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REVIEW

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

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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-

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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 pharmaceutics (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.

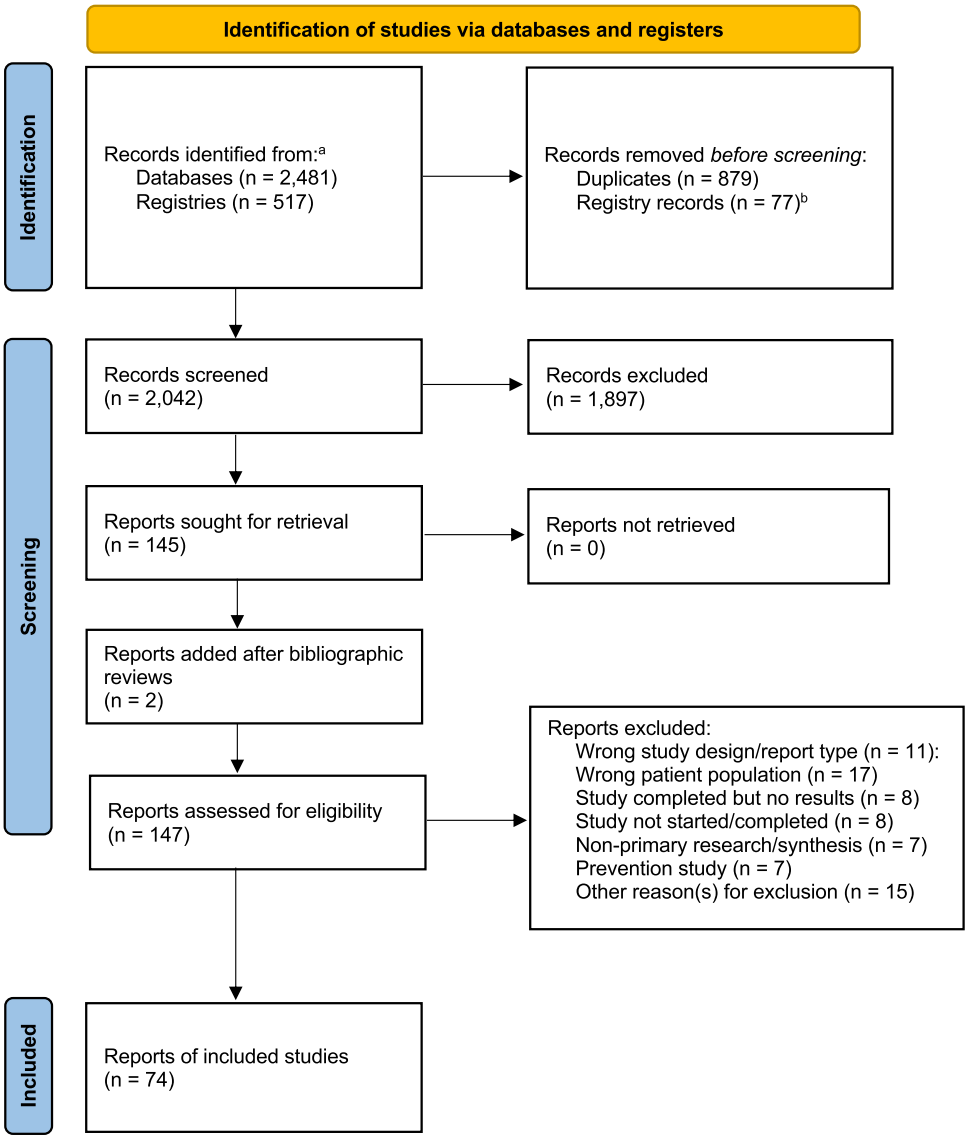

Figure 1 PRISMA flow diagram. [a]The search date for all databases and clinical trial registries was 08 January 2025. A total of 2998 records were identified (see Supplementary Table 1) – PubMed, n = 292; Ovid MEDLINE, n = 172; SCOPUS, n = 1387; EMBASE, n = 549; CINAHL, n = 71, PsycINFO, n = 10, CENTRAL, n = 408; ClinicalTrials.gov, n = 63). [b]Within 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

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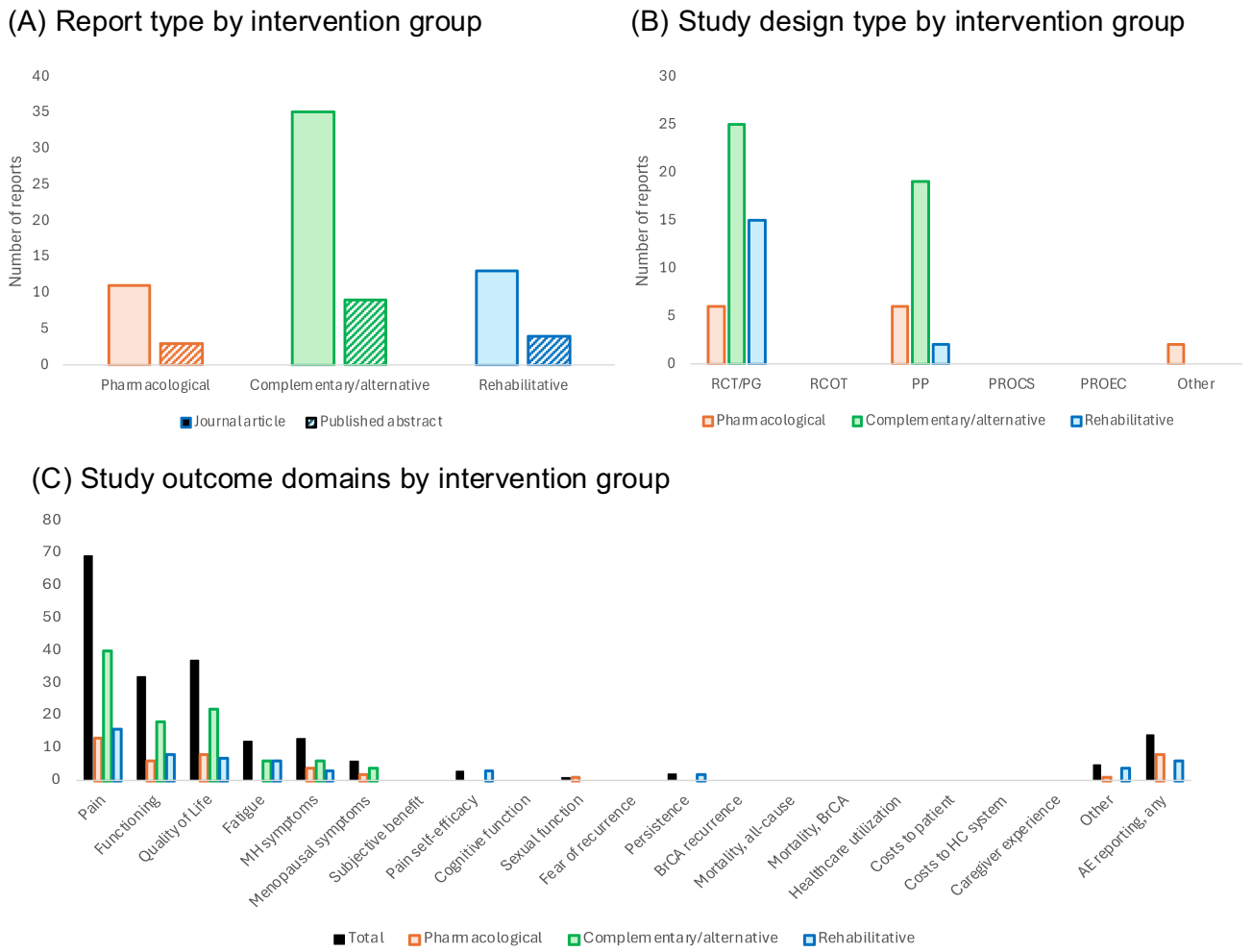

Figure 2 Visual summary of reviewed reports. (**A**) summarizes the total number of reports by report type (journal article [solid bars], published abstract [striped bars]) within subgroups defined by intervention (pharmacological, complementary/alternative, and rehabilitative). (**B**) summarizes the 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, electro-acupuncture, 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

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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 ≥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*)

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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 1 fatigue, 5 with grade 1 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 $\geq$ 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. [d] 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. [e] 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. [f] 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. [g] 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. [h] 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.

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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.	- 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.	- 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.	- Significant improvement in arthralgia score using NCI-CTCAE and PRAI. - Improvement in arthralgia symptoms from baseline wee 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. - Once 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 $\geq$ 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 deceased 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	*Uncaria tomentosa* (cat's claw) extract (n = 32)	Placebo (n = 29)	Unspecified	30 days	BPI, VAS, Lequesne (osteoarthritis) scale, DASH, SF-36 (quality of life)	– 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	- 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	- 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.

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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	- 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.	- 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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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, 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 electroacupuncture 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.

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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 WVV; 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).
Tajaesu 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 ≥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*)

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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 al[97] and Tamaki et al[82] were published in abstract form. Findings from Tamaki et al[82] 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

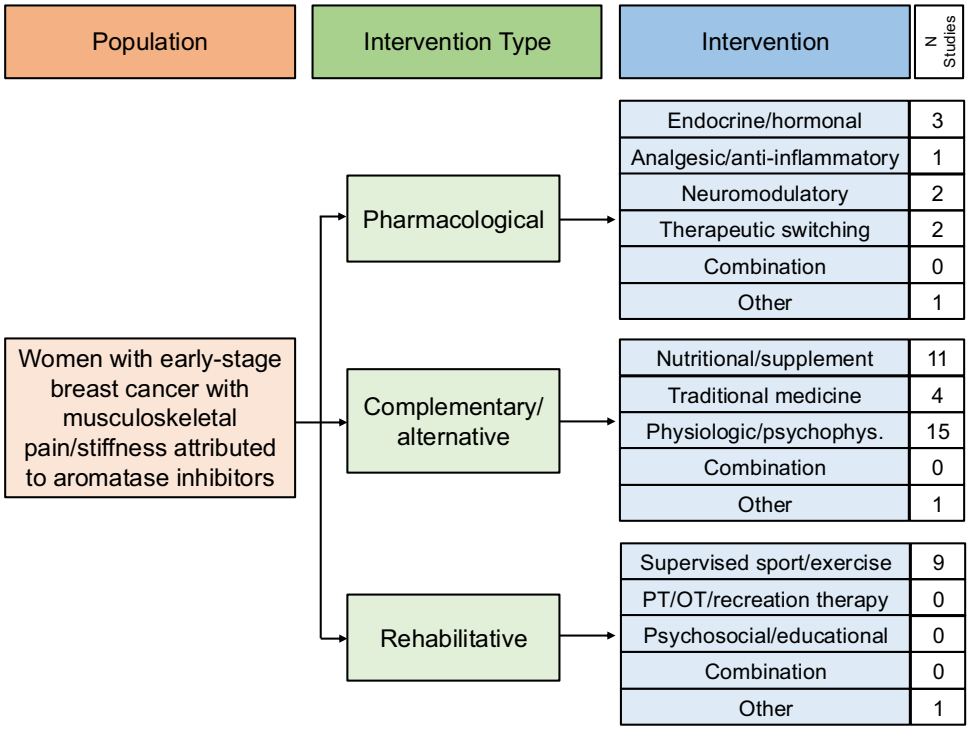

Figure 3 Number of reports by specific intervention.
Abbreviations: OT, occupational therapy; psychophys., psychophysiologic intervention; PT, physical therapy.

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(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 Test[116] 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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