Kolbus, A., & Tschugguel, W. (2006). Estrogen receptor-beta is the predominant estrogen receptor subtype in normal human synovia. *Journal of the Society for Gynecologic Investigation, 13,* 512–517.

Din, O.S., Dodwell, D., Wakefield, R.J., & Coleman, R.E. (2010). Aromatase inhibitor-induced arthralgia in early breast cancer: What do we know and how can we find out more? *Breast Cancer Research and Treatment, 120,* 525–538.

Dizdar, O., Ozcakar, L., Malas, F.U., Harputluoglu, H., Bulut, N., Aksoy, S., . . . Altundag, K. (2009). Sonographic and electrodiagnostic evaluations in patients with aromatase inhibitor-related arthralgia. *Journal of Clinical Oncology, 27,* 4955–4960.

Dowsett, M., Cuzick, J., Ingle, J., Coates, A., Forbes, J., Bliss, J., . . . Peto, R. (2010). Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *Journal of Clinical Oncology, 28,* 509–518. doi:10.1200/JCO.2009.23.1274

Ernst, E., Lee, M., & Choi, T. (2011). Acupuncture: Does it alleviate pain and are there serious risks? A review of reviews. *Pain, 152,* 755–764. doi:10.1016/j.pain.2010.11.004

Ezzo, J., Hadhazy, V., Birch, S., Lao, L., Kaplan, G., Hochberg, M., & Berman, B. (2001). Acupuncture for osteoarthritis of the knee: A systematic review. *Arthritis and Rheumatism, 44,* 819–825. doi:10.1002/1529-0131(200104)44:4<819::AID-ANR138>3.0.CO;2-P

Fernihough, J.K., Richmond, R.S., Carlson, C.S., Cherpes, T., Holly, J.M., & Loeser, R.F. (1999). Estrogen replacement therapy modulation of the insulin-like growth factor system in monkey knee joints. *Arthritis and Rheumatism, 42,* 2103–2111.

Freedman, R.A., & Winer, E.P. (2010). Adjuvant therapy for postmenopausal women with endocrine-sensitive breast cancer. *Breast, 19,* 69–75. doi:10.1016/j.breast.2009.11.009

Guise, T.A., Brufsky, A., & Coleman, R.E. (2010). Understanding and optimizing bone health in breast cancer. *Current Medical Research and Opinion, 26*(Suppl. 3), 3–20.

Hall, H. (2011). Acupuncture claims punctured: Not proven effective for pain, not harmless. *Pain, 152,* 711–712.

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., Giles, J.T., Ang, D., Mohan, M., Dadabhoy, D., Robarge, J., . . . Clauw, D.J. (2008). Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. *Breast Cancer Research and Treatment, 111,* 365–372. doi:10.1007/s10549-007-9774-6

Henry, N.L., & Stearns, V. (2010). One size does not fit all: Quality of life during adjuvant aromatase inhibitor therapy. *Breast Cancer Research and Treatment, 125,* 751–753.

Ingle, J.N., Schaid, D.J., Goss, P.E., Liu, M., Mushiroda, T., Chapman, J.A., . . . Weinshilboum, R.M. (2010). Genome-wide associations and functional genomic studies of musculoskeletal adverse events in women receiving aromatase inhibitors. *Journal of Clinical Oncology, 28,* 4674–4682. doi:10.1200/JCO.2010.28.5064

Jones, S.E., Cantrell, J., Vukelja, S., Pippen, J., O'Shaughnessy, J., Blum, J.L., . . . Asmar, L. (2007). Comparison of menopausal symptoms during the first year of adjuvant therapy with either exemestane or tamoxifen in early breast cancer: Report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. *Journal of Clinical Oncology, 25,* 4765–4771. doi:10.1200/JCO.2007.10.8274

Josefsson, M.L., & Leinster, S.J. (2010). Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for estrogen sensitive early breast cancer in post-menopausal women: Meta-analyses of monotherapy, sequenced therapy, and extended therapy. *Breast, 19,* 76–83. doi:10.1016/j.breast.2009.12.010

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. doi:10.1007/s10549-009-0495-x

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

Miaskowski, C., Shockney, L., & Chlebowski, R.T. (2008). Adherence to oral endocrine therapy for breast cancer: A nursing perspective. *Clinical Journal of Oncology Nursing, 12,* 213–221.

Millar, A. (2009). Exercise prescription for people with arthritis. In American College of Sports Medicine (Ed.), *ACSM's resources manual for guidelines for exercise testing and prescription* (6th ed., pp. 661–665). Philadelphia, PA: Lippincott Williams and Wilkins.

Morales, L., Pans, S., Paridaens, R., Westhovens, R., Timmerman, D., . . . Neven, P. (2007). Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: Associated tenosynovial changes on magnetic resonance imaging. *Breast Cancer Research and Treatment, 104,* 87–91. doi:10.1007/s10549-006-9394-6

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

Offit, K., & Robson, M.E. (2010). New pharmacogenomic paradigm in breast cancer treatment. *Journal of Clinical Oncology, 28,* 4665–4666. doi:10.1200/JCO.2010.31.2926

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 nonclinical trial patients. *Clinical Breast Cancer, 7,* 775–778.

Prieto-Alhambra, D., Javaid, M.K., Servitja, S., Arden, N.K., Martinez-Garcia, M., Diez-Perez, A., . . . Nogues, X. (2011). Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: A prospective cohort study. *Breast Cancer Research and Treatment, 125,* 869–878. doi:10.1007/s10549-010-1075-9

Sugamata, N., Koibuchi, Y., Iino, Y., & Morishita, Y. (1999). A novel aromatase inhibitor, vorozole, shows antitumor activity and a decrease of tissue insulin-like growth factor-I level in 7, 12-dimethylbenz[a]anthracene-induced rat mammary tumors. *International Journal of Oncology, 14,* 259–263.

Takeda, W., & Wessel, J. (1994). Acupuncture for the treatment of pain of osteoarthritic knees. *Arthritis Care and Research, 7,* 118–122. doi:10.1002/art.1790070304

Vanderschueren, D., van Herck, E., Nijs, J., Ederveen, A.G., De Coster, R., & Bouillon, R. (1997). Aromatase inhibition impairs skeletal modeling and decreases bone mineral density in growing male rats. *Endocrinology, 138,* 2301–2307.

Waltman, N.L., Ott, C.D., Twiss, J.J., Gross, G.J., & Lindsey, A.M. (2009). Vitamin D insufficiency and musculoskeletal symptoms in breast cancer survivors on aromatase inhibitor therapy. *Cancer Nursing, 32,* 143–150. doi:10.1097/01.NCC.0000339262.44560.92

Zhang, Y., McAlindon, T.E., Hannan, M.T., Chaisson, C.E., Klein, R., Wilson, P.W., & Felson, D.T. (1998). Estrogen replacement therapy and worsening of radiographic knee osteoarthritis: The Framingham study. *Arthritis and Rheumatism, 41,* 1867–1873.

For Exploration on the Go

Access information from the San Antonio Breast Cancer Symposium on the use of vitamin D to relieve musculoskeletal pain caused by treatment with an aromatase inhibitor by opening a barcode scanner on your smartphone. Point your phone at the code and take a photo. Your phone will link to the content automatically.

Retrieve this content at www.medpagetoday.com/MeetingCoverage/SABCS/17546.

Receive Continuing Nursing Education Credits

Receive free continuing nursing education credit* for reading this article and taking a brief quiz online. To access the test for this and other articles, visit http://evaluationcenter.ons.org/Login.aspx. After entering your Oncology Nursing Society profile username and password, select CNE Tests and Evals from the left-hand menu. Scroll down to *Clinical Journal of Oncology Nursing* and choose the test(s) you would like to take.

* The Oncology Nursing Society is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's COA.