

Treatment Modalities for Aromatase Inhibitor-Associated Musculoskeletal Syndrome (AIMSS): A Scoping Review of Prospective Treatment Studies

Justin Andrew Bobo¹, Barbara Lubrano², Raul Rosario-Concepcion³, Alejandra Cuartas-Abril², Pooja Advani⁴, Saranya Chumsri^{4,5}, Barbara K Bruce²

¹Department of Molecular Pharmacology & Experimental Therapeutics, Mayo Clinic, Rochester, MN, USA; ²Department of Psychiatry & Psychology, Mayo Clinic, Jacksonville, FL, USA; ³Miami Neuroscience Institute, Baptist Health, Miami, FL, USA; ⁴Department of Medical Oncology, Mayo Clinic, Jacksonville, FL, USA; ⁵Department of Medicine, Mayo Clinic, Jacksonville, FL, USA

Correspondence: Barbara K Bruce, Department of Psychiatry and Psychology, Mayo Clinic, Florida, 4315 Pablo Oaks Court, Jacksonville, FL, 32224, USA, Tel +1 (904) 953-7286, Fax +1 (904) 953-0461, Email bruce.barbara@mayo.edu

Abstract: Aromatase inhibitors (AI's) are effective adjuvant treatments for postmenopausal patients with hormone receptor-positive breast cancer. However, AIs are often associated with diffuse joint and muscle pain, referred to as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), the symptoms of which are associated with negative impacts and reduced adherence to AI therapy. As more interventions for AIMSS continue to be investigated, a scoping review is needed to survey and summarize the types of interventions and outcomes assessed in studies conducted to date, which may help identify areas needing attention or additional focus in future research. Online databases were searched (from inception to January 8, 2025) to identify 74 reports from prospective studies of interventions for AIMSS pain, stiffness, or interference with functioning. Such interventions were classified as pharmacological (14 reports), complementary/alternative (43 reports), or rehabilitative (17 reports). Included papers required the presence of AIMSS symptoms at enrollment. Several interventions were deemed promising for reducing AIMSS symptoms based on positive results from individual reports, including duloxetine (3 reports from 2 studies), vitamin B12 (2 reports), vitamin D (2 reports), calcitonin (1 report), prednisolone (1 report), glucosamine and chondroitin (1 report), various mind-body (14 reports from 12 studies) and traditional medicine interventions (3 reports), and switching to another AI (1 report). Many positive findings were from uncontrolled studies or were from single studies that await replication in independent cohorts, and no studies focused on structured psychological interventions. The durations for all reviewed studies were brief relative to the expected 5–10-year course of AI therapy. Intervention effects on a wide range of outcomes were studied, including pain or stiffness (70 reports), functioning/disability (34 reports), quality of life (37 reports), mental health symptoms (25 reports), pain self-efficacy (4 reports), and AI persistence (3 reports). However, intervention effects on other important endpoints such as cancer recurrence, survival, healthcare utilization/costs, and caregiver experiences are unclear. The knowledge gaps and limitations identified in this scoping review constitute areas in urgent need of further research and attention.

Keywords: aromatase inhibitor-associated musculoskeletal syndrome, AIMSS, aromatase inhibitors, breast cancer, pain management, musculoskeletal symptoms

Introduction

Breast cancer is the most common type of cancer among postmenopausal women, with approximately 1.4 million diagnosed cases worldwide in 2018, accounting for over 490,000 deaths.¹ The early detection of breast cancer increases the odds of a curative outcome with surgery.^{2,3} Following surgery, adjuvant therapy is often required to decrease the risk of breast cancer recurrence and increase long-term survival.⁴ For post-surgical patients with early-stage hormone-

sensitive breast cancer, aromatase inhibitors (AIs) are effective for reducing the risk of cancer recurrence and early mortality and are considered first-line adjuvant treatments.^{5,6}

Unfortunately, about 46% of AI-treated patients report diffuse joint and muscle pain after starting treatment,⁷ referred to as AI-associated musculoskeletal syndrome (AIMSS). AIMSS-related pain can be quite severe, so much so that it is a leading risk factor for premature discontinuation of adjuvant AI treatment.⁸ An estimated 32–50% of patients are only partially adherent to AI treatment and 30% discontinue AIs altogether after 12 months due to pain from AIMSS.⁹ The importance of this point rests on the expectation that adjuvant treatment with AIs will last 5–10 years, depending on the patient's risk factors for cancer recurrence. Furthermore, although estimates may vary, the preventive effects of AIs may confer an average societal cost savings of over \$17 million (in 2011 USD),¹⁰ suggesting the possibility of very high economic impacts of early AI discontinuation and consequent exposure to increased risk of breast cancer relapse and recurrence. The effective management of AIMSS-associated pain may thus increase the odds of persistence on AI therapy, preserving its preventive effects on cancer recurrence and its survival-promoting benefits while generating associated economic savings.

The pathophysiology for AIMSS is unknown, which has limited efforts at developing therapeutic interventions. Currently, there is no established treatment for AIMSS. However, several interventions have been tested that map to at least four major etiological hypotheses for AIMSS: (a) estrogen depletion,^{9,11,12} (b) activation of inflammatory and/or autoimmune pathways,^{13,14} (c) alteration of vitamin D activity,^{15–17} and (d) centrally mediated pain.¹⁸

Previous reviews have focused on specific interventions for AIMSS such as acupuncture and physical activity.^{19–22} The most recent systematic review of the broader spectrum of therapeutics for AIMSS focused on systemic interventions, only two of which were included for meta-analysis due to methodologic heterogeneity and unavailable data.²³ The level of evidence was rated as “very uncertain”, thus limiting the ability to provide evidence-based treatment recommendations. Not surprisingly, and despite published guidelines, the management of AIMSS remains driven primarily by expert opinion or practice experience.²⁴

This situation may be expected to change with the accumulation of high-quality evidence. As more interventions continue to be investigated, an updated review is needed to complement prior research syntheses by surveying and summarizing the types of evidence and the scope of interventions and outcomes being studied for (or applied to) AIMSS, including from unpublished (grey literature) sources. There is also an ongoing need to highlight important knowledge gaps as a potential guide for future research. The following research questions were formulated as they pertain to published and unpublished prospective intervention research for AIMSS: (1) What types of treatments have been studied?; (2) What types of outcomes have been focused on?; and (3) What interventions and outcomes need to be researched?

Methods

Inclusion and Exclusion Criteria

A literature search was conducted using PubMed, OVID Medline, EMBASE, SCOPUS, PSYCInfo, and CINAHL (from inception to January 8, 2025) to identify randomized trials, nonrandomized trials, and single-arm prospective (pre/post) studies that included subjects with existing AIMSS and were written in English (see [Supplementary Table 1](#)). ClinicalTrials.gov and CENTRAL registers were also searched to identify grey literature citations. We kept the scope of included studies as broad as possible while restricting the search to prospective intervention studies, given the objectives of this scoping review. Research letters, prospective case series, and conference abstracts reporting prospective findings were included if they specified, at minimum, inclusion criteria, intervention(s), outcome(s), and follow-up duration. Conference abstracts linked to published papers were replaced by the full-length research reports when appropriate.

We excluded papers that did not specify the use of AIs for breast cancer treatment. Given our focus on treatment studies, we also excluded reports of interventions to prevent the onset of AIMSS. We also excluded single case reports, case series numbering fewer than 10 subjects, case series with no statistical analyses, systematic or other reviews, and reports of study protocols.

Population/Participants

This review focused on studies of women with breast cancer receiving any AI treatment who had AIMSS symptoms present at baseline or at the beginning of follow-up. We did not restrict potentially eligible studies to a particular stage of breast cancer. However, we expected that study samples would consist primarily of postmenopausal women with stage I–III hormone receptor-positive (HR[+]) breast cancer.

Interventions

All forms of pain symptom management were considered. Interventions in this report were grouped into three broad categories (pharmacological, complementary/alternative, and rehabilitative), with additional sub-categories as defined in [Table 1](#). Pharmacological interventions included endocrine/hormonal, analgesic/anti-inflammatory, and neuromodulatory interventions, as well as therapeutic switching (from one AI to another). Neuromodulatory medications included centrally active medications (eg, antidepressants, anticonvulsants, gabapentinoids, cannabinoids, etc) and peripherally applied agents (eg, capsaicin, botulinum toxin, etc), consistent with previous research.²⁵ Complementary/alternative interventions included nutritional or supplement-based, physiological or psychophysiological, and traditional medicine therapies.²⁶ Rehabilitative interventions were classified into supervised sport or exercise, physiotherapy (including physical, occupational, and recreational therapies), and psychosocial or educational interventions.

Outcomes

We were interested in exploring the scope of outcomes and assessments across the qualifying intervention studies. Given our primary focus on AIMSS, we were interested in assessing outcome domains (eg, pain, stiffness, interference with functioning, etc) as well as specific outcome measures including objective assessments and subjective ratings. For this report, studies that reported pain, stiffness, and functioning outcomes as a secondary endpoint were still included. Although all reported outcomes from the individual reports were tracked, additional outcomes of particular interest included quality of life, mental health symptoms, additional symptoms (eg, fatigue and menopausal symptoms), sexual functioning, pain self-efficacy, persistence with AI therapy, breast cancer recurrence/survival, healthcare utilization/costs, caregiver experiences, and reporting of adverse events related to the intervention(s).

Report Screening and Data Extraction

Two investigators (JAB, BKB) screened titles and abstracts to exclude irrelevant reports. Three investigators (JAB, BL, BKB) then worked in pairs to complete full-text reviews to exclude reports that did not meet inclusion criteria and extract information on qualifying papers. All studies were classified according to report type (research report, conference abstract), study design (randomized parallel-group trial, randomized cross-over trial, nonrandomized study with at least 2 arms, pre/post study, other design, or design unclear), and intervention type. Additional data elements included participant characteristics (age, breast cancer stage), inclusion and exclusion criteria, AIMSS definition, intervention details (including intervention name, dose/intensity of exposure, and duration of exposure), control conditions, co-interventions (if applicable), study endpoints, study duration, reporting of adverse events, and main findings.²⁷

Synthesis of Results

We grouped studies by intervention type ([Table 1](#)). Within each intervention type, we summarized the specific intervention subtypes, specific interventions studied, outcomes assessed, and main results. These characteristics were summarized in graphical form, whenever possible. Other design features or outcome characteristics of special note were also recorded if such elements added important context to main objectives of this report. Examples included, but were not limited to, specific adaptations to established treatments and characteristics of investigator-developed assessment measures.

Table 1 Categories of Interventions for AIMSS

Major category or subcategory	Definition
Pharmacological interventions	
Endocrine or hormonal	Medication interventions acting on an endocrine system and/or by suppressing, enhancing, or otherwise altering the release or activity (or supplementing) hormones. This category includes bisphosphonates in addition to more traditionally defined endocrine interventions.
Analgesic or anti-inflammatory	Medication interventions acting directly on pain perception at the level of nociception including anti-inflammatory interventions as well as opioid and non-opioid analgesics. The latter includes NSAIDs, COX-2 inhibitors, and corticosteroids.
Neuromodulatory	The interventions for this review are centrally- and peripherally acting medications, not classified as direct analgesics or anti-inflammatory agents, that alter nerve impulse transmission. These include CNS-active medications (antidepressants, anticonvulsants, gabapentinoids, cannabinoids, etc) and peripherally applied pharmaceuticals (capsaicin, botulinum toxin, topical preparations, etc).
Therapeutic switching to alternative AI	Switching from one AI to a different AI, with or without an interim washout period.
Combination	Two or more interventions from the pharmacological intervention sub-categories above (including within the same sub-category) administered simultaneously.
Other pharmacological	Medication interventions not included among the above sub-categories.
Complementary/alternative interventions	
Nutritional or dietary supplements	This sub-category includes herbs/botanicals, vitamins and minerals, probiotics, and dietary supplements.
Traditional medicine	This sub-category includes traditional Chinese medicine, homeopathy, naturopathy, Ayurvedic medicine, and the use of traditional healers.
Physiological or psychophysiological	This sub-category includes tai chi, yoga, acupuncture, massage therapy, musculoskeletal manipulation, qigong, relaxation techniques, and hypnotherapy.
Combination	Two or more interventions from the complementary/alternative intervention sub-categories above (including within the same sub-category) administered simultaneously.
Other complementary/alternative	Complementary/alternative interventions not included among the above sub-categories
Rehabilitative interventions	
Supervised sport or exercise	Supervised sports activities or exercise in any form, excluding interventions classified as complementary/alternative.
Physio-/occupational/recreational therapy	Formal physical therapy, occupational therapy, or recreational therapy intervention(s).
Psychosocial/educational	Psychological or educational interventions, excluding interventions classified as complementary/alternative.
Combination	Two or more interventions from the rehabilitative intervention sub-categories above (including within the same sub-category) administered simultaneously.

Abbreviations: AI, aromatase inhibitor; COX-2, cyclooxygenase-2; NSAID, non-steroidal anti-inflammatory medication.

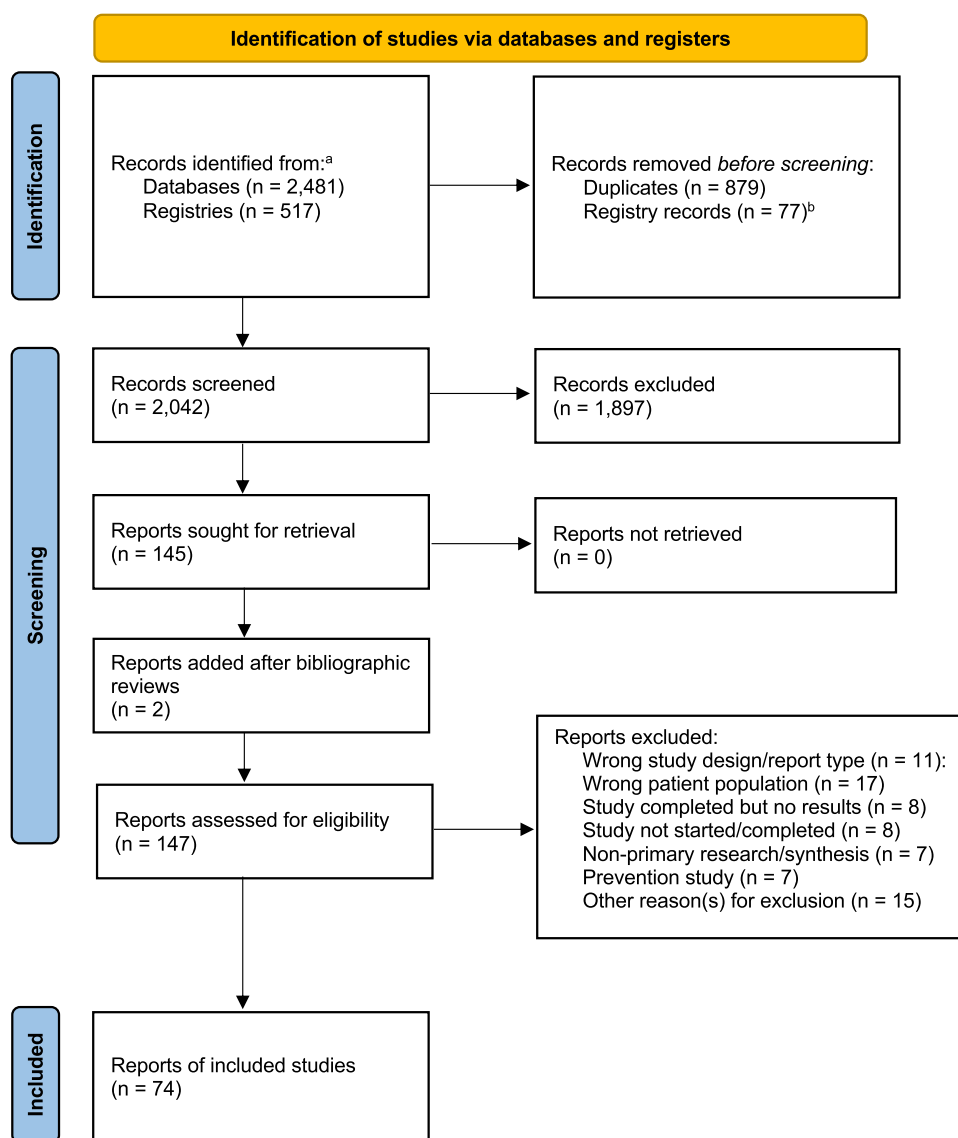


Figure 1 PRISMA flow diagram. ^aThe search date for all databases and clinical trial registries was 08 January 2025. A total of 2998 records were identified (see [Supplementary Table 1](#)) – PubMed, n = 292; Ovid MEDLINE, n = 172; SCOPUS, n = 1387; EMBASE, n = 549; CINAHL, n = 71, PsycINFO, n = 10, CENTRAL, n = 408; ClinicalTrials.gov, n = 63). ^bWithin clinical trials registries, a total of 77 records were removed. Thirty-six records were removed for studies that were recruiting or not yet recruiting (n = 27), withdrawn (n = 15), or in another or unknown status with no results available (n = 4). An additional 42 records of studies listed as complete but with no results available were removed. PRISMA figure adapted from Liberati A, Altman D, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Journal of clinical epidemiology*. 2009;62(10). Creative Commons.¹⁰⁰

Results

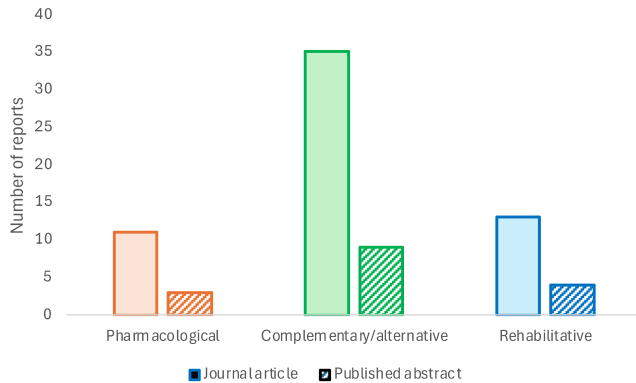
Search Results

The initial search retrieved 2481 records across 6 databases and an additional 517 records from trial registries ([Figure 1](#)). After removing duplicates and non-qualifying studies based on title and abstract screening, 145 records were initially sought for retrieval. Two studies were added after bibliographic review. After applying inclusion and exclusion criteria at full-text review, a total of 74 reports met inclusion criteria, 59 of which were published as journal articles,^{28–85} with 15 reports available as published abstracts ([Figure 2a](#)).^{52,86–99}

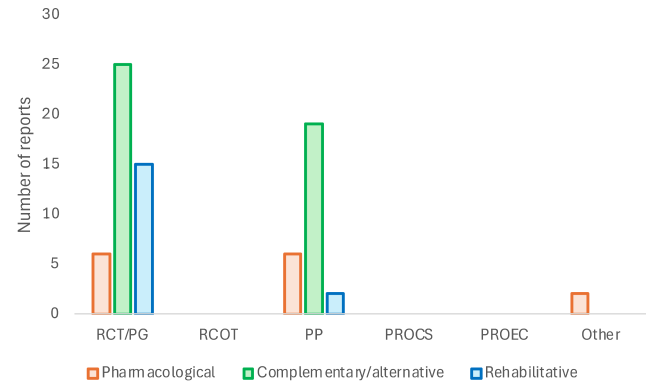
Description of Included Studies

Study design features, study location, key clinical characteristics of enrollees, and main results of the 74 reviewed reports are presented in [Tables 2–4](#), while the inclusion/exclusion criteria and definitions of AIMSS for each report are presented

(A) Report type by intervention group



(B) Study design type by intervention group



(C) Study outcome domains by intervention group

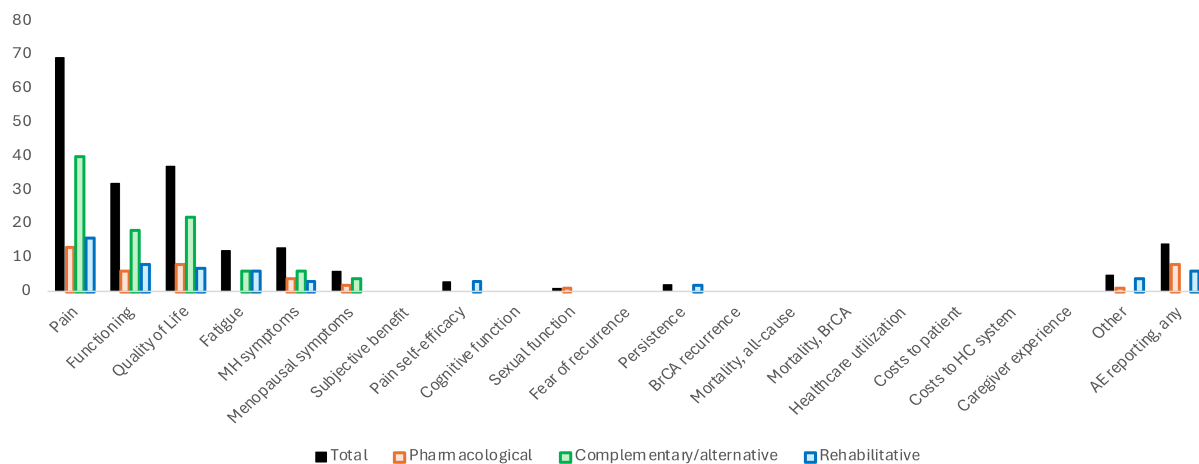


Figure 2 Visual summary of reviewed reports. (A) summarizes the total number of reports by report type (journal article [solid bars], published abstract [striped bars]) within subgroups defined by intervention (pharmacological, complementary/alternative, and rehabilitative). (B) summarizes the number of reports according to study design considering the type of intervention (pharmacological [pink bars], complementary/alternative [green bars], and rehabilitative [blue bars]). (C) summarizes the number of reports that include specific outcome domains, total (black bars) and by intervention type (pharmacological [pink bars], complementary/alternative [green bars], and rehabilitative [blue bars]).

Abbreviations: AE, adverse event; BrCA, breast cancer; PP, pre/post study design; PROCS, prospective case series; PROEC, prospective study with concurrent/external control group; RCOT, randomized cross-over trial; RCT/PG, randomized controlled trial/parallel-group.

in [Supplementary Tables 1–3](#). Six reports were included because they extended the results of other reports reviewed herein or presented additional information on outcomes of interest.^{30,32,33,78,82} Approximately half of the reviewed studies were conducted in the US ($n = 40$ reports), while 11 were conducted in East Asia, 10 in Europe (including the United Kingdom), 3 in Australia, 3 in South America, and the remaining 4 in Turkey, Egypt, and India (primary site could not be identified in 3 reports). Fifteen of the reviewed reports were published only as conference abstracts. The number of participants across studies ranged from 10 to 256 and the mean or median ages of participants ranged from 44.0 to 69.9 years. In one study, 26 out of 29 participants (89.7%) were reported as being <45 years of age.⁷⁴ Follow-up durations ranged from 4 weeks to 12 months.

Most studies enrolled postmenopausal women with Stage I–III, HR[+] breast cancer and required treatment with AIs for at least one month, often longer, as explicit requirements for study enrollment, with either self-reported or clinician-diagnosed joint symptoms that began after starting AI therapy or worsened after AI initiation. Six studies explicitly allowed enrollment of postmenopausal participants with Stage 0 disease.^{32,53,61,62,65,70} Fourteen studies included (or reported having included) patients with a history of prior taxane use. Metastatic breast cancer (Stage IV),

receiving concurrent chemotherapy or radiation therapy, pre-existing arthralgias, recent trauma or surgery to the joints or extremities of interest, and contraindications to the interventions under investigation were common exclusion criteria.

Explicit definitions for AIMSS, including definitions used as inclusion criteria, were provided in most of the included reports (see [Supplementary Tables 2–4](#)), several of which required complaints of arthralgias during AI therapy and a pre-specified threshold of subjective pain intensity measured using pain rating scales or on a 10- or 11-point scale (33 reports). In other cases, the definitions of AIMSS required diagnosed or self-reported arthralgias associated with AI treatment (22 reports) or the presence of arthralgias or other joint symptoms in people taking AIs at enrollment (6 reports).

Most of the reviewed reports were from randomized, parallel-group studies that used mainly placebo or sham controls (43 reports). Twenty-six studies used a single-arm, pre/post study design. Two reports involving complementary/alternative treatments were from randomized cross-over studies^{45,95} and one pharmacological and one rehabilitative intervention study, each, used a non-randomized parallel-group design.^{39,71} As shown in [Figure 2b](#), randomized trials were the predominant study design for reports on complementary/alternative and rehabilitative interventions, while a more even distribution between randomized trials and pre-post study designs was observed for pharmacological interventions. One study enrolled subjects who had discontinued anastrozole due to musculoskeletal symptoms and were willing to take letrozole as part of a prospective switch study.³⁷ An amendment to the protocol for another study allowed patients to switch to an alternative AI if they could not tolerate their originally assigned AI,⁶² thus providing the opportunity to study the effects of a therapeutic switch.

Interventions for AIMSS

A summary of interventions for AIMSS is presented in [Figure 3](#). Most reports focused on the effects of complementary/alternative medicine (CAM) approaches ($n = 43$), followed by rehabilitative ($n = 17$) and pharmacological interventions ($n = 14$). The clinical effects of a wide variety of individual treatments were studied within each of these broad categories. Physiological/psychophysiological interventions were the most common broad subtype of intervention studied (26 reports from 21 studies), while the most investigated single group of treatments was acupuncture, electroacupuncture, or acupressure (14 reports from 12 studies).

As shown in [Tables 2–4](#), several treatments were associated with positive therapeutic effects on various measures of AIMSS symptom intensity, dysfunction owing to AIMSS symptoms, or quality of life measures. In many cases, positive results were from small, uncontrolled studies or single studies needing replication in independent cohorts. For example, multiple randomized trials of complementary/alternative treatments supported the effectiveness of acupuncture,^{45,46,58,59} electroacupuncture,^{68,69} and yoga.^{76,83} However, beneficial effects of tai chi and vitamin B12 supplementation were documented only in single-arm studies^{38,51,53,96} and positive findings for several nutritional/supplemental and traditional medicine interventions (eg, glucosamine and chondroitin, tart cherry extract, other individual dietary supplements, Bionic tiger bone powder, and blue citrus) came only from single reports.^{49,54,63,65,70,77,80,95}

Among the pharmacological interventions, positive effects of calcitonin, prednisolone, furosemide + spironolactone, and sulindac on AIMSS symptoms were documented only in single reports ([Table 2](#)).^{28,64,66,71} Although two reports each suggested possible benefit from the use of cannabinoid-based formulations and from switching AIs,^{37,62,90,99} duloxetine was the only pharmacological intervention with replicated positive findings in a well-powered randomized trial.⁵⁶

For rehabilitative interventions, several supervised exercise approaches were found to be helpful. Although multiple reports documented beneficial effects of various forms of exercise on AIMSS symptoms ([Table 4](#)), the specific techniques or regimens that were applied in the individual reports varied substantially, making it difficult to subdivide exercise interventions into smaller, more homogenous subgroups. For instance, there were 3 reports of the effects of walking for AIMSS symptoms, one of which involved a combination of supervised and independent Nordic walking,⁵⁰ while the remaining two reports focused on low-intensity unsupervised or self-directed walking as main interventions.^{72,73} Other exercise interventions included multimodal regimens that combined resistance training with land-based aerobic exercise,^{30,47,60,89} whole-body vibration combined with exercise,⁴⁸ Pilates combined with circuit-based training or dance,³⁶ aquatic aerobic exercise,³⁹ and unspecified directed exercise.⁹⁸ In one randomized study, participants assigned to the exercise intervention (instead of usual care) could choose to participate in one of three

Table 2 Prospective Studies of Pharmacological Interventions for AIMSS

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Endocrine or Hormonal Interventions									
Birrell & Tilley, 2009 ^b	Australia	RCT/PG	Testosterone 80 mg (n = 30) Testosterone 40 mg (n = 30)	Placebo (PBO) (n = 30)	Unspecified	12 weeks	VAS	- No significant androgenic side-effects	- VAS scores reduced (improved) for all groups – 70% for 80 mg testosterone group (p=0.04 vs PBO), 43% for 40 mg testosterone group (p=0.06 vs PBO), and 35% for PBO.
Cathcart-Rake et al, 2021	USA	RCT/PG	Testosterone pellets or Testosterone gel ^c (n = 80)	Placebo pellets or gel ^c (n = 77)	Unspecified	6 months	Average pain rating (0–10-point scale) using the modified BPI-AIA item #3	- No significant differences between groups in hot flash scores or frequencies.	- No significant between-group differences in average joint pain at 3- and 6 months. - No significant differences in proportion of subject reporting a \geq 1-point improvement in BPI-AIA average pain score at 3 months.
Liu et al, 2014	China	RCT/PG	Calcitonin 200 IU + vitamin D 600 mg (n = 42)	Vitamin D 600 mg (n = 40)	Unspecified	3 months	VAS	- Unspecified.	- Significantly greater improvement in VAS scores with calcitonin + vitamin D relative to vitamin D only.
Analgesic or Anti-Inflammatory Medications									
Kubo et al, 2012	Japan	Pre/post	Prednisolone 5 mg (n = 27)	None	Unspecified	2 months	VAS, investigator-developed questionnaire ^d	- Unspecified	- 67% of patients reported improved pain using VAS at 1 week, 63% at 1 month, 52% at 2 months. Differences from baseline were significant at 1 week and 1 month, but not at 2 months. - 41% and 33% of subjects reported amelioration of symptoms at 1- and 2 months, respectively.
Martinez et al, 2022	USA	NRT/PG	Sulindac 150 mg (twice daily) (n = 43)	Observation only (n = 40)	Low-dose aspirin was permitted (\leq 81 mg/day)	12 months	BPI, WOMAC, FACT-G	- Most common adverse effects were grade 1 and 2 nausea, abdominal pain, or reflux; one case each of transient pancreatitis and cerebral hemorrhage (in patient with amyloid angiopathy) occurred as SAE's.	- Significant improvement from baseline with sulindac in WOMAC pain, stiffness, and physical function subscales, but not BPI-SF worst pain scores. - 35% of participants assigned to sulindac with above-median baseline WOMAC total scores experienced \geq 50% improvement in WOMAC and FACT-G total scores. - No significant improvement from baseline in musculoskeletal symptoms or quality of life measures over 12 months in the observation group.

Neuromodulatory Medications									
Henry et al, 2011	USA	Pre/post	Duloxetine 60–120 mg following titration ^d (n = 35 enrolled)	None	Participants taking stable doses of medication for pain ^e at enrollment were allowed to continue them.	8 weeks	BPI, VAS, HAQ, CES-D (depression), Menopause-Specific Quality of Life questionnaire, Hot Flash Related Daily Interference Scale, PSQI	- The most common adverse effects were fatigue, drowsiness, nausea, dry mouth, constipation, and headache.	- 72.4% achieved $\geq 30\%$ decrease in average pain score at 8 weeks. - Of the 23 completers, 21 (91.3%) experienced at least a 2-point absolute decrease in average pain and a mean percent reduction in average pain of 60.9%. - Significant improvement in HAQ, hot flash interference, depression, and sleep scores.
Henry et al, 2018 and Schnell et al, 2021	USA	RCT/PG	Duloxetine 60 mg following titration (n = 127)	Placebo (n = 129)	Unspecified	12 weeks	BPI, WOMAC, M-SACRAH, Global Rating of Change Scale (pain), FACT-ES Trial Outcome Index, PHQ-9 (depression)	- 23.4% of duloxetine-treated subjects reported an adverse event. The most common included fatigue, nausea, headache, dry mouth, muscle aches, hot flashes, insomnia, diarrhea, dizziness, and constipation.	- Significantly greater improvement in average pain score with duloxetine than placebo at each time point (weeks 2–12). - Significantly higher rates of clinically meaningful improvement (≥ 2 point reduction) in pain with duloxetine than placebo at week 6 (68% vs 49%), but not at weeks 2 (52% vs 40%) or 12 (68% vs 59%). - Significant advantages with duloxetine over placebo were documented for BPI worst pain and pain interference scores using the BPI; WOMAC functioning, pain, and stiffness scores; and M-SACRAH scores; functional quality of life and global rating of change scores. - No significant between-group differences in PHQ-9 (depression) scores. - A higher proportion of subjects reported perception of treatment as beneficial with duloxetine than placebo (73.3% vs 41.8%) despite no statistically significant between-group difference FACT-ES scores.

(Continued)

Table 2 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Therapeutic Switching to an Alternative Aromatase Inhibitor									
Briot et al, 2010	France	Pre/post	Switch to letrozole 2.5 mg/day after 1 month washout (n = 179)	None	Patients could continue "minor" analgesics and "moderate" opioids	6 months	Discontinuation of letrozole due to severe musculoskeletal symptoms	- Not reported.	- 72.5% of enrollees were still taking letrozole after 6 months. - 28.5% discontinued letrozole due to musculoskeletal symptoms. - 15.3% reported having no joint pain.
Kadakia et al, 2017	USA	Other ^f	Switch from letrozole to exemestane (n = 34) or from exemestane to letrozole (n = 49)	None	Unspecified	3 months following initiation of second AI	VAS, HAQ, EuroQOL (quality of life), CES-D (depression), HADS-A (anxiety)	- Not reported.	- VAS mean change in pain ratings with first AI and second AI were similar (0.8 vs -0.2), but differences were not significant. - Patients who discontinued their first AI medication reported less negative impacts on functional status, depression, and vasomotor symptoms during treatment with the second AI.
Other Pharmacological Interventions									
Alhanafy et al, 2018	Egypt	Pre/post	Furosemide 20 mg + spironolactone 50 mg (n = 50)	None	Patients could continue NSAIDs, COX-2 inhibitors, and/or bisphosphates	4 weeks	WOMAC (lower extremity pain) and DASH (upper extremity pain)	- Four subjects with morning diuresis that interfered with work, 3 with grade I fatigue, 5 with grade I nausea.	- Significantly improved WOMAC total, pain, functioning, and stiffness scores. - Significantly improved DASH total, functional, and activity scores but no significant improvement in DASH pain score.
Fleege et al, 2024	USA	Pre/post	CBD oral solution ^g , maximum tolerated dose (n = 39)	None	Unspecified	15 weeks	BPI, PROMIS physical function and social roles and activities scales	- Five discontinued due to adverse events; no grade 3–4 toxicities.	- Significantly improved BPI worst pain scores from baseline for all 39 participants. - 60.7% of completers reported improvement in BPI worse pain scores by ≥ 2 points from baseline. - Significant improvements from baseline in PROMIS physical function and participation in social roles and activities scores.

Zhang et al, 2010	China	Pre/post	Thymosin alpha-1 SQ, 1.6 mg	None	Unspecified	4 weeks	BPI, WOMAC, FACT-G, 11-point Likert scale rating subjective pain intensity	- Not reported.	- Significantly improved BPI-SF worst pain, pain severity, and pain-related functional interference scores. - Significantly improved COMAC functional subscale and FACT-G physical well-being scores.
Zylla et al, 2024 ^h	USA	RCT/PG	CBD topical balm, 2210 mg CBD:< 0.3% THC (n = 10)	Delta-9-THC predominant balm, 375 mg THC:< 20 mg CBD (n = 10)	Unspecified	2 weeks	BPI, M-SACRAH, PRO-CTCAE measures	- One subject discontinued due to greasy texture of the balm.	- Improvements in BPI average pain and pain interference scores and M-SACRAH scores were observed in both treatment arms, but statistical comparisons (within and between subjects) were not reported.

Notes: ^a Refers to subjects whose data were analyzed unless otherwise specified; ^b Results were published only in abstract form. ^c Study protocol was amended to allow for the substitution of testosterone topical gel or gel placebo, each applied daily for 6 months. ^d Investigator-developed questionnaire consisted of 6 items assessing to what degree "stiffened joint pain" weighed on the respondent's mind, which joints were affected, the degree their pain intensity when using the VAS, how much joint pain affected the respondent's quality of life, when anastrozole or letrozole treatment was initiated, and when symptoms of arthralgia appeared. ^e Duloxetine was initiated at a dose of 30 mg/day for 7 days, followed by titration to an initial target dose of 60 mg daily for 21 days. Subjects then had the option of continuing the 60 mg/day dose or increasing the dose to 60 mg twice daily. Those who could not tolerate duloxetine 60 mg/day were discontinued from the study. ^f Includes NSAIDs, COX-2 inhibitors, opioids, gabapentin, pregabalin, cyclobenzaprine, or glucosamine chondroitin, if they were being taken at the time of enrollment. Otherwise, subjects could take up to 2 g of acetaminophen daily for pain and up to 325 mg of aspirin daily for cardiac prophylaxis. ^g In original trial, patients were randomized to letrozole or exemestane. An amendment to the protocol allowed patients who could not tolerate their assigned AI to switch to the other study-provided AI. Such patients discontinued the first AI and remained off any AI therapy during a washout period lasting 2–8 weeks. Following washout, patients started treatment with the second AI until discontinuation for any reason during follow-up. ^h The cannabidiol (CBD) oral solution formulation used in this study is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex. ⁱ This trial was listed as active/not recruiting on ClinicalTrials.gov on the literature search date. The information presented in this table was available from a conference abstract (see reference list).

Abbreviations: BPI-AIA, Brief Pain Inventory for Aromatase Inhibitor Arthralgia; CBD, cannabidiol; COX-2, cyclo-oxygenase-2; DASH, Quick Disabilities of the Arm, Shoulder, and Hand scale; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Scale; FACT-G, Functional Assessment of Cancer Therapy-General Scale; HAQ, Health Assessment Questionnaire; NRT/PG, non-randomized clinical trial (parallel-group design); NSAIDs, non-steroidal anti-inflammatory drugs; PSQI, Pittsburgh Sleep Quality Index; PRO-CTCAE, National Cancer Institute Patient Reported Outcomes Common Terminology Criteria for Adverse Events measures; PROMIS, Patient-Reported Outcomes Measurement Information System measures; RCT/PG, randomized controlled trial (parallel-group design); SAE, serious adverse event; SQ, subcutaneous delivery; THC, tetrahydrocannabinol; VAS, pain visual analog scale; WOMAC, Western Ontario and McMaster Universities index.

Table 3 Prospective Studies of Complementary/Alternative Interventions for AIMSS

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Nutritional Intervention or Dietary Supplement									
Arul Vijaya Vani et al, 2016	India	Pre/post	Vitamin D, dosed according to serum 25-OH vitamin D levels (n = 82)	None	Unspecified	12 weeks	HAQ-II	Not reported.	<ul style="list-style-type: none"> - HAQ-II total score improved in subjects with insufficient and deficient serum vitamin D levels. - HAQ-II total scores increased in those with sufficient vitamin D levels (did not receive intervention). - There was a negative correlation between HAQ-II scores and serum vitamin D levels.
Campbell et al, 2018 ^b	USA	Pre/post	Vitamin B12 2500 mcg/day (n = 36)	None	Patients could continue the same analgesic regimen but stopped multi-vitamins or supplements containing vitamin B12.	12 weeks	BPI-SF question 5 (average pain) and question 3 (worst pain), FACT-ES (quality of life)	No significant adverse effects were observed. The most frequent included dry mouth, nausea, diarrhea, and blurred vision.	<ul style="list-style-type: none"> - BPI-SR average pain and worst pain scores improved by 34% and 23%, respectively, at 12 weeks. - No significant changes in FACT-ES scores.
Desideri et al, 2022	Italy	Pre/post	OPERA dietary supplement ^c (n = 46)	None	None allowed	6 months	NCI-CTCAE, VAS, PRAI	- Reported no relevant toxicities.	<ul style="list-style-type: none"> - Significant improvement in arthralgia score using NCI-CTCAE and PRAI. - Improvement in arthralgia symptoms from baseline were also captured using the VAS.

Greenlee et al, 2013	USA	Pre/post	Glucosamine 250 mg + chondroitin 200 mg (n = 40)	None	Participants were permitted to use acetaminophen or ibuprofen.	24 weeks	Self-reported response (using OMERACT-OARSI criteria), BPI-SF, FACT-B/ES, WOMAC, M-SACRAH	- The most common side-effects were headache, nausea, dyspepsia, diarrhea, flatulence, fatigue, and heartburn.	- 46.2% met the criteria for self-reported response at 24 weeks. - Significant improvement in WOMAC and M-SACRAH scores for pain 24 weeks.
Hershman et al, 2015	USA	RCT/PG	Omega-3 fatty acid 3.3g (n = 102)	Placebo (n = 107)	Unspecified	12 weeks	BPI-SF, WOMAC, M-SACRAH, FACT-ES	- Significantly greater reduction in serum triglycerides with omega-3 fatty acid than placebo. - One case each of diarrhea, dyspepsia and pain in the extremity with omega-3 fatty acid. - One case each of arthralgia, pain, peripheral motor neuropathy, and rash with placebo.	- Numerically greater improvement in BPI worst pain scores with omega-3 fatty acid than placebo, but between-group differences were non-significant. - Non-significant between-group differences in 2-point change in BPI worst pain scores (61% vs 57%). - No significant between-group differences in other measures.

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Table 3 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Hershman et al, 2014	USA	RCT/ PG	Omega-3 fatty acid 3.3 g (n = 122)	Placebo (n = 127)	Unspecified	24 weeks	BPI-WP, WOMAC, M-SACRAH, FACT-ES	- 21 subjects developed diarrhea.	- BPI worse pain scores (primary endpoint) improved to numerically greater degree in intervention group compared with placebo; adjusted (baseline scores, osteoarthritis, and taxane use) BPI worse pain scores were similar in both groups at 12 weeks (end of active treatment). - Similar proportion of subjects in active treatment and placebo groups achieved ≥ 2-point improvement in BPI-worst pain scores at 12 weeks.
Kiyomi et al, 2015	Japan	Pre/ post	Vitamin E 150 mg (n = 62 enrolled)	None	Unspecified	Mean 29.8 days	Likert scale with osteoarthropathy scores ranging from 0 (no symptoms) to 3 (worst possible) for stiffness and for low back pain	- No increase in inflammatory biomarkers.	- Osteoarthropathy scores significantly decreased after starting vitamin E.
Martinez et al, 2019	Spain	Pre/ post	Supplement containing EPA, DHA, hydroxy- tyrosol, and curcumin (n = 45)	None	Unspecified	30 days	BPI-SF	- Constipation and abnormal/fish taste were the most common adverse effects. No subjects withdrew from the study due to adverse effects.	- Significant decrease in BPI- SF worst pain, least pain, current pain, and pain severity scores.

Nahleh et al, 2018 ^b	Unspecified	Pre/post	Vitamin B12 2500 mcg (n = 36 enrolled)	None	Unspecified	3 months	BPI-SF	- None reported.	- Significant improvement from baseline for all BPI-SF items.
Rastelli et al, 2011	USA	RCT/PG	Vitamin D2 50,000 IU ^d (n = 21)	Placebo (n = 26)	Unspecified	6 months	FIQ, BPI-SF, HAQ-DI	- No toxicities or significant adverse events were observed in the vitamin D group.	- Significantly greater reduction in pain with active treatment than placebo at 2 months, as measured by FIQ pain and BPI worst pain, average pain, pain severity, and pain interference scores. - No significant between-groups differences were observed at 4- and 6 months (when subjects were switched from weekly to monthly vitamin D3).
Shapiro et al, 2016	USA	RCT/PG	Vitamin D3 4000 IU (n = 57)	Vitamin D3 600 IU (n = 56)	Both groups received calcium carbonate 500 mg.	6 months	BCPT-MS, PROMIS PI-SF, AUSCAN, WOMAC, AI adherence	- The most frequent adverse events were musculoskeletal (18%) and gastrointestinal (17%), with no significant between-group differences.	- No significant between-group differences for any AIMSS outcome measures.
Shenouda et al, 2022	USA	RCT/PG	Tart cherry extract (n = 23)	Placebo (n = 25)	Subjects were asked to refrain from taking new medication to alleviate pain.	6 weeks	VAS	- 2 subjects randomized to active treatment developed diarrhea and were not included in the final analysis.	- Significantly greater percent reduction in pain with active treatment than placebo (34.7% vs 1.4%).

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Table 3 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Traditional Medicine									
Li et al, 2017	China	RCT/PG	Bionic tiger bone powder ^e (n = 34)	Placebo (n = 35)	Unspecified	12 weeks	M-BPI, VAS, FACT-B (quality of life)	- Mild stomach discomfort in 2 bionic tiger bone powder patients and 4 placebo patients.	- Significantly greater improvement in average pain, worst pain, pain interference, stiffness, and VAS scores with bionic tiger bone powder than with placebo.
Massimino et al, 2011 ^b	Unspecified	RCT/CO	Blue citrus (n = 31)	Placebo (n = 31)	Unspecified	3 months	VAS	- None reported.	- At 30 days, VAS score was lower with blue citrus than placebo (3.4 vs 4.7). VAS scores “became more similar” between groups by 90 days. - The blue citrus group experienced an increase in pain when changed to placebo. The opposite did not occur when the placebo group was crossed over to blue citrus. - At study end, the VAS scores were 2.6 for blue citrus and 3.0 for placebo.
Peng et al, 2018	China	RCT/PG	Yishen Jiangu granules (n = 40)	Placebo (n = 37)	Calcium carbonate 600 mg + vitamin D3 125 IU.	3 months	BPI-SF, WOMAC, M-SACRAH, FACT-B (quality of life)	- Possible active treatment-related adverse effects included nausea (10%) and diarrhea (2%).	- Significantly greater improvement in worst pain scores in active treatment group than the placebo group. - Significantly greater improvements were also observed with active treatment for WOMAC and M-SACRAH scores.

Sordi et al, 2019	Brazil	RCT/ PG	<i>Uncaria tomentosa</i> (cat's claw) extract (n = 32)	Placebo (n = 29)	Unspecified	30 days	BPI, VAS, Lequesne (osteoarthritis) scale, DASH, SF- 36 (quality of life)	<ul style="list-style-type: none"> - 2 subjects discontinued AI therapy due to adverse events. - 3 subjects discontinued placebo due to adverse events. 	- No significant between-group differences on any of the outcome measures except VAS pain, where improvement was significantly greater with placebo.
Zhang et al, 2018	China	Pre/ post	Yishen Jiangu granules (n = 34)	None	Calcium 1200 mg and vitamin D3 250 IU supplements were allowed.	12 weeks	BPI, WOMAC, M-SACRAH, FACT-B	<ul style="list-style-type: none"> - Epigastric discomfort, heartburn, hiccup, diarrhea were most common adverse events. - Two patients experienced small decrease in leukocyte count, one patient experienced elevated alanine aminotransferase (ALT) at baseline and 12 weeks 	<ul style="list-style-type: none"> - Significant improvement in BPI-SF worst pain scores, as well as scores on the pain severity and pain interference subscales. - Significant improvement in WOMAC and M-SACRAH scores. - FACT-B physical well-being and functional well-being scores were significantly improved.
Physiological or Psychophysiological Interventions									
Bahcaci et al, 2024	Turkey	RCT/ PG	Progressive relaxation exercise (n = 22)	Advice on relaxation for daily life (n = 22)	Unspecified	6 weeks	BPI, FACT-B, HADS	- None reported.	- Significant improvement from baseline in BPI pain severity and pain interference with active intervention. Pain severity and patient pain experience scores were significantly lower with active treatment than the control condition.

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Table 3 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Bao et al, 2012, 2013, 2014	USA	RCT/ PG	Acupuncture (n = 23)	Sham acupuncture (n = 24)	Unspecified	8 weeks	HAQ-DI, VAS, NSABP menopausal symptoms questionnaire, CES-D, HADS, PSQI, hot flash daily diary, HFRDIS, EuroQoL	- No significant side-effects reported in either study arm.	- No significant between-group differences in reduction of HAQ-DI or VAS scores. - Significantly greater improvement in CES-D scores with acupuncture than sham. - Significant reductions from baseline in HFRDIS, hot flash frequency, and NSABP menopausal symptoms score with acupuncture. - Significant improvement from baseline in EuroQoL, HFRDIS, and NSABP menopausal symptom scores with sham acupuncture.
Barzaghi et al, 2015	Italy	Pre/post	Acupuncture (n = 26)	None	Subjects were evaluated for reduction in use of NSAIDs.	6 weeks	BPI-SF, HAQ-DI, VAS (stiffness), and FACT-G (quality of life)	- No adverse effects reported.	- Significant improvement in BPI-SF worst pain, pain severity, and functional interference scores. - Significant improvement in HAQ-DI and VAS (stiffness) scores. - Significant improvement in FACT-G physical and emotional well-being scores. - NSAID use reduced from 77% at baseline to 42% at end of follow-up.

Cheng et al, 2023 ^b	China	RCT/ PG	Acupressure (n = 8)	Sham acupressure (n = 7) or usual care (n = 6)	Unspecified	6 weeks	Pain, fatigue, sleep disturbance and QOL were assessed but no instruments or scales specified.	- None reported.	- Pain, fatigue and sleep disturbance improved in both the active and sham acupressure groups compared with usual care but no between-group comparisons on any outcomes reached statistical significance.
Crew et al, 2007	USA	RCT/ CO	Acupuncture (n = 21 enrolled)	Delayed acupuncture (n = 21 enrolled)	Unspecified	6 weeks	BPI-SF, WOMAC, FACT-G (well-being)	- 13% of patients rated acupuncture as very painful. No other adverse effects of acupuncture were observed.	- Significant improvement with acupuncture in BPI-SF worst pain, pain severity, and functional interference scores, as well as WOMAC function subscale and FACT-G physical well-being scores.
Crew et al, 2010	USA	RCT/ PG	Acupuncture (n = 20)	Sham acupuncture (n = 18)	Existing NSAIDs or acetaminophen could be continued.	6 weeks	BPI-SF, WOMAC, M-SACRAH, FACT-G, FACT-B, PSFS, Functional sit and reach	- 3 participants rated acupuncture as moderately painful. No other adverse effects of acupuncture were reported.	- Significantly greater improvement in BPI-SF worst pain, pain severity, and pain interference with true acupuncture, compared with sham. - Similar findings for WOMAC and M-SACRAH scores.
Galantino et al, 2012a and 2012b ^b	USA	Pre/ post	Yoga (n = 10)	None	Unspecified	8 weeks	BPI, PSFS, FACT-B, functional sit and reach	- None reported.	- Significant improvement in BPI pain severity and trend for improvement in pain interference. - Significant improvements for functional reach and sit and reach, PSFS, and FACT-B.

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Table 3 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Galantino et al, 2013	USA	Pre/post	Tai chi (n = 12)	None	None	8 weeks	BPI, FACT-B, FACIT-Fatigue, HADS, functional sit and reach, Berg balance scale, timed up and go	- None reported.	- Trend level change in BPI pain severity subscale (p = 0.058). - Significant improvement in HADS anxiety and depression subscales, FACT-B emotional well-being, and FACIT-Fatigue scores.
Gomaa et al, 2022	USA	Pre/post	Tai chi classes by telehealth (n = 39 enrolled)	None	Engagement efforts through social media and text messaging.	12 weeks	WOMAC, BPI, AUSCAN, FSI, HFRDIS, PSQI, CES-D	- None reported.	- Significant improvement from baseline in WOMAC pain, stiffness, and functioning scales. - Significant improvement in BPI, AUSCAN pain, and AUSCAN functioning scales. - Significant improvement in FSI. - Significant improvement in HFRDIS, PSQI, and CES-D.

Hershman et al, 2018, 2021	USA	RCT/ PG	Acupuncture (n = 100)	Sham acupuncture (n = 54) or waitlist control (n = 51)	Unspecified	12 weeks, 52 weeks	BPI-SF, WOMAC, M-SACRAH, FACT-ES, PROMIS PI-SF	<ul style="list-style-type: none"> - Bruising was the most common adverse effect for true acupuncture and sham. - One episode of grade 2 presyncope observed in the true acupuncture group and one episode observed in the sham group. 	<ul style="list-style-type: none"> - Significantly greater reduction in mean BPI worst pain, average pain, pain severity, and worst stiffness scores with true acupuncture than sham acupuncture or waitlist controls at 6 weeks. - At 12 weeks, significantly greater reduction in average pain (but not worst pain, pain severity, pain interference, or worst stiffness), WOMAC, and PROMIS PI-SF scores with true acupuncture than sham. - At 52 weeks, follow up assessments were available for 82.5%-89.8% of randomized subjects. Adjusted mean BPI worse pain scores were significantly lower with true acupuncture than sham acupuncture and waitlist controls. Adjusted pain interference scores were significantly lower with true acupuncture than sham acupuncture but not waitlist controls.
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Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Hershman et al, 2022	USA	RCT/ PG	Acupuncture (n = 110)	Sham acupuncture (n = 59) or waitlist control (n = 57)	Baseline and new pain medications were tracked.	52 weeks	BPI, PROMIS PI-SF, grip strength, Timed Get Up and Go test, pain medication use	- None reported.	- Significantly lower BPI worst pain scores at 52 weeks with true acupuncture compared with sham acupuncture and waitlist controls. - Significantly lower BPI pain interference scores at 52 weeks with true acupuncture than sham acupuncture.
Jacobsen et al, 2016	USA	Pre/post	Yoga (n = 10)	None	Unspecified	12 weeks	BPI-SF, WOMAC, AUSCAN, FSI, HFRDIS, Insomnia Severity Index, CES-D (depression)	- No intervention-related safety issues were encountered.	- Significant improvement in AUSCAN, WOMAC, BPI severity and interference, FSI, and HFRDIS scores. - No significant improvement in CES-D or Insomnia Severity Indices scores.
Leibel et al, 2022	Multiple	Pre/post	Yoga facilitated by social media (n = 26)	None	Unspecified	4 weeks	BPI, DASH, PRAI, WOMAC	- None reported.	- Significant improvement from baseline in all pain and quality of life measures.
Mao et al, 2009	USA	Pre/post	Acupuncture (n = 12)	None	Unspecified	8 weeks	BPI, Brief Fatigue Inventory, PSQI, HADS	- 2 subjects reported mild pain at needling sites that spontaneously resolved.	- Significant improvement in pain severity, stiffness, and joint symptom interference scores.

Mao et al, 2014	USA	RCT/ PG	Electroacupuncture (n = 19)	Sham electroacupuncture (n = 19) or waitlist controls (n = 21)	Waitlist patients could still get acupuncture for reasons other than pain, such as relaxation.	8 weeks	BPI, WOMAC, DASH, Patient Global Impression of Change	- Tingling and numbness reported by 8 subjects during sessions in the electroacupuncture and sham groups, all of which spontaneously resolved without medical intervention.	- Significantly greater improvement in BPI pain severity and pain interference scores with electroacupuncture than sham at 8 weeks (end of treatment) and 12 weeks (4 weeks after end of treatment). - Significantly greater improvement in WOMAC pain, stiffness, and function scores and DASH scores at 8 weeks.
Mao et al, 2021 and Bao et al, 2023	USA	RCT/ PG	Electroacupuncture (n = 145) Auricular acupuncture (n = 143)	Treatment as usual (n = 72)	Analgesic medications allowed	12 weeks	BPI, PROMIS- Global Health, quantitative analgesic medication scores	- Ear pain was most common adverse event in auricular acupuncture group. - Bruising was most common adverse effect in electroacupuncture group.	- Significantly greater reduction in pain severity with electroacupuncture and auricular acupuncture vs treatment as usual. - Electroacupuncture found to be more effective than auricular acupuncture for reducing pain severity.
Oh et al, 2013	Australia	RCT/ PG	Electroacupuncture (n = 14)	Sham electroacupuncture (n = 15)	Usual medication, including pain medication, could be continued as needed.	6 weeks	BPI-SF, WOMAC, FACT-G (quality of life)	- 5 subjects had minor bruising at electroacu- puncture points. - No major adverse effects occurred.	- No significant between- group differences in outcome measures.

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Table 3 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Peppone et al, 2015	USA	RCT/ PG (sub-analysis)	Yoga + Treatment as usual (n = 75)	Treatment as usual (n = 92)	Standard follow-up cares provided by oncologists	4 weeks	Selected questions from the URCC-SI, FACIT Fatigue subscale, and MFSI-SF	- None reported.	- Significantly greater improvement in musculoskeletal symptoms including general pain, muscular aches and total physical discomfort in intervention group than control group.
Tsai et al, 2021	Taiwan	RCT/ PG ^f	Yoga (n = 30)	Massage (n = 30)	Unspecified	6 weeks ^f	WOMAC	- Yoga adverse events included five patients with dizziness, 13 with muscle aches, and 8 with tiredness.	- Yoga intervention resulted in significantly greater reduction in AI-associated knee pain (WOMAC pain score).
Yeh et al, 2017	USA	Pre/post	Auricular acupressure (n = 19)	None	Patients could continue analgesics; change in use of these medications was a study endpoint.	4 weeks	BPI-SF, QuickDASH, WOMAC, PSEQ-2, AES, PROMIS-29 (quality of life), Medication Quantification Scale	- None reported.	- Significant improvement in BPI-SF worst pain, pain intensity, and pain interference scores. - Clinically significant improvement (>30%) in worst pain, pain interference, and improved physical function were observed in 50%, 42%, and 31% of subjects, respectively. - Significant improvement in PSEQ-2 scores.

Other Complementary/Alternative Intervention									
Chan et al, 2017	Australia	RCT/ PG	Pure emu oil (n = 36)	Placebo oil (n = 37)	Patients were allowed to continue or initiate oral analgesics	8 weeks	VAS, BPI (pain severity and interference sub-scales)	- No adverse effects associated with pure emu oil.	- No significant between-group differences in VAS joint pain or BPI pain severity or interference scores. - Significant improvement in Brief Fatigue Inventory and HADS anxiety scores. - There was a non-significant reduction in HADS depression score.

Notes: ^a Indicates the number of subjects whose data were analyzed, unless otherwise specified. ^b Research was published in abstract form and as a full research report. ^c OPERA dietary supplement contains several compounds believed to improve symptoms of osteoarthritis and inflammatory conditions, including alpha lipoic acid 240 mg, Boswellia serrata 40 mg, Methylsulfonylmethane 200 mg, and Bromelain 20 mg. ^d Dosing of vitamin D2 supplementation proceeded according to baseline 25-OH vitamin D levels. Those with baseline 25-OH vitamin D levels of 20–29 ng/mL received either high-dose supplementation (vitamin D2 50,000 IU) weekly for 8 weeks and then monthly for 4 months or placebo. Participants with baseline 25-OH vitamin D levels of 10–19 ng/mL received either high-dose supplementation for 16 weeks and then monthly for 2 months or placebo. ^e Refers to a formula approved by the China Food and Drug Administration for treatment of arthralgias that contains ingredients intended to mimic natural tiger bone (including collagen, analgesic peptide, bone morphogenetic protein, bone growth factors, and polyose). ^f Study subjects were divided into “yoga-first” or “massage-first” groups. All subjects received their initially assigned intervention and were then crossed over to the other intervention (and received the alternate intervention for 6 weeks) with a 2-week rest period in between.

Abbreviations: AES, Acupressure Expectancy Scale; AUSCAN, Australian/Canadian Hand Osteoarthritis Index; BCPS-MS, Breast Cancer Prevention Symptom Scales-MS (musculoskeletal) subscale; BCPT-MS, Breast Cancer Prevention Trial Symptom Scale-Musculoskeletal Subscale; BPI, Brief Pain Inventory; BPI-SF, Brief Pain Inventory-Short Form; CES-D, Center for Epidemiological Studies Depression Scale; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy Fatigue scale; FACT-B, Functional Assessment of Cancer Therapy-Breast; FACT-G, Functional Assessment of Cancer Therapy-General scale; FACT-ES, Functional Assessment of Cancer Therapy-Endocrine Symptoms scale; FACT-G, Functional Assessment of Cancer Therapy-General; FACIT, Functional Assessment of Chronic Illness Therapy scales; FIQ, Fibromyalgia Impact Questionnaire; FSI, Fatigue Severity Inventory; HADS, Hospital Anxiety and Depression Scale; HAQ-DI, Health Assessment Questionnaire Disability Index; HAQ-II, Health Assessment Questionnaire-II; HFRDIS, Hot Flash Related Daily Interference scale; M-SACRAH, Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; M-BPI, Modified Brief Pain Inventory; MDASI, MD Anderson Symptom Inventory; MFSI, Multidimensional Fatigue Symptom Inventory-Short Form; MQS, Medication Quantification Scale; NCI-CTCAE, National Cancer Institute-Common Toxicity Criteria for Adverse Events; NSABP, National Surgical Adjuvant Breast and Bowel Project; OMERACT-OARSI, Outcome Measure in Rheumatology Clinical Trials and Osteoarthritis Research Society International; PRAI, 16-item Patient-Reported Arthralgia Inventory; PROMIS-29, Patient-Reported Outcomes Measurement Information System (PROMIS)-29; PROMIS PI-SF, PROMIS Pain Impact-Short Form; PSEQ-2, two-item Pain Self-Efficacy Questionnaire; PSFS, Patient Specific Functional Scale; PSQI, Pittsburgh Sleep Quality Inventory; QOL, quality of life; QuickDASH, Quick Disabilities of the Arm, Shoulder, and Hand score; RCT/CO, randomized cross-over trial; RCT/PG, randomized controlled trial (parallel-group study); URCC-SI, University of Rochester Cancer Center Symptom Inventory; VAS, pain visual analog scale.

Table 4 Prospective Studies of Rehabilitative Interventions for AIMSS

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Supervised Sport or Exercise									
Barbosa et al, 2021	Brazil	RCT/PG	Pilates (n = 20) Circuit-based exercise (n = 20)	No study intervention (n= 20)	Analgesic medications allowed.	8 weeks	BPI, DASH, Numerical rating pain scale, PSQI	- One participant reported back pain.	- Significant reduction in pain intensity with Pilates, but not with circuit-based exercise and not in the control group. Pain ratings at end of intervention were significantly lower with Pilates than both comparator groups. - Function and sleep measures were significantly improved from baseline in the Pilates group; sleep function was also significantly improved in the circuit-based exercise group.
Boing et al, 2023	Brazil	RCT/PG	Pilates (n = 25) Belly dance (n = 25)	Educational sessions (n = 24)	None specified.	12 months	VAS, FACT-F, PSQI, Perceived Stress Scale, Life Orientation Test, BDI	- Unspecified.	- No significant treatment effects were observed for pain, stress, optimism, or depressive symptoms. - Significant improvement in fatigue scores from baseline noted in all 3 groups.
Cantarero-Villanueva et al, 2013 ^a	Spain	Non-randomized/PG	Aquatic exercise (n = 20)	Wait-list (n = 20)	Paracetamol use mentioned but with unclear distribution between groups.	8 weeks	Pressure pain thresholds, Piper Fatigue Scale	- No adverse events or development of worsening pain was observed.	- Significantly greater increase in pressure pain threshold with intervention (vs wait-list controls).
Crespo-Bosque et al, 2016 ^b	USA	RCT/PG	Supervised exercise ^c	Usual care ^c	None specified.	12 months	WOMAC, QuickDash, pressure pain threshold (wrist, knee) using an algometer	- Unspecified.	- WOMAC and QuickDash scores and pressure pain threshold measures improved with supervised exercise and worsened with usual care.
De Sire et al, 2021	Italy	RCT/PG	Whole body vibration (WBV) + exercise (n = 11)	Sham WBV + exercise (n = 11)	Subjects washed out from prior treatment with analgesics and NSAIDs.	4 weeks	NPRS, WOMAC, QLQ-C30 (quality of life)	- 1 patient in the WBV + exercise group reported nausea after the 1st session of physical exercise plus WBV; however, the subject was able to complete the study.	- Significant improvement on NPRS scores in WBV + exercise group, but not sham WBV + exercise group; between-group differences were non-significant. - WOMAC score increased significantly in both groups. - QLQ-C30 scores improved significantly in both groups, with no significant between-group differences.
DeNysschen et al, 2014	USA	Pre/post	Exercise, individually tailored (n = 26)	None	Unspecified	8 weeks	AIMS-2, MOS SF-36v2 (quality of life)	- No significant adverse effects reported.	- Significant improvement on AIMS-2 pain, physical activity, dexterity, and arm function measures. - No significant improvement in self-care, mobility, and household activities; however, baseline values for these measures were low.

Fields et al, 2016	UK	RCT/PG	Nordic walking (n = 16)	Usual care (n = 20)	Contact from the study team every 2 weeks to check for any pain, injury, or lymphedema	12 weeks	BPI-SF, CES-D (mood), PSEQ (self-efficacy), SF-36 (quality of life)	- 2 participants in the Nordic walking group reported new-onset pain that resolved with physiotherapy.	- Pain symptoms reduced in both the Nordic walking and usual care groups. Study was not powered to investigate between-group differences.
Irwin et al, 2015 and Baglia et al, 2019	USA	RCT/PG	Exercise (n = 61 enrolled)	Usual care (n = 60 enrolled)	Usual care participants were not discouraged from exercising on their own but were not given any exercise instruction until the end of the study.	12 months	BPI, WOMAC, DASH, FACT, SF-36	- Unspecified.	- Significantly greater improvement in BPI worst pain, pain severity, and pain interference scores with exercise than usual care. - Similar findings for DASH and WOMAC scores. - Greater improvement in overall, breast cancer-specific, endocrine-specific, and fatigue-specific quality of life measures in the exercise group.
Nyrop et al, 2017	USA	RCT/PG	Exercise (walking) (n = 31 randomized)	Waitlist controls (n = 31 randomized)	Unspecified	6 weeks	VAS, WOMAC, FACT-G, RAI, Arthritis Self-Efficacy Scale, Outcome Expectations from Exercise, Self-Efficacy for Physical Activity Scale	- Unspecified.	- Significant improvements in WOMAC stiffness, difficulty/function, and total scores; and RAI perceived helplessness score, in the walking group. - Similar results reported for waitlist controls after completing their walking intervention from weeks 7 through 12. - Data were not presented for weeks 1–6 for the waitlist control group. - At 6-month follow-up, walking minutes per week decreased significantly and RAI perceived helplessness scores returned to baseline values; however, improvements in WOMAC stiffness, difficulty/function, and total scores were largely maintained.
Nyrop et al, 2014	USA	Pre/post	Exercise (n = 20)	None	Unspecified	6 weeks	VAS (one each for pain, stiffness, and fatigue), ASE	- Unspecified.	- Decreases in joint pain, fatigue, and joint stiffness decreased from baseline by 10% (pain) to 32% (stiffness).
Tajaeu et al, 2017 and Tamaki et al, 2018 ^b	Japan	RCT/PG	Exercise (n = 80)	Treatment as usual (n = 28)	Unspecified	12 months	BPI, AI adherence	- Unspecified.	- Statistical trend reported for differentiating effects by treatment group on pain interference at 12 months, but scores by treatment group were not reported. - For those with $\geq 70\%$ adherence, there was significantly greater improvement in pain interference scores with exercise than treatment as usual at 12 months.
Varadarajan et al, 2016 ^b	Unspecified	RCT/PG	Supervised exercise (n = 15)	Walking (n = 12)	Unspecified	8 weeks	PDI, Pain Scale, PHQ-4 (depression)	- Unspecified.	- No significant between-group differences in PDI, Pain Scale, PCI, or PHQ4 scores.

(Continued)

Table 4 (Continued).

Author [Ref.]	Study Location	Study Design	Intervention, N ^a	Control(s), N ^a	Co-Interventions	Duration	Main Outcome Measure(s)	Tolerability/ Safety	Main Findings
Physical Therapy, Occupational Therapy, Recreation Therapy Intervention									
Cantarero-Villanueva et al, 2011	Spain	RCT/PG	Multimodal PT program (n = 29)	Treatment as usual (n = 26)	Unspecified	6 months	PFS, MLTPAQ, shoulder and cervical ROM assessments	- Unspecified.	- Significantly greater improvement in fatigue and ROM measures in the intervention group compared with the control group.
Lippi et al, 2022	Italy	RCT/PG	Whole body vibration + exercise (n = 11)	Sham whole body vibration + exercise (n = 11)	Unspecified	4 weeks	Numerical Pain Rating Scale, WOMAC, handgrip strength, 10-meter walking test, EORTC QLQ-C30	- Investigators did not register dropouts or side-effects in either group.	- Significant improvement in pain was observed in the intervention group but not the control group. - There were significant improvements in muscle strength, physical performance, and quality of life measures in both groups, with no significant between-group differences.
Other Rehabilitative Intervention									
Conejo et al, 2018	Spain	RCT/PG	Neuromuscular taping (NMT) (n = 20)	Sham NMT (n = 20)	Pain medications were prescribed to participants in both arms following usual care guidelines.	5 weeks	VAS, QuickPiper Fatigue Scale, QLQ-C30 (quality of life), Spine Functional Index, Upper Limbs Functional Index, BADIX	- None reported.	- There were significant improvements in VAS scores with NMT at 5 weeks, but not sham NMT.

Notes: ^a Refers to the number of subjects whose data were analyzed, unless otherwise specified. ^b Both of the reports from Tajaesu et al⁹⁷ and Tamaki et al⁸² were published in abstract form. Findings from Tamaki et al⁸² are presented in the table ^c The information provided in the published abstract only specifies that 121 subjects were enrolled, 99 of whom had pain and pressure pain threshold data available at 6 months.

Abbreviations: AIMS-2, Arthritis Impact Measurement Scale; ASE, Arthritis Self-Efficacy Scale; BADIX, Backache Disability Index; COX-2, cyclo-oxygenase-2; DASH, Quick Disabilities of the Arm, Shoulder, and Hand scale; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; MLTPAQ, Minnesota Leisure Time Physical Activity Questionnaire; MOS SF-36v2, Medical Outcomes Study 36-item Short Form; NPRS, numerical pain rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; PDI, Pain Disability Index; PFS, Piper Fatigue Scale; PHQ-4, 4-item Public Health Questionnaire; PSEQ, Pain Self-Efficacy Questionnaire; RAI, Rheumatology Attitudes Index; RCT/PG, randomized controlled trial (parallel-group design); ROM, range of motion; SF-36, Medical Outcomes Short Form 36; VAS, pain visual analog scale; WOMAC, Western Ontario and McMaster Universities index.

physical activity regimens classified as low-intensity (120–150 minutes per week of walking or running), moderate-intensity (a daily regimen that was publicly broadcasted over the radio), or higher-intensity (climbing stairs).⁸² We were unable to locate reports from studies of structured individual or group-based psychotherapies or psychoeducational interventions for AIMSS. One report described the effects of a 4-week, physiotherapist-led progressive relaxation exercise intervention; however, the intervention, as described, did not focus specifically on psychological or behavioral reactions to pain.³¹

Outcomes Assessed

As shown in Figure 2c, the most frequently assessed outcomes across the reviewed reports were pain intensity (70 reports), followed by various measures of quality of life (37 reports) and functioning (34 reports). Relatively fewer reports highlighted adverse intervention effects, and very few studies focused on more downstream outcomes such as persistence on AI therapy. We were unable to locate any reports highlighting intervention effects on other cancer survivorship outcomes such as breast cancer recurrence, survival, fear of disease recurrence, service utilization, care costs, or caregiver experiences.

Most reports of intervention effects on pain outcomes incorporated multiple measures that assessed global pain intensity, pain levels in various body regions or joints, and/or interference with life activities and functioning due to pain symptoms. Pain sensitization (pressure pain thresholds) and pain self-efficacy (subjects' levels of confidence in their ability to function adequately despite persisting pain) were assessed in two^{39,89} and four studies,^{43,50,72,73} respectively. The most frequently used individual pain rating scales were self-administered questionnaires such as the Brief Pain Inventory (BPI, including short-form versions and subscale measures of pain intensity and impact, 43 reports),¹⁰¹ the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)¹⁰² pain scale (25 reports), the 30-item and short versions of the Disabilities of the Arm, Shoulder and Hand (DASH, QuickDASH)^{103,104} questionnaire (8 reports), modified versions of existing rating scales or investigator developed measures (4 reports), the modified (shortened) version of the Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands

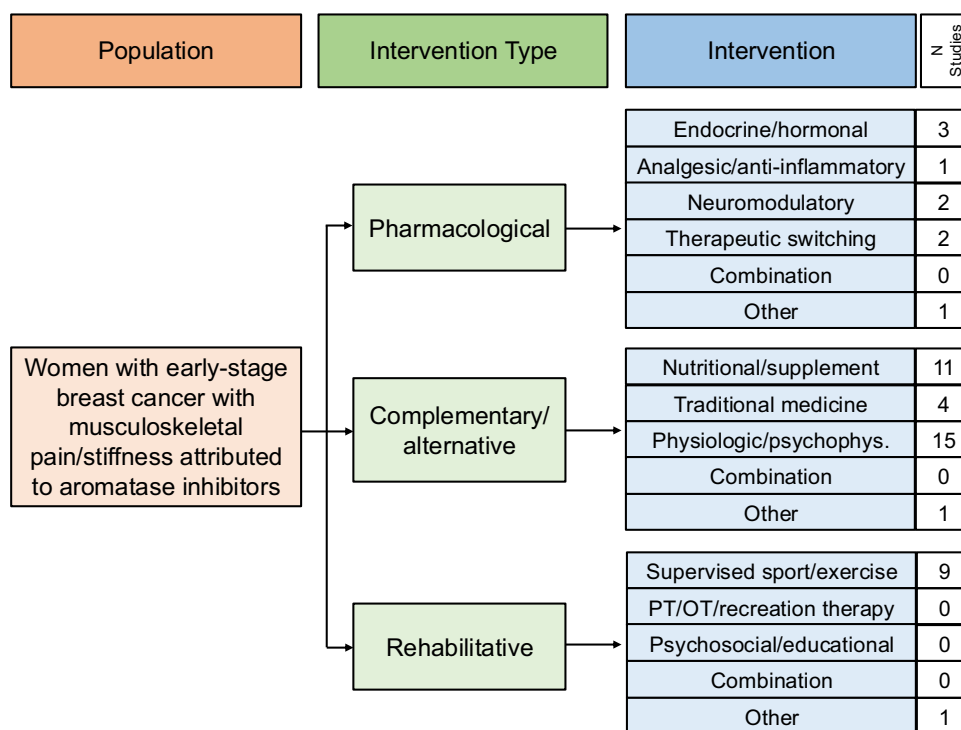


Figure 3 Number of reports by specific intervention.

Abbreviations: OT, occupational therapy; psychophys., psychophysiological intervention; PT, physical therapy.

(M-SACRAH)¹⁰⁵ scale (3 reports), various Patient-Reported Outcomes Measurement Information System (PROMIS)¹⁰⁶ pain measures (3 reports), and the Australian/Canadian (AUSCAN)¹⁰⁷ Osteoarthritis Hand Index (3 reports). Visual analog scales and similar ordinal measures were used to rate pain intensity and/or interference in 21 reports, while five reports included analgesic medication use or changes in the frequency of analgesic administration as outcome measures. Pain self-efficacy measures included the full or shortened versions of the Pain Self-Efficacy Questionnaire (PSEQ, 3 studies)¹⁰⁸ and the Arthritis Self-Efficacy Scale (1 study).¹⁰⁹

Functioning and quality of life measures also consisted mainly of self-administered questionnaires including the Functional Assessment of Cancer Therapy (FACT)¹¹⁰ subscales (23 reports), specific subdomains from pain rating scales that assessed perceived functional capacity and quality of life/wellbeing (14 reports), the Health Assessment Questionnaire (HAQ)¹¹¹ Disability Index and Pain Scale (8 reports), versions of the 36-item Short Form Survey (SF-36)¹¹² quality of life measures (4 reports), EuroQoL Group quality of life (EuroQoL)¹¹³ measures (3 reports), and the Backache Disability Index (BADIX)¹¹⁴ and Minnesota Leisure Time Physical Activity Questionnaire (1 report each).¹¹⁵ Direct measures of physical functioning were assessed in 11 reports, including the Functional Sit and Reach Test¹¹⁶ and other standardized measures of flexibility, strength, and range of motion.

Intervention effects on mental health symptoms (including perceived levels of stress) and fatigue were assessed in 13 and 12 reports, respectively. Specific mental health outcomes in the reviewed reports were predominantly depressive and anxiety symptoms assessed using subject-reported scales. These scales included the Hospital Anxiety and Depression (HADS)¹¹⁷ depression and/or anxiety subscales (5 reports), the Public Health Questionnaire (PHQ) 9- and 4-item scales^{118,119} (5 reports), the Center for Epidemiologic Studies Depression Scale (CES-D, 4 reports),¹²⁰ and the Profile of Mood States (POMS)¹²¹ scale (1 report). There were no formal or structured assessments for discrete mental health diagnoses, conditions, or comorbidities based on diagnostic criteria or other standardized definitions. In one report, subjective stress levels were assessed using the Perceived Stress Scale.¹²²

Additional symptom measures in the reviewed reports included assessments of sleep quality (10 reports), the intensity and burden from menopausal symptoms (6 reports), and perceived sexual functioning (one report). The most used sleep measure was the Pittsburgh Sleep Quality Index (7 studies).¹²³ Other sleep measures included the Insomnia Severity Index,¹²⁴ subjective ordinal ratings, and unspecified measures (one study each). Menopausal symptoms were assessed using the Hot Flash-Related Daily Interference Scale (HFRDIS, 4 reports)¹²⁵ and the National Surgical Adjuvant Breast and Bowel Project (NSABP) menopause symptom items, hot flash symptoms recorded in diaries, and the Menopause-Specific Quality of Life scale (2 reports each).¹²⁶

Discussion

This scoping review summarized the existing evidence from prospective studies of the full spectrum of interventions for AIMSS in women with breast cancer. Reviewed interventions included pharmacological treatments with a variety of mechanisms and as diverse an array of complementary/alternative and rehabilitative therapies. Nearly 60% of included studies tested the effects of complementary/alternative interventions. The remaining studies were a more even split between traditional pharmacological interventions and rehabilitative therapies. Most reviewed studies were randomized trials, the majority of which used placebo or sham controls. Although operational definitions of AIMSS and pain or stiffness-related outcome measures had reasonable overlap across studies, other clinical and methodological characteristics such as inclusion and exclusion criteria (which were intervention-dependent, as expected), study designs, sample sizes, non-pain-related outcome measures, co-interventions, and completeness of adverse event reporting varied widely across studies. The evidence base does not yet point to clearly preferred interventions for AIMSS, nor does it provide a clear means of stratifying treatments or channeling them to specific types of patients. Intervention effects on other important endpoints are uncertain (ie, persistence on AIs) or untested (eg, breast cancer recurrence, survival, costs of care, and caregiver experiences).

Prior reviews of interventions for AIMSS have focused on effectiveness for pain symptoms and the quality of that evidence—and not necessarily on providing a comprehensive summary of the full spectrum of AIMSS interventions and outcomes assessed. For instance, a systematic review of 17 studies that investigated systemic therapies for preventing or treating AIMSS in women with early-stage breast cancer highlighted positive findings for duloxetine, testosterone,

calcitonin, vitamin D, omega-3 fatty acids, Yi Shen Jian Gu granules, cat's claw, pure emu oil, and BTBP for improving pain scores.²³ The overall evidence for effective and safe systemic treatments for AIMSS was rated as “minimal”. An earlier systematic review of 38 studies also examined the clinical effects of pharmacological and non-pharmacological interventions for treating AIMSS in postmenopausal patients with early breast cancer,²² and called attention to the relatively sparse evidence base for nearly all interventions of interest and the limitations of conclusions that could be drawn from the available literature (through 2016) owing to small sample sizes, heterogeneity of interventions, low clarity in methodological details, and high risks of bias across several studies. The present scoping review also highlights promising treatment approaches across 74 reports published through January 8, 2025, and extends prior reviews by providing a current summary of the full spectrum of interventions and outcomes that have been systematically investigated for treating prevalent AIMSS symptoms.

Guidelines for managing AIMSS symptoms that were recently published by the American Society for Clinical Oncology recommended yoga, other types of exercise, duloxetine, acupuncture, and omega-3 fatty acids (especially for obese patients) as reasonable therapeutic options, along with holding AI treatment followed by re-initiation or therapeutic switch for treatment-resistant cases.²⁴ However, there is still no standardized approach to treating AIMSS and improving AI persistence. The importance of this crucial knowledge gap is highlighted by the positive association between AIMSS pain/discomfort and premature discontinuation of adjuvant AI therapy,¹⁴ which may justify applying safe and potentially effective interventions, given the evidence in hand, even if the quality of that evidence is currently less than optimal. Partial adherence, which can limit the effectiveness of oral medications in patients with breast cancer,¹²⁷ may also be foreseeably related to AIMSS symptoms although, to our knowledge, this has not been thoroughly investigated. Nevertheless, from this perspective, the relative sparsity of direct evidence for improving AI adherence or persistence for any of the reviewed interventions is surprising. Furthermore, as there appears to be no clinically significant difference in the efficacies of different AIs as adjuvant therapies in postmenopausal women with early breast cancer,¹²⁸ the scarcity of switch studies and head-to-head studies of AIs powered to detect differences in AIMSS and other toxicity profiles is also surprising, calling attention to high-priority areas in need of systematic clinical investigation.

Although the term, AIMSS, would seem to imply the presence of a single syndrome, it is really a collection of diverse symptoms that have in common only their link to a single presumed cause. Indeed, the clinical features of AIMSS classically include joint pain and stiffness; however, additional defining symptoms can include diffuse pain, myalgias, bone pain, carpal tunnel syndrome, morning stiffness, and neuropathic-like pain symptoms.^{129–131} Beyond localization and distribution, the severity of pain and stiffness can vary widely from patient to patient.¹²⁹ The proposed pathophysiological or pharmacological mechanisms by which AIs may lead to AIMSS symptoms are also heterogeneous and no unifying etiology has been discovered. As such, it should come as little surprise that a widely diverse array of interventions has been tested. Future prospective studies of the most promising interventions in more clinically homogeneous subgroups of AI-treated breast cancer patients with AIMSS symptoms (based on symptom patterns, presumed underlying etiologies, and other factors) are now needed.

Several of the interventions included in this scoping review such as duloxetine, acupuncture, and exercise (especially when combined with psychological treatment) have shown promise for reducing centrally sensitized pain.^{132–134} Centrally sensitized pain is a more recent etiological hypothesis for cancer pain in general and for AIMSS in particular.¹³⁵ Central sensitization is more commonly applied to classical pain syndromes such as fibromyalgia, temporomandibular joint disorder, chronic headache, and complex regional pain syndrome.¹³⁶ Of interest, breast cancer survivors often report a constellation of symptoms including pain, fatigue, depression, insomnia, and cognitive dulling that are also frequently reported in patients with fibromyalgia and temporomandibular joint disorder.^{137,138} In a prospective study of pain in breast cancer survivors taking anti-estrogen treatments,¹²⁹ the authors referenced frequent discrepancies between the objective exam findings and subject-reported pain intensities and functional impairment, which are characteristic of central sensitization. Moreover, a cross-sectional study of the prevalence of three types of pain (nociceptive, neuropathic, or central sensitization) in a cohort of breast cancer survivors with chronic pain documented central sensitization in 44% of participants, 75% of whom were experiencing arthralgia due to AIs or SERMs.¹⁶ Although a central sensitization hypothesis for AIMSS awaits confirmation, it may still be an important mechanism to consider given its multifactorial nature and limited response to traditional analgesics.¹³⁹ Additional studies of

interventions for AIMSS that have been shown to have beneficial effects for centrally sensitized pain in other clinical contexts (outside or hormonal treatment effects) are thus encouraged.

Our literature search did not identify any studies investigating the effects of structured psychotherapy or psychoeducational interventions on AIMSS pain, mental health symptoms and functioning, or pain interference in AI-treated women with breast cancer. Such interventions address not only the negative psychological consequences of pain but also key mediators of pain persistence and suffering, including pain catastrophizing, pain-related fear, non-adherence to treatment, and other behavioral markers of poor illness coping.¹⁴⁰ Specific evidence-based psychological interventions for chronic non-cancer pain include cognitive-behavioral therapy and acceptance and commitment therapy, although other approaches have shown promise.¹⁴¹ Psychological treatments may also be effective for persistent pain after breast cancer treatment in general, although clinical evidence is preliminary.¹⁴² High-quality investigations of individual and group-based psychological interventions for AIMSS symptoms, emotional and physical functioning, quality of life, and AI persistence are needed.

This scoping review has some limitations. The treatment of AIMSS and the identification of clinical predictors of AIMSS onset is a rapidly evolving field of inquiry, and our results are current only up to January 8, 2025. In addition, although our review addressed the full scope of interventions that have been studied for treating existing AIMSS symptoms and correlated outcomes, we excluded reports on interventions to prevent AIMSS occurrence. From a practical point of view, establishing best practices for preventing AIMSS onset may be as high a therapeutic priority as how prevalent AIMSS cases should be managed.

In conclusion, a very broad range of pharmacological, complementary-alternative and rehabilitative interventions have been studied for the treatment of AIMSS. Although the evidence base for AIMSS treatments continues to expand, the existing literature does not yet identify first-line or preferred interventions for AIMSS or a clearly evidence-based means of prioritizing or sequencing treatments based on individual patient characteristics. Our scoping review highlights key gaps that need to be addressed in future AIMSS intervention studies. Most positive findings from individual reports were from uncontrolled studies or single studies that await replication in independent cohorts and high-quality comparative effectiveness investigations are generally lacking. The sample sizes for most of the reviewed studies were small and the durations for all reviewed studies were brief relative to the expected 5–10-year course of AI therapy. There is a critical need for well-powered, longer-term studies that focus on persistence in adjuvant AI treatment and associated survival, as well as thorough comparative cost–benefit analyses across interventions for AIMSS. Well-designed studies of structured psychological treatments are also needed, given the success of these interventions for improving pain-related symptoms, functioning, and pain adjustment in other chronic or persisting pain disorders. And finally, the field awaits additional studies of intervention effects on AI persistence, survival, healthcare utilization, costs of care, and caregiver experiences.

Disclosure

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References

1. Heer E, Harper A, Escandor N, et al. Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study. *Lancet Glob Health*. 2020;8(8):e1027–e1037. doi:10.1016/S2214-109X(20)30215-1
2. DeSantis CE, Fedewa SA, Sauer AG, et al. Breast cancer statistics, 2015: convergence of incidence rates between black and white women. *CA a Cancer J Clin*. 2015;66:31–42. doi:10.3322/caac.21320
3. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26 suppl 5:V8–V30. doi:10.1093/annonc/mdv298
4. Kerr AJ, Dodwell D, McGale P, et al. Adjuvant and neoadjuvant breast cancer treatments: a systematic review of their effects on mortality. *Cancer Treat Rev*. 2022;105:102375. doi:10.1016/j.ctrv.2022.102375
5. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386:1341–1352. doi:10.1016/S0140-6736(15)61074-1
6. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor–positive breast cancer: ASCO clinical practice guideline focused update. *J Clin Oncol*. 2018;36. doi:10.1200/JCO.18.01160

7. Beckwée D, Leysen L, Meuwis K, Adriaenssens N. Prevalence of aromatase inhibitor-induced arthralgia in breast cancer: a systematic review and meta-analysis. *Support Care Cancer*. 2017;25:1673–1686. doi:10.1007/s00520-017-3613-z
8. Henry NL, Azzouz F, Desta Z, et al. Predictors of aromatase inhibitor discontinuation as a result of treatment-emergent symptoms in early-stage breast cancer. *J Clin Oncol*. 2012;30:936–942. doi:10.1200/JCO.2011.38.0261
9. Grigorian N, Baumrucker SJ. Aromatase inhibitor-associated musculoskeletal pain: an overview of pathophysiology and treatment modalities. *SAGE Open Med*. 2022;10:1–5. doi:10.1177/20503121221078722
10. Ito K, Elkin E, Blinder V, et al. Cost-effectiveness of full coverage of aromatase inhibitors for medicare beneficiaries with early breast cancer. *Cancer*. 2013;119(3):2494–2502. doi:10.1002/cncr.28084
11. Burstein HJ. Aromatase inhibitor-associated arthralgia syndrome. *Breast*. 2007;16:223–234. doi:10.1016/j.breast.2007.01.011
12. Tenti S, Correale P, Chelieschi S, et al. Aromatase inhibitor-induced musculoskeletal disorders: current knowledge on clinical and molecular aspects. *Int J Mol Sci*. 2020;21:5625. doi:10.3390/ijms21165625
13. Andrikopoulou A, Fiste O, Lontos M, et al. Aromatase and CKD4/6 inhibitor-induced musculoskeletal symptoms: a systematic review. *Cancers*. 2021;13:465. doi:10.3390/cancers13030465
14. Hyder T, Marino CC, Ahmad S, et al. Aromatase inhibitor-associated musculoskeletal syndrome: understanding mechanisms and management. *Front Endocrinol*. 2021;12:713700. doi:10.3389/fendo.2021.713700
15. Garcia-Giralt N, Rodríguez-Sanz M, Prieto-Alhambra D, et al. Genetic determinants of aromatase inhibitor-related arthralgia: the B-ABLE cohort study. *Breast Cancer Res Treat*. 2013;140:385–395. doi:10.1007/s10549-013-2638-3
16. Niravath P, Chen B, Chapman JW, et al. Vitamin D levels, vitamin D receptor polymorphisms, and inflammatory cytokines in aromatase inhibitor-induced arthralgias: an analysis of CCTG MA.27. *Clin Breast Cancer*. 2018;18:78–87. doi:10.1016/j.clbc.2017.10.009
17. Suskin J, Shapiro CL. Osteoporosis and musculoskeletal complications related to therapy of breast cancer. *Gland Surg*. 2018;7:411–423. doi:10.21037/gs.2018.07.05
18. Leysen L, Adriaenssens N, Nijs J, et al. Chronic pain in breast cancer survivors: nociceptive, neuropathic, or central sensitization pain? *Pain Pract*. 2019;19:183–195. doi:10.1111/papr.12732
19. Bae K, Yoo HS, Lamoury G, et al. Acupuncture for aromatase inhibitor-induced arthralgia: a systematic review. *Integr Cancer Ther*. 2015;14:496–502. doi:10.1177/1534735415596573
20. Chiu HY, Hsieh YJ, Tsai PS. Systematic review and meta-analysis of acupuncture to reduce cancer-related pain. *Eur J Cancer Care*. 2017;26(2):e12457. doi:10.1111/ecc.12457
21. Roberts KE, Rickett K, Feng S, et al. Exercise therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. *Cochrane Database Syst Rev*. 2020;1:CD012988. doi:10.1002/14651858.CD012988.pub2
22. Roberts K, Rickett K, Greer R, Woodward N. Management of aromatase inhibitor induced musculoskeletal symptoms in postmenopausal early breast cancer: a systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2017;111:66–80. doi:10.1016/j.critrevonc.2017.01.010
23. Roberts KE, Adsett IT, Rickett K, et al. Systemic therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer. *Cochrane Database Syst Rev*. 2022;(1):CD-13167. doi:10.1002/14651858.CD013167.pub2
24. Gupta A, Henry NL, Loprinzi CL. Management of aromatase inhibitor-induced musculoskeletal symptoms. *JCO Oncol Pract*. 2020;16:733–739. doi:10.1200/OP.20.00113
25. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2012;1(1):CD008921. doi:10.1002/14651858.CD008921.pub2
26. NCCIH (National Center for Complementary and Integrative Health). Complementary, alternative, or integrative health: what's in a name? Available from: <https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name>. Accessed December 9, 2023.
27. Ramsey I, Corsini N, Hutchinson AD, et al. A core set of patient-reported outcomes for population-based cancer survivorship research: a consensus study. *J Cancer Surviv*. 2021;15:201–212. doi:10.1007/s11764-020-00924-5
28. Alhanafy AM, Labeeb A, Khalil A. The role of diuretics in treatment of aromatase inhibitors induced musculoskeletal symptoms in women with non metastatic breast cancer. *Asian Pac J Cancer Prev*. 2018;19:3525–3531. doi:10.31557/APJCP.2018.19.12.3525
29. Vijaya Vani S A, Ananthanarayanan PH, Kadambari D, et al. Effects of vitamin D and calcium supplementation on side effects profile in patients of breast cancer treated with letrozole. *Clin Chim Acta*. 2016;459:53–56. doi:10.1016/j.cca.2016.05.020
30. Baglia ML, Lin I-H, Cartmel B, et al. Endocrine-related quality of life in a randomized trial of exercise on aromatase inhibitor-induced arthralgias in breast cancer survivors. *Cancer*. 2019;125:2262–2272. doi:10.1002/cncr.32051
31. Bahcaci U, Atasavun US, Erdogan Iyigu'n Z, et al. Progressive relaxation training in patients with breast cancer receiving aromatase inhibitor therapy-randomized controlled trial. *PLoS One*. 2024;19(4):e0301020. doi:10.1371/journal.pone.0301020
32. Bao T, Cai L, Giles JT, et al. A dual-center randomized controlled double blind trial assessing the effect of acupuncture in reducing musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors. *Breast Cancer Res Treat*. 2013;138:167–174. doi:10.1007/s10549-013-2427-z
33. Bao T, Cai L, Snyder C, et al. Patient-reported outcomes in women with breast cancer enrolled in a dual-center, double-blind, randomized controlled trial assessing the effect of acupuncture in reducing aromatase inhibitor-induced musculoskeletal symptoms. *Cancer*. 2014;120:381–389. doi:10.1002/cncr.28352
34. Barbosa KDP, da Silva LGT, Garcia PA, et al. Effectiveness of Pilates and circuit-based exercise in reducing arthralgia in women during hormone therapy for breast cancer: a randomized, controlled trial. *Support Care Cancer*. 2021;29:6051–6059. doi:10.1007/s00520-021-06180-2
35. Barzaghi S, Gozzo S, Giardina G, et al. Acupuncture for the treatment of arthralgia related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. *Ann Oncol*. 2015;26(suppl. 6):v3–v25. doi:10.1093/annonc/mdv336.75
36. Boing L, de Bem Fretta T, Lynch BM, et al. Mat Pilates and belly dance: effects on patient-reported outcomes among breast cancer survivors receiving hormone therapy and adherence to exercise. *Complementary Therapies Clin Pract*. 2023;50:101683. doi:10.1016/j.ctcp.2022.101683
37. Briot K, Tubiana-Hulin M, Bastit L, et al. 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 Res Treat*. 2010;120:127–134. doi:10.1007/s10549-009-0692-7

38. Campbell A, Heydarian R, Ochoa C, et al. Single arm Phase II study of oral vitamin B12 for the treatment of musculoskeletal symptoms associated with aromatase inhibitors in women with early stage breast cancer. *Breast J*. 2018;24:260–268. doi:10.1111/tbj.12951
39. Cantarero-Villanueva I, Fernandez-Lao C, Caro-Moran E, et al. Aquatic exercise in a chest-high pool for hormone therapy-induced arthralgia in breast cancer survivors: a pragmatic controlled trial. *Clin Rehabil*. 2013;27:123–132. doi:10.1177/0269215512448256
40. Cantarero-Villanueva I, Fernandez-Lao C, Diaz-Rodriguez L, et al. A multimodal exercise program and multimedia support reduce cancer-related fatigue in breast cancer survivors: a randomized controlled clinical trial. *Eur J Int Med*. 2011;3:e189–e200. doi:10.1016/j.eujim.2011.08.001
41. Cathcart-Rake E, Novotny P, Leon-Ferre R, et al. A randomized, double-blind, placebo-controlled trial of testosterone for treatment of postmenopausal women with aromatase inhibitor-induced arthralgias: alliance study A221102. *Support Care Cancer*. 2021;29:387–396. doi:10.1007/s00520-020-05473-2
42. Chan A, De Boer R, Gan A, et al. Randomized phase II placebo-controlled study to evaluate the efficacy of topical pure emu oil for joint pain related to adjuvant aromatase inhibitor use in postmenopausal women with early breast cancer: JUST (Joints Under Study). *Support Care Cancer*. 2017;25:3785–3791. doi:10.1007/s00520-017-3810-9
43. Yeh CH, Lin W-C, Kwai-Ping Suen L, et al. Auricular point acupressure to manage aromatase inhibitor-induced arthralgia in postmenopausal breast cancer survivors: a pilot study. *ONF*. 2017;44:476–487. doi:10.1188/17.ONF.476-487
44. Conejo I, Pajares B, Alba E, et al. Effect of neuromuscular taping on musculoskeletal disorders secondary to the use of aromatase inhibitors in breast cancer survivors: a pragmatic randomized clinical trial. *BMC Compl Altern Med*. 2018;18:180. doi:10.1186/s12906-018-2236-3
45. Crew KD, Capodice JL, Greenlee H, et al. Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. *J Cancer Surviv*. 2007;1:283–291. doi:10.1007/s11764-007-0034-x
46. Crew KD, Capodice JL, Greenlee H, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early-stage breast cancer. *J Clin Oncol*. 2010;28:1154–1160. doi:10.1200/JCO.2009.23.4708
47. DeNysschen CA, Burton H, Ademuyiwa F, et al. Exercise intervention in breast cancer patients with aromatase inhibitor-associated arthralgia: a pilot study. *Eur J Cancer Care*. 2014;23:493–501.
48. DeSire A, Lippi L, Ammendolia A, et al. Physical exercise with or without whole-body vibration in breast cancer patients suffering from aromatase inhibitor-induced musculoskeletal symptoms: a pilot randomized clinical study. *J Pers Med*. 2021;11:1369. doi:10.3390/jpm11121369
49. Desideri I, Lucidi S, Francolini G, et al. Use of an alfa-lipoic, Methylsulfonylmethane, Boswellia serrata and Bromelain dietary supplement (OPERA[®]) for aromatase inhibitors-related arthralgia management (AIA): a prospective phase II trial (NCT04161833). *Med Oncol*. 2022;39:113. doi:10.1007/s12032-022-01723-x
50. Fields J, Richardson A, Hopkinson J, Fenlon D. Nordic walking as an exercise intervention to reduce pain in women with aromatase inhibitor-associated arthralgia: a feasibility study. *J Pain Symptom Manag*. 2016;52:548–559.
51. Galantino ML, Callens ML, Cardena GJ, Piela NL, Mao JJ, Tai chi for well-being of breast cancer survivors with aromatase inhibitor-associated arthralgias: a feasibility study. *Altern Ther Health Med*. 2013;19:38–44.
52. Galantino ML, Desai K, Greene L, et al. Impact of yoga on functional outcomes in breast cancer survivors with aromatase inhibitor-associated arthralgias. *Integr Cancer Ther*. 2012;11:313–320. doi:10.1177/1534735411413270
53. Gomaa S, West C, Lopez AM, et al. A telehealth-delivered tai chi intervention (TaiChi4Joint) for managing aromatase inhibitor-induced arthralgia in patients with breast cancer during COVID-19: longitudinal pilot study. *JMIR Format Res*. 2022;6:e34995. doi:10.2196/34995
54. Greenlee H, Crew KD, Shao T, et al. Phase II study of glucosamine with chondroitin on aromatase inhibitor-associated joint symptoms in women with breast cancer. *Support Care Cancer*. 2013;21:1077–1087. doi:10.1007/s00520-012-1628-z
55. Henry NL, Banerjee M, Wicha M, et al. Pilot study of duloxetine for treatment of aromatase inhibitor-associated musculoskeletal symptoms. *Cancer*. 2011;117:5469–5475. doi:10.1002/ncr.26230
56. Henry NL, Unger JM, Schott AF, et al. Randomized, multicenter, placebo-controlled clinical trial of duloxetine versus placebo for aromatase inhibitor-associated arthralgias in early-stage breast cancer: SWOG S1202. *J Clin Oncol*. 2018;36:326–332. doi:10.1200/JCO.2017.74.6651
57. Hershman DL, Unger JM, Crew KD, et al. Randomized multicenter placebo-controlled trial of omega-3 fatty acids for the control of aromatase inhibitor-induced musculoskeletal pain: SWOG S0927. *J Clin Oncol*. 2015;33:1910–1917. doi:10.1200/JCO.2014.59.5595
58. Hershman DL, Unger JM, Greenlee H, et al. Comparison of acupuncture vs sham acupuncture or waiting list control in the treatment of aromatase inhibitor-related joint pain: a randomized clinical trial. *JAMA Network Open*. 2022;5:e2241720. doi:10.1001/jamanetworkopen.2022.41720
59. Hershman DL, Unger JM, Greenlee H, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer. *JAMA*. 2018;320:167–176. doi:10.1001/jama.2018.8907
60. Irwin ML, Cartmel B, Gross CP, et al. Randomized exercise trial of aromatase inhibitor-induced arthralgia in breast cancer survivors. *J Clin Oncol*. 2015;33:1104–1111. doi:10.1200/JCO.2014.57.1547
61. Jacobsen PB, Muchnick S, Marcus S, et al. Pilot study of Iyengar yoga for management of aromatase inhibitor-associated arthralgia in women with breast cancer. *Psychooncology*. 2015;24:1578–1580. doi:10.1002/pon.3756
62. Kadakia KC, Kidwell KM, Seewald NJ, et al. Prospective assessment of patient reported outcomes and estradiol of drug concentration in patients experiencing toxicity from adjuvant aromatase inhibitors. *Breast Cancer Res Treat*. 2017;164:411–419. doi:10.1007/s10549-017-4260-2
63. Kiyomi A, Makita M, Iwase T, et al. Clinical significance of female-hormones and cytokines in breast cancer patients complicated by aromatase inhibitor-related osteoarthropathy—efficacy of vitamin E. *J Cancer*. 2015;6:367. doi:10.7150/jca.10695
64. Kubo M, Onishi H, Kuroki S, et al. Short-term and low-dose prednisolone administration reduces aromatase inhibitor-induced arthralgia in patients with breast cancer. *Anticancer Res*. 2012;32:2331–2336.
65. Li Y, Zhang Z, Cui F, et al. Traditional Chinese medicine bionic tiger bone powder for the treatment of AI-associated musculoskeletal symptoms. *Evid Based Complement Alternat Med*. 2017;2478565. doi:10.1155/2017/2478565
66. Liu P, Yang DQ, Xie F, et al. Effect of calcitonin on anastrozole-induced bone pain during aromatase inhibitor therapy for breast cancer. *Genet Mol Res*. 2014;13:5285–5291. doi:10.4238/2014.July.24.7

67. Mao JJ, Bruner DW, Stricker C, et al. Feasibility trial of electroacupuncture for aromatase inhibitor-related arthralgia in breast cancer survivors. *Integr Cancer Ther.* 2009;8:123–129. doi:10.1177/1534735409332903
68. Mao JJ, Liou KT, Baser RE, et al. Effectiveness of electroacupuncture or auricular acupuncture vs usual care for chronic musculoskeletal pain among cancer survivors: the PEACE randomized clinical trial. *JAMA Oncol.* 2021;7:720–727. doi:10.1001/jamaoncol.2021.0310
69. Mao JJ, Xie SX, Farrar JT, et al. A randomized trial of electro-acupuncture for arthralgia related to aromatase inhibitor use. *Eur J Cancer.* 2014;50:267–276. doi:10.1016/j.ejca.2013.09.022
70. Martinez N, Herrera M, Frias L, et al. A combination of hydroxytyrosol, omega-3 fatty acids and curcumin improves pain and inflammation among early stage breast cancer patients receiving adjuvant hormonal therapy: results of a pilot study. *Clin Transl Oncol.* 2019;21:489–498. doi:10.1007/s12094-018-1950-0
71. Martinez JA, Wertheim BC, Rose DJ, et al. Sulindac improves stiffness and quality of life in women taking aromatase inhibitors for breast cancer. *Breast Cancer Res Treat.* 2022;192:113–122. doi:10.1007/s10549-021-06485-0
72. Nyrop KA, Callahan LF, Cleveland RJ, et al. Randomized controlled trial of a home-based walking program to reduce moderate to severe aromatase inhibitor-associated arthralgia in breast cancer survivors. *Oncologist.* 2017;22:1238–1248. doi:10.1634/theoncologist.2017-0174
73. Nyrop KA, Muss HB, Hackney B, et al. Feasibility and promise of a 6-week program to encourage physical activity and reduce joint symptoms among elderly breast cancer survivors on aromatase inhibitor therapy. *J Geriatr Oncol.* 2014;5:148–155. doi:10.1016/j.jgo.2013.12.002
74. Oh B, Kimble B, Costa DSJ, et al. Acupuncture for treatment of arthralgia secondary to aromatase inhibitor therapy in women with early breast cancer: pilot study. *Acupunct Med.* 2013;31:264–271. doi:10.1136/acupmed-2012-010309
75. Peng N, Yu M, Yang G, et al. Effects of the Chinese medicine Yi Shen Jian Gu granules on aromatase inhibitor-associated musculoskeletal symptoms: a randomized, controlled clinical trial. *Breast.* 2018;37:18–27. doi:10.1016/j.breast.2017.08.003
76. Peppone LJ, Janelins MC, Kamen C, et al. The effect of YOCAS[®] yoga for musculoskeletal symptoms among breast cancer survivors on hormonal therapy. *Breast Cancer Res Treat.* 2015;150:597–604. doi:10.1007/s10549-015-3351-1
77. Rastelli AL, Taylor ME, Gao F, et al. Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): a Phase II, double-blind, placebo-controlled, randomized trial. *Breast Cancer Res Treat.* 2011;129:107–116. doi:10.1007/s10549-011-1644-6
78. Schnell PM, Lustberg MB, Henry NL. Adverse events and perception of benefit from duloxetine for treating aromatase inhibitor-associated arthralgias. *JNCI Cancer Spectrum.* 2021;5:pkab018. doi:10.1093/jncics/pkab018
79. Shapiro AC, Adlis SA, Robien K, et al. Randomized, blinded trial of vitamin D3 for treating aromatase inhibitor-associated musculoskeletal symptoms (AIMSS). *Breast Cancer Res Treat.* 2016;155:501–512. doi:10.1007/s10549-016-3710-6
80. Shenouda M, Copley R, Pacioles T, et al. Effect of tart cherry on aromatase inhibitor-induced arthralgia (AIA) in nonmetastatic hormone-positive breast cancer patients: a randomized double-blind placebo-controlled trial. *Clin Breast Cancer.* 2022;22:e30–e36. doi:10.1016/j.clbc.2021.06.007
81. Sordi R, Castro SN, Lera AT, et al. Randomized, double-blind, placebo-controlled phase II clinical trial on the use of *Uncaria tomentosa* (cat's claw) for aromatase inhibitor-induced arthralgia: a pilot study. *J Nat Remedies.* 2019;19:24–31. doi:10.18311/jnr/2019/22867
82. Tamaki K, Takaesu M, Nagamine S, et al. Final results of the randomized trial of exercise intervention vs. usual care for breast cancer patients with aromatase inhibitor to prevent and improve the aromatase inhibitor induced arthralgia. *Cancer Res.* 2018;78(4 suppl):P6–11–01–P6–11–01. doi:10.1158/1538-7445.SABCS17-P6-11-01
83. Tsai C-L, Liiu L-C, Liao C-Y, et al. Yoga versus massage in the treatment of aromatase inhibitor-associated knee joint pain in breast cancer survivors: a randomized controlled trial. *Sci Rep.* 2021;11:14843. doi:10.1038/s41598-021-94466-0
84. Zhang Q, Tang D, Zhao H. Immunological therapies can relieve aromatase inhibitor-related joint symptoms in breast cancer survivors. *Am J Clin Oncol.* 2010;33:557–560. doi:10.1097/COC.0b013e3181cae782
85. Zhang X, Peng N, Yu M-W, et al. Chinese medicine Yishen Jiangu Granules on aromatase inhibitor-associated musculoskeletal symptoms. *Chin J Integr Med.* 2017;24:867–872.
86. Bao T, Betts K, Tarpinian K, et al. Changes in patient-reported outcomes in women with breast cancer in a multicenter double-blind randomized controlled trial assessing the effect of acupuncture in reducing aromatase inhibitor-induced musculoskeletal symptoms (AIMSS). *J Clin Oncol.* 2012;30(15 suppl):1.
87. Birrell S, Tilley W. Treatment reduces joint morbidities induced by anastrozole therapy in postmenopausal women with breast cancer: results of a double-blind, randomized phase II trial. *Cancer Res.* 2009;69(24 suppl):804. doi:10.1158/0008-5472.SABCS-09-804
88. Cheng H-L, Yeung WF, Li CY, et al. Self-acupressure for pain, fatigue, and sleep disturbance in breast cancer survivors receiving aromatase inhibitors: a pilot trial. *Support Care Cancer.* 2023;31(suppl 1):S260–S261.
89. Crespo-Bosque M, Brown N, Cartmel B, et al. Pain and sensitization in women with aromatase inhibitor-associated arthralgias. *Arthritis Rheumatol.* 2016;68(suppl 10):1.
90. Fleege NMG, Miller E, Kidwell KM, et al. The impact of cannabidiol (CBD) on aromatase inhibitor (AI)-associated musculoskeletal symptoms (AIMSS). *J Clin Oncol.* 2024;42(16 suppl):1.
91. Hershman CL, Unger JM, Crew KD, et al. Omega-3 fatty acids for aromatase inhibitor-induced musculoskeletal symptoms in women with early-stage breast cancer (SWOG S0927). *J Clin Oncol.* 2014;32(15 suppl):9532. doi:10.1200/jco.2014.32.15_suppl.9532
92. Hershman DL, Unger JM, Greenlee H, et al. Long-term results from a randomized blinded sham- and waitlist-controlled trial of acupuncture for joint symptoms related to aromatase inhibitors in early stage breast cancer (S1200). *J Clin Oncol.* 2021;39(15 suppl):12018. doi:10.1200/JCO.2021.39.15_suppl.12018
93. Leibel L, Metri K, Prasad R, et al. Effect of Sukshma vyayama yoga on aromatase inhibitor-induced arthralgia in breast cancer patients: a feasibility study conducted on Facebook. *Support Care Cancer.* 2022;30(suppl 1):S14.
94. Lippi L, de Sire A, Ammendolia A, et al. Abstract P4-10-15: whole-body vibration combined with physical exercise to treat aromatase inhibitor-induced musculoskeletal symptoms in breast cancer women: results of a pilot randomized controlled study. *Cancer Res.* 2022;82(4 suppl):P4-10-15–P4-10-15. doi:10.1158/1538-7445.SABCS21-P4-10-15
95. Massimino K, Glissmeyer M, Wagie T, et al. Use of blue citrus, a Chinese herbal remedy, to reduce side effects of aromatase inhibitors. *J Clin Oncol.* 2011;29:170. doi:10.1200/jco.2011.29.27_suppl.170
96. Nahleh ZA, Campbell A, Heydarian R, et al. Effects of oral vitamin B12 for the treatment of aromatase inhibitors (AI)-related musculoskeletal symptoms in women with early stage breast cancer. *J Clin Oncol.* 2018;36:86. doi:10.1200/JCO.2018.36.7_suppl.86

97. Tajaesu M, Tamaki K, Nagamine S, et al. Abstract P5-12-01: randomized trial of exercise intervention vs. usual care for breast cancer patients with aromatase inhibitor to prevent and improve the aromatase inhibitor induced arthralgia. *Cancer Res.* 2017;77(4 suppl):P5-12-01-P5-12-01. doi:10.1158/1538-7445.SABCS16-P5-12-01
98. Varadarajan R, Helm E, Arnold C, et al. Directed exercise intervention in breast cancer patients with arthralgias receiving aromatase inhibitors: a randomized pilot study. *Cancer Res.* 2016;76(4 suppl):P5-12-04-P5-12-04. doi:10.1158/1538-7445.SABCS15-P5-12-04
99. Zylla M, Idossa D, Borrero M, et al. A randomized trial of topical cannabis balms for the treatment of aromatase inhibitor-associated musculoskeletal syndrome (AIMSS). *J Clin Oncol.* 2024;42(16 suppl):e24129-e24129. doi:10.1200/JCO.2024.42.16_suppl.e24129
100. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;62(10). doi:10.1136/bmj.b2700
101. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23:32129-32138.
102. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): a review of its utility and measurement properties. *Arthritis Care Res.* 2001;45:453-461. doi:10.1002/1529-0131(200110)45:5<453::AID-ART365>3.0.CO;2-W
103. Beaton DE, Katz JN, Fossel AH, et al. Measuring the whole or the parts? Validity, reliability, and responsiveness of the Disabilities of the Arm, Shoulder and Hand outcome measure in different regions of the upper extremity. *J Hand Ther.* 2001;14:128-146. doi:10.1016/S0894-1130(01)80043-0
104. Mintken PE, Glynn P, Cleland JA. Psychometric properties of the shortened disabilities of the arm, shoulder, and hand questionnaire (QuickDASH) and numeric pain rating scale in patients with shoulder pain. *J Shoulder Elbow Surg.* 2009;18:920-926. doi:10.1016/j.jse.2008.12.015
105. Sautner J, Andel I, Rintelen B, Leeb BF. Development of the M-SACRAH, a modified, shortened version of SACRAH (score for the assessment and quantification of chronic rheumatoid affections of the hands). *Rheumatology.* 2004;43:1409-1413. doi:10.1093/rheumatology/keh360
106. Amtmann DA, Cook KF, Jensen MP, et al. Development of a PROMIS item bank to measure pain interference. *Pain.* 2010;150:173-182. doi:10.1016/j.pain.2010.04.025
107. Askew RL, Cook KF, Keefe FJ, et al. A PROMIS measure of neuropathic pain quality. *Value Health.* 2016;19:623-630. doi:10.1016/j.jval.2016.02.009
108. Allen KD, DeVellis RF, Renner JB, et al. Validity and factor structure of the AUSCAN osteoarthritis hand index in a community-based sample. *Osteoarthritis Cartilage.* 2007;15:830-836. doi:10.1016/j.joca.2007.01.012
109. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. *Eur J Pain.* 2007;11:153-163. doi:10.1016/j.ejpain.2005.12.008
110. Cella DF, Tulsy DS, Gray G, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol.* 1993;11:570-579. doi:10.1200/JCO.1993.11.3.570
111. Fries J, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. *J Rheumatol.* 1982;9:789-793.
112. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473-483. doi:10.1097/00005650-199206000-00002
113. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33:337-343. doi:10.3109/07853890109002087
114. Farasyn A, Meeusen R, Nijs J, Cuesta-Vargas A. Exploration of the validity and reliability of the "backache disability index" (BADIX) in patients with non-specific low back pain. *J Back Musculoskelet Rehabil.* 2013;26:451-459. doi:10.3233/BMR-130405
115. Richardson MT, Leon AS, Jacobs DR, et al. Comprehensive evaluation of the Minnesota leisure time physical activity questionnaire. *J Clin Epidemiol.* 1994;47:271-281. doi:10.1016/0895-4356(94)90008-6
116. Duncan P, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol.* 1990;45:M192-M197. doi:10.1093/geronj/45.6.M192
117. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand.* 1983;67:361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
118. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med.* 2001;16:606-613. doi:10.1046/j.1525-1497.2001.016009606.x
119. Kroenke K, Spitzer RL, Williams JBW, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics.* 2009;50:613-621. doi:10.1176/appi.psy.50.6.613
120. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Measurement.* 1977;1:385-401.
121. Norcross JC, Guadagnoli E, Prochaska JO. Factor structure of the profile of mood states (POMS): two partial replications. *J Clin Psychol.* 1984;40:1270-1277. doi:10.1002/1097-4679(198409)40:5<1270::aid-jclp2270400526>3.0.co;2-7
122. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Social Behav.* 1983;24:385-396.
123. Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;28:193-213. doi:10.1016/0165-1781(89)90047-4
124. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep.* 2011;34(5):601-608. doi:10.1093/sleep/34.5.601
125. Carpenter JS. The hot flash related daily interference scale: a tool for assessing the impact of hot flashes on quality of life following breast cancer. *J Pain Symptom Manage.* 2001;22:979-989. doi:10.1016/S0885-3924(01)00353-0
126. Radtke JV, Terhorst L, Cohen SM. The menopause-specific quality of life (MENQOL) questionnaire: psychometric evaluation among breast cancer survivors. *Menopause.* 2011;18:289-295. doi:10.1097/gme.0b013e3181ef975a
127. Palmieri FM, Barton DL. Challenges of oral medications in patients with advanced breast cancer. *Seminars Oncol Nurs.* 2007;23(suppl 2):S17-S22. doi:10.1016/j.soncn.2007.10.004
128. De Placido S, Gallo C, De Laurentiis M, et al. Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, Phase 3 trial. *Lancet Oncol.* 2018;19:474-485. doi:10.1016/S1470-2045(18)30116-5

129. Henry NL, Giles JT, Ang D, et al. Prospective characterization of musculoskeletal symptoms in early stage breast cancer patients treated with aromatase inhibitors. *Breast Cancer Res Treat.* 2008;111:365–372. doi:10.1007/s10549-007-9774-6
130. Presant CA, Bosserman L, Young T, et al. Aromatase inhibitor-associated arthralgia and/ or bone pain: frequency and characterization in non-clinical trial patients. *Clin Breast Cancer.* 2007;7:775–778. doi:10.3816/CBC.2007.n.038
131. Sestak I, Sapunar F, Cuzick J. Aromatase inhibitor-induced carpal tunnel syndrome: results from the ATAC trial. *J Clin Oncol.* 2009;27:4961–4965. doi:10.1200/JCO.2009.22.0236
132. Birkinshaw H, Fridrich CM, Cole P, et al. Antidepressants for pain management in adults with chronic pain: a network meta-analysis. *Cochrane Database Syst Rev.* 2023;5(5):CD014682. doi:10.1002/14651858.CD014682.pub2
133. Lai H-C, Lin Y-W, Hsieh C-L. Acupuncture-Analgesia-Mediated Alleviation of Central Sensitization. *Evid Based Complement Alternat Med.* 2019;2019:6173412. doi:10.1155/2019/6173412
134. Deegan O, Fullen BM, Segurado R, Doody C. The effectiveness of a combined exercise and psychological treatment programme on measures of nervous system sensitisation in adults with chronic musculoskeletal pain - a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2024;25:140. doi:10.1186/s12891-024-07274-8
135. Nishigami T, Manfuku M, Lahousse A. Central sensitization in cancer survivors and its clinical implications: state of the art. *J Clin Med.* 2023;12:4606. doi:10.3390/jcm12144606
136. Verspyck E, Attal N. Diagnosing nociplastic pain in cancer survivors: a major step forward. *Br J Anaesthesia.* 2023;130:515–518.
137. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch Intern Med.* 2000;160:221–227. doi:10.1001/archinte.160.2.221
138. Kidwell KM, Harte SE, Hayes DF, et al. Patient-reported symptoms and discontinuation of adjuvant aromatase inhibitor therapy. *Cancer.* 2014;120:2403–2411. doi:10.1002/cncr.28756
139. Nijs J, Lahousse A, Fernandez-de-las-Penas C, et al. Towards precision pain medicine for pain after cancer: the cancer pain phenotyping network multidisciplinary international guidelines for pain phenotyping using nociplastic pain criteria. *Br J Anaesthesia.* 2023;130:611–621. doi:10.1016/j.bja.2022.12.013
140. Sturgeon JA. Psychological therapies for the management of chronic pain. *Psychol Res Behav Manag.* 2014;7:115–124. doi:10.2147/PRBM.S44762
141. Driscoll MA, Edwards RR, Becker WC, et al. Psychological interventions for the treatment of chronic pain in adults. *Psychol Sci Public Interes.* 2021;22:52–95. doi:10.1177/15291006211008157
142. Johannsen M, Farver I, Beck N, et al. The efficacy of psychosocial intervention for pain in breast cancer patients and survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2013;138:675–690. doi:10.1007/s10549-013-2503-4

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