

**FAST FACTS AND CONCEPTS #402**  
**AROMATASE INHIBITOR ASSOCIATED MUSCULOSKELETAL SYMPTOMS**  
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**Background:** Breast cancer is the leading cause of cancer in the United States (1). It is estimated that 84% of breast cancers are hormone positive and may benefit from treatment with estrogen inhibition (2). Aromatase inhibitors (AIs) prevent the production of androgens to estrogen by blocking an enzyme called aromatase. There are three AIs used in the United States: anastrozole (Arimidex), exemestane (Aromasin), and letrozole (Femara). While AIs play a significant role in preventing recurrence and treating metastatic disease (3), many experience aromatase inhibitor associated musculoskeletal symptoms (AIMSS). Incidence of AIMSS may be as high as 50-82% (4). When combined with other recognized adverse effects (cost, pill burden, weight gain, decreased libido, diarrhea, depression), AIMSS may compel many patients to discontinue AI therapy (4-7). While the mechanism of action is not entirely clear, there is emerging evidence that estrogen is chondroprotective; therefore, reducing estrogen levels may lead to AIMSS via cartilage loss and an increase in inflammatory cytokines (7,8).

**Presentation and Diagnosis of AIMSS:** The primary symptoms are arthralgias, joint stiffness, and tendinopathies; AIs are not known to cause neuropathies. Arthralgias may occur anywhere but most commonly occur in the legs, lower back, hands, and wrists (10). Tendinopathies commonly occur in the wrist/hand area and can manifest as de Quervain's tenosynovitis, trigger fingers, or carpal tunnel syndrome. A possible presenting sign is a wedding ring that no longer fits due to finger swelling. AIMSS symptoms usually start 6-8 weeks after AI initiation and resolve or improve within 2-4 weeks of discontinuation (11). While non-validated criteria for diagnosis are available (12), the presence of stereotypical symptoms within the appropriate time frame should be enough for diagnosis.

**Treatment:** Often cancer specialists try to palliate AIMSS, so that patients can continue AI therapy. Hence, referral to palliative care specialists or pain management specialists may be pursued in the hopes the patient can remain on AI therapy. Appropriate palliative treatment should consider whether AIMSS symptoms are focal or diffuse.

- **Focal symptoms** most often occur in the hand or wrist. Conservative management includes NSAIDs, icing, splinting (thumb spica splint for de quervain's and neutral hand splint for carpal tunnel syndrome), and a course of occupational therapy. Refractory symptoms may respond to corticosteroid injections (13), usually performed by rheumatologists, orthopedic surgeons, physiatrists, or sports medicine physicians.
- **Diffuse symptoms** require a systemic approach with a combination of pharmacologic therapy and cardiovascular exercise.
  - Mild symptoms: consider NSAIDs and/or 2-3 grams per day of acetaminophen (4,14).
  - Patients with moderate to severe symptoms and/or concomitant depression should be considered for duloxetine (starting at 30 mg daily with titration to 60 mg daily after 1 week) (14).
  - All patients should participate in a regular exercise program of 30 minutes five days per week of moderate intensity cardiovascular exercise in addition to two days a week of resistance training which has been shown to significantly reduce pain scores (15).
  - Alternative treatments options to consider include a short course of systemic steroids (e.g. prednisone 5 mg PO for 1 week) or acupuncture (16,17).
  - Opioids have not been studied for AIMSS but could be considered in refractory cases and/or patients with a limited prognosis.

**When should AI therapy be modified for AIMSS?** Oncologists may consider rotation to a different AI or a different type of endocrine therapy if there is an equally effective systemic cancer treatment that is in line with the patient's goal of care. In cases of widespread visceral disease with limited life expectancy, cessation of AI and systemic cancer treatment in general may be warranted. Palliative care and generalist clinicians should involve oncologists in these decisions considering the prognostic complexities involved.

**Summary:**

- Have a strong index of suspicion for arthralgias/stiffness within 1-2 months of initiating AI therapy

- Consider whether symptoms are focal vs diffuse and if non-pharmacologic management may be better indicated
- Patients with AIMSS and a limited life expectancy from widespread metastases should discuss treatment options with their oncologist including rotation or cessation of treatment.

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**Version History:** First electronically published in July 2020; originally edited by Sean Marks MD

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**Conflicts of Interest:** Nothing to disclose

**Fast Facts and Concepts** are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a

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