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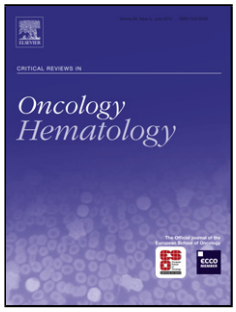

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Management of Aromatase Inhibitor Induced Musculoskeletal Symptoms in Postmenopausal Early Breast Cancer:

A Systematic Review and Meta-analysis

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Introduction

Aromatase Inhibitors (AI) are recommended for the adjuvant treatment of hormone receptor positive breast cancers in the post-menopausal population. These agents block the synthesis of oestrogen by inhibition of peripheral aromatase (1). Compared with Tamoxifen, third generation aromatase inhibitors have been shown to significantly improve disease free survival (DFS) (2-4), and include the steroidal inhibitor exemestane, and the nonsteroidal inhibitors, anastrozole and letrozole. In the 2013 meta-analysis by Aydiner et al (5), five years of adjuvant therapy with aromatase inhibitors improved DFS (HR 0.89, p=0.001), and also overall survival (OS) (HR 0.92, p=0.046) when compared to tamoxifen. Aromatase inhibitors have also demonstrated improvement in DFS, OS and distant metastasis rate when sequenced with tamoxifen (HR 0.70, p<0.001; HR 0.81, p=0.003, HR 0.74, p<0.001 respectively), and an improvement in DFS as extended adjuvant treatment after 5 years of tamoxifen (HR 0.62, p=0.001) (5). Recent evidence has revealed a benefit of continuing aromatase inhibitors for a period of 10 years, as reported in the MA.17R trial, which displayed significant improvement in breast cancer recurrence rates, and decreased contralateral breast cancer (6).

Aromatase inhibitors are associated with joint and muscular symptoms, commonly referred to as aromatase inhibitor-associated musculoskeletal syndrome (AIMSS) (7). AIMSS adversely impacts on the quality of life of many patients. Studies recently investigating AIMSS have shown incidence of musculoskeletal symptoms to be as much as 50% (8-10), higher than the pivotal aromatase inhibitor trials with rates of approximately 20-35% (11-13). The prevalence of musculoskeletal symptoms impacts the long-term care of these patients. Analysis of longitudinal claims data from three American commercial health programs revealed sub-optimal adherence to anastrozole in 19-28% of patients in their first year of treatment (14). These statistics are consistent with other studies of aromatase inhibitor adherence (15-18), which report a significant percentage of patients displaying early discontinuation of treatment. There are important clinical implications of this data, as non-compliance with adjuvant endocrine therapies in early breast cancer has been shown to be detrimental to the patients' survival (16).

AIMSS usually presents as symmetrical pain or soreness in the hands, knees, hips, lower back, shoulders, and/or feet. It is often associated with early-morning stiffness and difficulty sleeping (19). There may be additional extra-articular symptoms present, such as myalgia, fibromyalgia, neuropathy and carpal tunnel syndrome (20). MRI studies conducted on patients taking aromatase inhibitors have shown the development of tenosynovial changes and increased intra-articular fluid in patients with AIMSS (7). Most of the symptoms will develop within the first two to three months of AI treatment

(19, 21). This systematic review aims to summarise the recent literature on the symptom management intervention strategies for AIMSS. Meta-analyses have been conducted where feasible.

Methods

Search Strategy

A systematic search of the electronic literature was designed and conducted by an information specialist (KR) to identify the relevant evidence. The following databases were searched: PubMed, EMBASE, CINAHL and CENTRAL. Controlled terminology (MESH, EMTREE, CINAHL headings) and free text words were used. Google scholar was also searched for unpublished literature. The final search of all the databases was conducted on 24th February 2016. Reference lists of relevant review articles and of the full text reviewed papers were also cross checked and any relevant papers included for review. The complete search strategies for all the databases can be found in Appendix 1.

Study Selection: Inclusion and Exclusion criteria

Type of studies

Although the best type of study to assess the efficacy of an intervention is a randomised controlled trial (RCT), the scope of studies for inclusion in this review has been expanded. This is to reflect the recognition that there are very few RCT in the area, and to be inclusive of as many intervention types as possible to inform clinical practice and respond to patient enquiries. Therefore, all clinical trials (prospective and retrospective), cohort and case control studies and preventative trials were considered. Conference abstracts were included, but where a later full paper has been published, the abstract was excluded and replaced with the full paper. Letters to the editor detailing clinical trial results were also included. Conference abstracts and letters to the editor were only considered in the narrative analysis and were not included in the risk of bias assessment or meta-analysis as there was not enough information to make an accurate analysis. Case studies and small case series were excluded. Papers detailing protocols only, as well as systematic reviews were excluded from the review, although these are considered in the discussion. Only papers published in English were considered.

Types of participants

Women with stage I-III Breast Cancer on an adjuvant treatment with any aromatase inhibitor with, or at risk of, AIMSS were included. AIMSS was defined as any new onset, or worsening, of any musculoskeletal symptom after commencement of an AI. Women with advanced/metastatic breast cancer (Stage IV) were excluded. Papers which did not clearly define the use of aromatase inhibitors distinct to other hormonal therapies were excluded, along with papers which included endocrine therapies other than aromatase inhibitors

Types of intervention

All types of symptom management interventions for AIMSS in this population were considered including – pharmacological, non-pharmacological and CAM (Complementary and Alternative Medicine).

Types of outcome measures

Primary outcomes and secondary outcomes included the improvement in AIMSS (pain, stiffness, mobility or functionality) from baseline, the improvement in persistence and compliance of patients continuing to take their aromatase inhibitor medication due to the intervention, the reduction in incidence of AIMSS, and the adverse events in relation to the intervention treating AIMSS symptoms.

Data synthesis and analysis

Where sufficient quantitative results were reported, meta-analysis was performed. I^2 was used to measure heterogeneity between studies, as per the Cochrane handbook (22). An I^2 value of 50-75% is defined as substantial heterogeneity and an I^2 value of ≥75% is defined as considerable heterogeneity. Heterogeneity was expected between studies, and therefore a random-effects meta-analysis model was used for the meta-analyses. A separate meta-analysis was attempted for each sub-group of intervention. R programming software was used for the statistical analysis (23).

Methodological Quality

RCTs were assessed using the Jadad Scale (24). Trials were deemed high quality studies if score 3-5, whilst score 0-2 was deemed low quality (25). Case control studies were assessed using the Newcastle-Ottawa Scale, where a score of 7 to 9 indicates high methodological quality, a score of 4 to 6 indicates moderate quality and a score of 0 to 3 indicates low quality.

Results

Search results

The search retrieved 1389 articles and after the removal of 458 duplicates, 931 remaining abstracts were screened, as shown in Figure 1. After 836 of these abstracts were excluded, 95 full text articles were assessed, with 38 meeting the inclusion criteria. 57 papers were excluded: In 17 studies the relevant outcomes were not covered; in 12 studies hormonal therapy was not distinguished as AI; in 11 studies the abstracts were superseded by later full text papers; 10 papers were the wrong study design or publication type; 6 papers had the wrong patient setting; and 1 paper was not in English.

Methodological Quality of Selected Studies

Studies were unable to be assessed if they had only been published as an abstract, due to lack of available information. Out of 17 RCTs, only 11 could be adequately assessed for methodological quality, as the rest were only published in abstract form. Of the 11 assessable RCTs, eight studies had a high Jadad score ≥3 (26-33). Three studies scored poorly on the Jadad scale for methodological quality (34-36). Only six cohort studies had full-text available for assessment with the Newcastle Ottowa Scale. Of these six studies, two were assessed as high methodological quality (37, 38); two studies were median methodological quality (17, 39, 40); and one study was of poor methodological quality (41).

Overall Characteristics of Selected Studies

38 studies were included in the final analysis (see Table 1). These included 18 randomised control trials (RCTs)/ controlled clinical trials (CCT), 14 pre/post studies, and 6 cohort studies. Studies were published between 2007 – 2016. The countries in which the studies were conducted include: United States (n=26), Japan (n=2), Spain (n=2), China (n=2), Canada (n=1), England (n=1), Australia (n=1),

Greece (n=1), France (n=1) and Italy (n=1). Of the trials which reported median ages of participants, the median age was 59.5 years (range 29-89). The scoring systems used across trials were extremely diverse, including Health Assessment Questionnaire (HAQ), Visual Analogue Scale (VAS), Brief Pain Inventory (BPI), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Modified Score for the assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH), Functional Assessment of Cancer Therapy – General (FACT-G), Arthritis Impact Measurement Scale (AIMS2), Medical Outcome Study Short Form 36 (SF 36), Pain self-efficacy questionnaire (PSEQ), OMERACT-OARSI criteria, Disabilities of the Arm, Shoulder and Hand (DASH), AUStralian CANadian Osteoarthritis Hand Index (AUSCAN), Breast Cancer Prevention Trial – Musculoskeletal Symptom (BCPT-MS), 5 point Likert Scale, and the use of an electronic algometer and hand grip strength.

The studies were analysed in four separate subgroups: Complementary Therapies; Acupuncture; Physical Therapies and Pharmacological Interventions.

Analysis of Acupuncture Interventions

Study Characteristics

Six studies were included that investigated the use of acupuncture for AIMSS, involving 221 patients in total. There were five RCTs, three of which investigated the use of acupuncture (31, 32, 34) and two of which investigated the use of electro-acupuncture (28, 29). There was also one single-arm pilot study, which investigated the use of electroacupuncture (42). Of the RCTs, three studies investigated true acupuncture/electro-acupuncture versus sham acupuncture (28, 31, 32); one study had three arms consisting of true electro-acupuncture, sham electro-acupuncture and a waitlist control (29) and one trial was a crossover design, investigating acupuncture versus observation, then crossover after six weeks (34). The methods of sham acupuncture differed between trials, with some trials using sham, non-penetrating needles on real acupuncture points (28), and others using sham, non-penetrating needles at non-acupuncture, non-trigger points (29, 32). Crew et al (31), used superficial needle insertion at non-acupuncture points as the control. The median sample size for the studies was 37 (range 12 – 67). The primary outcome of all the studies included change in pain scores after the intervention. One study also listed primary outcomes as perceived benefit of acupuncture, hand strength and inflammatory markers (ESR and CRP) (28).

Results

In the two RCTs by Crew et al (31, 34), there was a reported benefit in the symptoms of AIMSS with the use of acupuncture. In the 2007 trial of 21 patients (34), patients underwent six weeks of

acupuncture followed by six weeks of observation, or vice versa. The mean BPI worst pain score at baseline was 5.3 compared with the mean BPI worst pain score after acupuncture of 3.3 (p=0.008). The benefits of acupuncture did not persist after six weeks of observation. In the 2010 RCT by Crew et al (31), 43 patients were randomised to either real or sham acupuncture for six weeks. There was a difference in pain scores at six weeks between true acupuncture and sham acupuncture arms, with mean BPI-SF worst pain scores 3.0 for true acupuncture versus 5.5 for sham acupuncture (p=0.002). Similar benefits were seen in pain severity (2.59 v 4.53; p<0.001) and pain-related interference (2.48 v 4.54; p<0.002). No follow-up was performed after acupuncture cessation. In all the remaining RCTs investigating the use of acupuncture there was no statistical difference in pain outcomes between real and sham arms (28, 29, 32). In the trial by Bao et al (32), 47 patients were randomised to real or sham acupuncture for eight weeks. After eight weeks, there was no difference between treatment arms in either HAZ-DI scores (p=0.15) or VAS scores (p=0.31). Oh et al (28), investigated real versus sham electroacupuncture for six weeks of treatment in 32 patients. There was no difference between real and sham arms in regards to pain, function and stiffness using WOMAC scores, or pain severity and interference using BPI-SF scores. In the trial by Mao et al (29), 67 patients were enrolled into a three arm RCT, investigating real and sham electroacupuncture versus a waitlist control arm, for eight weeks. Both true electroacupuncture (EA) and sham electroacupuncture (SA) arms revealed a significant improvement in pain severity compared with the waitlist control arm (-2.0 vs -0.2, p=0.0004), but there was no difference between EA and SA arms.

Two studies could be included in the method of meta-analysis, as they used the same scoring systems within their studies (29, 31). There was significant between-study heterogeneity for the effects of acupuncture on BPI-SF worst pain score (I^2=79%). The overall mean difference in worst pain scores after acupuncture, using the random effects model was -0.98 (95% CI, -3.01 – 1.06).

Analysis of Pharmacological Interventions

Study Characteristics

Twelve studies were included that investigated pharmacological interventions for the management of AIMSS, including 3 RCTs, 5 pre/post studies, and 4 cohort studies. Pharmacological therapies used were diverse, and included testosterone (43), etoricoxib (44), calcitonin (36), duloxetine (47), prednisolone (48), thymosin (49), bisphosphonates (40, 50), diuretics (41) and switching of aromatase inhibitor therapy (45, 46). There were 1407 patients analysed in total between all the pharmacological

trials, with a median sample size of 82.5 patients (range 16 – 316). The RCTs used a matched placebo in the control arms, and one of the retrospective cohort studies used controls from the ELPh Trial (Exemestane and Letrozole Pharmacogenetics Trial) (50). The other studies did not include a control arm. The primary outcome for majority of the studies was either the impact of the pharmacological intervention on musculoskeletal symptoms, or the prevention of musculoskeletal symptoms through use of the pharmacological intervention. The study by Liu et al, had a primary outcome of the efficacy of calcitonin as therapy for osteoporosis in patients with bone pain during anastrozole therapy (36). In the study of switch therapy by Briot et al (46), the primary outcome was the percentage of women who discontinued letrozole secondary to musculoskeletal symptoms, after switching from anastrozole. Likewise, in the study of switch therapy by Kadakia et al, the primary outcome was tolerance of, and persistence with aromatase inhibitors (45). In the study of etoricoxib (44), the primary end-point was 5 years event free survival.

Results

Patients in all three RCTs experienced a reduction in pain, which was the primary outcome (36, 43, 44). In the trial by Birrell et al (43), which has only been published as an abstract, 80mg testosterone resulted in a 70% decrease in Visual Analogue Scores (VAS) scores at 3 months, compared to only 35% decrease in VAS scores in the placebo arm ($p=0.04$). The third arm in this trial, testing 40mg testosterone, did not result in a substantial decrease in pain scores ($p=0.06$). The use of testosterone was not associated with a significant elevation in serum oestradiol. Rosati et al studied the use of etoricoxib (60mg/day) versus placebo, in addition to anastrozole (44). This study has also only been published as an abstract. During the trial, there was a U.S. Food and Drug Administration (FDA) alert on the use of etoricoxib and the potential risk for cardiovascular toxicity, resulting in a 38% discontinuation rate. Despite this, the incidence of musculoskeletal pain was still significantly higher in the placebo arm (RR 2.1, 95% CI 1.29 – 3.43, $p=0.002$). The third RCT, by Liu et al investigated calcitonin 200 IU/day plus caltrate D 600mg/day versus caltrate D alone for a period of three months (36). An improvement in pain scores, measured by VAS, was identified in both the placebo arm (score difference -1.00, $p=0.0013$) and intervention arm (score difference -3.00, $p<0.0001$). There was also notably a difference between the improvement in pain scores between the two arms ($p<0.0001$) (36).

Analysis of Complementary Interventions

Study Characteristics

Ten studies were included that investigated the use of complementary therapies, including 6 RCTs, 2 cohort studies and 2 pre/post studies. The interventions included Blue Citrus Herbal (51), omega-3-

fatty-acids (O3FA) (30, 52), vitamin D (26, 27, 37, 39, 53) vitamin E (54) and glucosamine/chondroitin (55). The total number of patients investigated with complementary interventions was 403. The median sample size was 61 (range 31 – 209). All RCTs used a placebo as the comparator arm. The primary endpoint of majority of studies included the impact of the intervention on AIMSS. In the pilot study investigating O3FA, the primary outcome was feasibility (52), but the secondary outcome included patient-reported outcomes (PRO) of AIMSS. In the pre/post study of vitamin E, the primary outcome was the effect of vitamin E administration on female hormones and cytokines in patients experiencing AIMSS (54). Secondary outcomes included the effects of vitamin E on severity of AIMSS. In the vitamin D RCTs, the dosing of vitamin D in the intervention arms varied between studies, with interventions including 4000IU/day vitamin D3 (26); 50000IU vitamin D weekly (27); and 30000 IU vitamin D3 weekly (53).

Results

All three of the RCTs investigating the use of vitamin D (26, 27, 53), showed no benefit in the use of vitamin D for the management of AIMSS. The RCT investigating the use of Blue Citrus Herbal (51), which included 37 patients in the study, reported improvement in VAS pain scores with the use of Blue Citrus Herbal, but it was unclear if these improvements were statistically significant compared to the control arm. Some Blue Citrus herbal formulations can include up to 15 different herbs, including Curcuma (63). Caution is advised for usage of Curcuma in women with hormone sensitive conditions as theoretically it may exacerbate hormone sensitive breast, uterine or ovarian cancers (64). The specific formulation of the herb used in this trial is unclear. The two RCTs investigating the use of O3FA (30, 52) did not find any benefit of O3FA when compared to placebo. The larger of the O3FA RCTs, comprising 249 patients (30), reported a substantial improvement in AIMSS at 12 weeks in both the O3FA arm (BPI-SF score change -1.74, $p<0.001$) and the placebo arm (BPI-SF score change -1.50, $p<0.001$), but no significant difference between groups ($p=0.38$). These results were sustained at the 24 week evaluation. The only positive result in the smaller O3FA RCT (52) was greater pain relief from medications in the O3FA arm at both 12 weeks ($p=0.043$) and 24 weeks ($p=0.011$).

Analysis of Physical Therapy Interventions

Characteristics of Studies

Ten studies were included that investigated the use of physical therapies on the management of AIMSS, including 3 RCTs, 6 pre/post studies and a CCT. Three studies investigated a combined aerobic and resistance exercise program, including two randomised control trials (35, 56), and one pre/post

study (57). One pre/post study investigated a home-based exercise program (58), and two studies investigated walking programs, including one RCT involving Nordic Walking (33), and one pre/post study investigating a self-directed walking program (59). One pre/post study investigated Tai Chi (60), and two other pre/post studies investigated yoga (61, 62). A CCT investigated aquatic exercise (38). Therefore, the physical therapy interventions were extremely heterogeneous, ranging from two one hour tai chi sessions per week for 8 weeks (60), to 150 minutes of aerobic exercise weekly plus supervised strength training twice weekly (35). The mean sample size between studies was 31 patients (range 10-121). The total number of patients investigated in exercise trials was 313.

Results

Of the 3 RCTs, there was only one study showing benefit with physical therapy (35). The HOPE study, by Irwin et al, was the largest of the exercise studies in our analysis, with 121 participants (35). The study reported a 29% improvement in worst BPI scores in the exercise group at 12 months, as compared to a 3% increase in worst pain scores in the usual care group at 12 months ($p<0.001$) (35). The RCT by Fields investigating the use of Nordic walking versus waitlist control did not report any significant benefit in regards to AIMSS (33). The RCT by Lohrisch et al (56), closed early due to poor recruitment, and did not identify any significant benefit in the use of a mixed aerobic/resistance exercise program for the management of AIMSS.

Two studies could be included in a meta-analysis of physical therapy interventions, as only two studies had the same pain scoring system within their studies, with available results (33, 35). There was significant between-study heterogeneity for the effects of physical therapy on BPI-SF worst pain score (I^2=93%). The overall mean difference in worst pain scores after exercise intervention, using the random effects model was -0.29 (95% CI, -3.32 – 2.75).

Discussion

With the improving long-term prognosis for breast cancer patients, there is an increasing focus on survivorship, and the quality of life for breast cancer survivors. Despite the burden of AIMSS in the treatment of hormone receptor positive breast cancer, there is a paucity of large, well-designed trials to provide evidence on the management of this condition. It should be emphasized that there is currently no standardised definition of AIMSS. The condition encompasses a broad range of symptoms, and therefore a standardised definition would not only assist trial design in the future, but also assist oncologists to recognise and manage this condition in the clinical setting.

In compiling this analysis, we identified a variety of factors which unfortunately compromise the quality of the available evidence. The majority of trials considered in this analysis included patients who either already experienced musculoskeletal symptoms which worsened after the initiation of an AI, or patients who developed new onset musculoskeletal symptoms after initiation of an AI. However, several trials which did not stipulate their inclusion requirement for AIMSS at entry. Poorly defined entry criteria may have resulted in some trials investigating long-standing musculoskeletal conditions, such as osteoarthritis, rather than AIMSS specifically. Furthermore, interventions with low perceived toxicity would be more likely to have uptake in patient groups with less severe symptoms leading to differences in patient groups between trials (65). The retrospective studies would have likely used physician-reported AIMSS and outcomes, whereas the most reliable process for reporting patient quality of life outcomes includes patient reported outcomes (PRO). (66)

In the trials included in this analysis, a diverse range of scoring symptoms were used to record patient symptoms. Due to the heterogeneity of scoring systems used, it was difficult to compare the benefit of interventions between trials. The more simplistic scoring systems, such as VAS, may result in either overestimation or underestimation of the perceived benefit of an intervention. Multiple studies did not disclose their complete list of scoring results, which may indicate a risk of bias in the reporting of results.

Our analysis included many studies investigating the management of AIMSS, but overall they provide poor quality evidence in this area. The majority of studies had small sample sizes and a high risk of inherent bias. As expected, it is extremely difficult to blind the intervention group in certain studies, and impossible to blind treatment arms in the physical therapy groups. The placebo effect has been found to be significant in other studies of pharmacological treatment of debilitating toxicities of cancer treatment (65, 67, 68). In addition, the choice of placebo or control arm may have contributed to some borderline results. Careful consideration should be given to the choice of placebo, as contamination may be a problem. For example, in one trial investigating the use of O3FA (30), soybean was used in the placebo tablet. It has been hypothesised that an oestrogenic component in soy may have impacted on the pain scores in the control arm. In a number of acupuncture trials, there was an improvement in pain scores in both the real acupuncture and sham acupuncture arms. It is theorised that sham acupuncture may provide a therapeutic benefit by triggering the release of endorphins or activation of pain related neural matrix (69). Many of the acupuncture trials have gone to great lengths to attempt to eliminate the risk of bias from their study, but as expected, they have not been able to successfully blind their treatment arms to patients. This may have resulted in a bias of results stemming from positive patient expectations. Most of the studies also did not report trial participants'

usage of other medications, including analgesia. There should be rigorous control for medications taken by trial participants, to prevent confounding variables affecting the trial outcome.

There are a number of trials currently ongoing, with interventions such as duloxetine (NCT01598298), the interplay of pain, sleep quality and fatigue (NCT01983995), hypnosis (NCT02657993), testosterone (NCT01573442), acupuncture (NCT01535066), vitamin D (NCT01988090), and kinesiotaping (NCT02406794). Hopefully these trials will provide further evidence for the optimal management of AIMSS.

Conclusion

Suboptimal compliance with AI adjuvant therapy due to inadequately managed AIMSS remains a major unmet need in oncology practice. Patients who have failed to control AIMSS with over the counter analgesics may be willing to try other interventions, including complementary therapies, for symptom relief. Many of these women have been financially impacted by their cancer and its treatment and some of the therapies discussed here may involve considerable financial commitment. Caution may also need to be advised if the CAM potentially contains oestrogenic compounds which may explain the mechanism of action and which theoretically could compromise breast cancer survival. Pharmacological treatment is often recommended by health professionals for AIMSS, however in conclusion, there is limited published evidence for its use. Exercise showed benefit in a single RCT (35), but the other studies showed little evidence of benefit. Information from the meta-analysis is limited by inclusion of only two studies with opposing results. The evidence for acupuncture is not strong enough to recommend it for the treatment of AIMSS. Although the interventions generally appear tolerable with minimal adverse effects, the current level of evidence is low, and additional large RCTs with more rigorous control for contamination from other interventions are required to confirm some of the reported promising results.

APPENDIX 1

PubMed

1."Aromatase Inhibitors"[Mesh]
2. "exemestane"[Supplementary Concept])
3. "letrozole"[Supplementary Concept])
4. "Aminoglutethimide"[Mesh])
5."atamestane"[Supplementary Concept])
6. "Fadrozole"[Mesh])
7. "formestane"[Supplementary Concept])
8. "vorozole"[Supplementary Concept])
9. "aromatase inhibitor"
10. "aromatase inhibitors"
11. anastrozole
12. arimidex
13. exemestane
14. letrozole
15. aromasin
16. femara
17. fadrozole
18. formestane
19. lentaron
20. vorozole
21. rivizor
22. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
23. "Musculoskeletal Diseases"[Mesh])
24. "Pain"[Mesh]
25. "Pain Measurement"[Mesh]
26. "Carpal Tunnel Syndrome"[Mesh])
27. musculoskeletal OR musculo-skeletal
28. (joint* OR hand OR hands OR elbow* OR knee* OR wrist*) AND (pain* OR discomfort* OR tender* OR stiff*)
29. tendinitis
30. tendinopath*
31. tenosynovitis
32. arthralg*
33. rheumat*
34. "trigger finger"
35. "carpal tunnel syndrome"
36. fibromyalg*
37. myalg*
38. #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37
39. "Postmenopause"[Mesh]
40. “Breast Neoplasms"[Mesh]
41. breast AND (cancer OR cancers OR carcinoma* OR malignan* OR tumor OR tumors OR tumour*)
42. #39 OR #40 OR #41
43. Clinical[Title/Abstract]) AND Trial*[Title/Abstract]
44. "Clinical Trials as Topic"[Mesh]

45. "Clinical Trial" [Publication Type]
46. random*[Title/Abstract]
47. "Prospective Studies"[Mesh]
48. “Follow-Up Studies"[Mesh]
49. "Feasibility Studies"[Mesh]
50. pilot[Title/Abstract]
51. prospective[Title/Abstract]
52. #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
53. #22 AND #38 AND #42 AND #52

EMBASE

1. aromatase NEAR/2 inhibit*
2. 'aromatase inhibitor'/exp
3. anastrozole
4. exemestane
5. 'letrozole'
6. aminoglutethimide*
7. atamestane
8. formestane
9. vorozole
10. arimidex
11. aromasin
12. femara
13. fadrozole
14. lentaron
15. rivizor
16. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17. 'breast cancer'/exp
18. breast NEAR/3 (cancer* OR carcinoma* OR malignan* OR tumo*r*)
19. #17 OR #18
20. 'clinical trial'/exp
21. 'feasibility study'/exp
22. `pilot study'/exp OR
23. 'prevention study'/exp
24. 'comparative study'/exp
25. 'intervention study'/exp
26. 'prospective study'/exp
27. random*:ab,ti
28. (clinical:ab,ti AND trial:ab,ti)
29. pilot*:ab,ti
30. prospective:ab,ti
31. group*:ab,ti
32. feasability:ab,ti
33. controlled:ab,ti
34. #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR 26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
35. 'pain measurement'/exp
36. 'pain assessment'/exp
37. musculo*skeletal:ab,ti

38. arthralg*:ab,ti
39. 'carpal tunnel syndrome':ab,ti
40. 'trigger finger':ab,ti
41. tendin*:ab,ti
42. myalg*:ab,ti
43. fibromyalg*:ab,ti
44. tenosynov*:ab,ti
45. ((joint* OR muscl* OR hand* OR knee* OR hip* OR shoulder* OR feet OR foot OR elbow*) NEAR/3 (pain* OR stiff* OR sore* OR discomfort* OR symptom*)):ab,ti
46. 'morning stiffness'/exp
47. 'musculoskeletal stiffness'/exp
48. 'musculoskeletal disease'/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
49. 'arthropathy'/exp/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm-_pc
50. 'pain'/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
51. 'arm pain'/de
52. OR 'hand pain'/de
53. 'leg pain'/exp/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
54. 'limb pain'/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
55. 'limb pain'/de OR
56. 'myalgia'/exp/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
57. 'neuralgia'/exp/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
58. 'shoulder pain'/dm_su,dm_dt,dm_th,dm_rh,dm_dm,dm_pc
59. 'wrist pain'/de
60. #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59
61. #16 AND #19 AND #34 AND #60

CENTRAL

#1 MeSH descriptor: [Aromatase Inhibitors] explode all trees
#2 aromatase inhibit* (Word variations have been searched)
#3 anastrozole or exemestane or letrozole or aminoglutethimide* or ata mestane or fadrozole or formestane or vorozole or arimidex or aromasin or femara or fadrozole or lentaron or rivizor (Word variations have been searched)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Breast Neoplasms] explode all trees
#6 breast near cancer
#7 breast near (tumour or tumor)
#8 breast near malignan*
#9 breast near carcinoma
#10 #6 or #7 or #8 or #9
#11 MeSH descriptor: [Musculoskeletal Diseases] 1 tree(s) exploded
#12 myalg*
#13 fibromyalg*
#14 arthropath*
#15 (joint or muscl* or arm* or leg* or shoulder* or elbow* or knee* or hip* or hand* or feet or foot)
#16 (pain* or stiff* or sore* or discomfort* or symptom*)
#17 #15 near #16

#18 tendin*
#19 (musculoskeletal or musculo-skeletal)
#20 "trigger finger" or "carpal tunnel"
#21 tenosynov*
#22 #12 or #13 or #14 or #17 or #18 or #19 or #20 or #21
#23 #11 or #22
#24 #4 and #10 and #23 in Trials

CINAHL

1. (MH "Aromatase Inhibitors+")
2. TX (aromatase N3 inhibit*)
3. TX exemestane
4. TX letrozole
5. TX aminoglutethimide*
6. TX atamestane
7. TX fadrozole
8. TX formestane
9. TX vorozole
10. TX arimidex
11. TX aromasin
12. TX femara
13. TX fadrozole
14. (TX hormon* W1 therap*)
15. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16. ((TX (joint* OR muscl* OR hand* OR knee* OR hip* OR shoulder* OR feet OR foot OR elbow* OR rheumat* OR arthrit*) N4 TX (pain* OR stiff* OR discomfort* OR symptom* OR mobil*))
17. (MH "Treatment Related Pain")
18. (MH "Pain Measurement")
19. (MH "Pain+")
20. (MH "Knee Pain+")
21. (MH "Metatarsalgia")
22. (MH "Muscle Pain")
23. (MH "Arthralgia+")
24. (MH "Shoulder Pain")
25. (MH "Musculoskeletal Diseases")
26. (MH "Foot Diseases+")
27. (MH "Joint Diseases+")
28. (MH "Muscular Diseases+")
29. (MH "Rheumatic Diseases+")
30. TX musculo#skeletal
31. TX arthralg*
32. TX myalg*
33. TX tendin*
34. TX fibromyalg*
35. TX tenosynov*
36. TX "trigger finger"
37. TX "carpal tunnel"
38. (MH "Joints+")

39. (MH "Pain Threshold")
40. (MH "Range of Motion")
41. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
42. (MH "Breast Neoplasms") OR (MH "Carcinoma, Ductal, Breast") OR (MH "Hereditary Breast and Ovarian Cancer Syndrome"))
43. (TX(breast N3 (cancer* OR carcinoma* OR malignan* OR tumo#r*))))
44. ((MH "Cancer Survivors")))
45. #42 OR #43 OR #44
46. #15 AND #41 AND #45

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Figure 1: PRISMA FLOW CHART

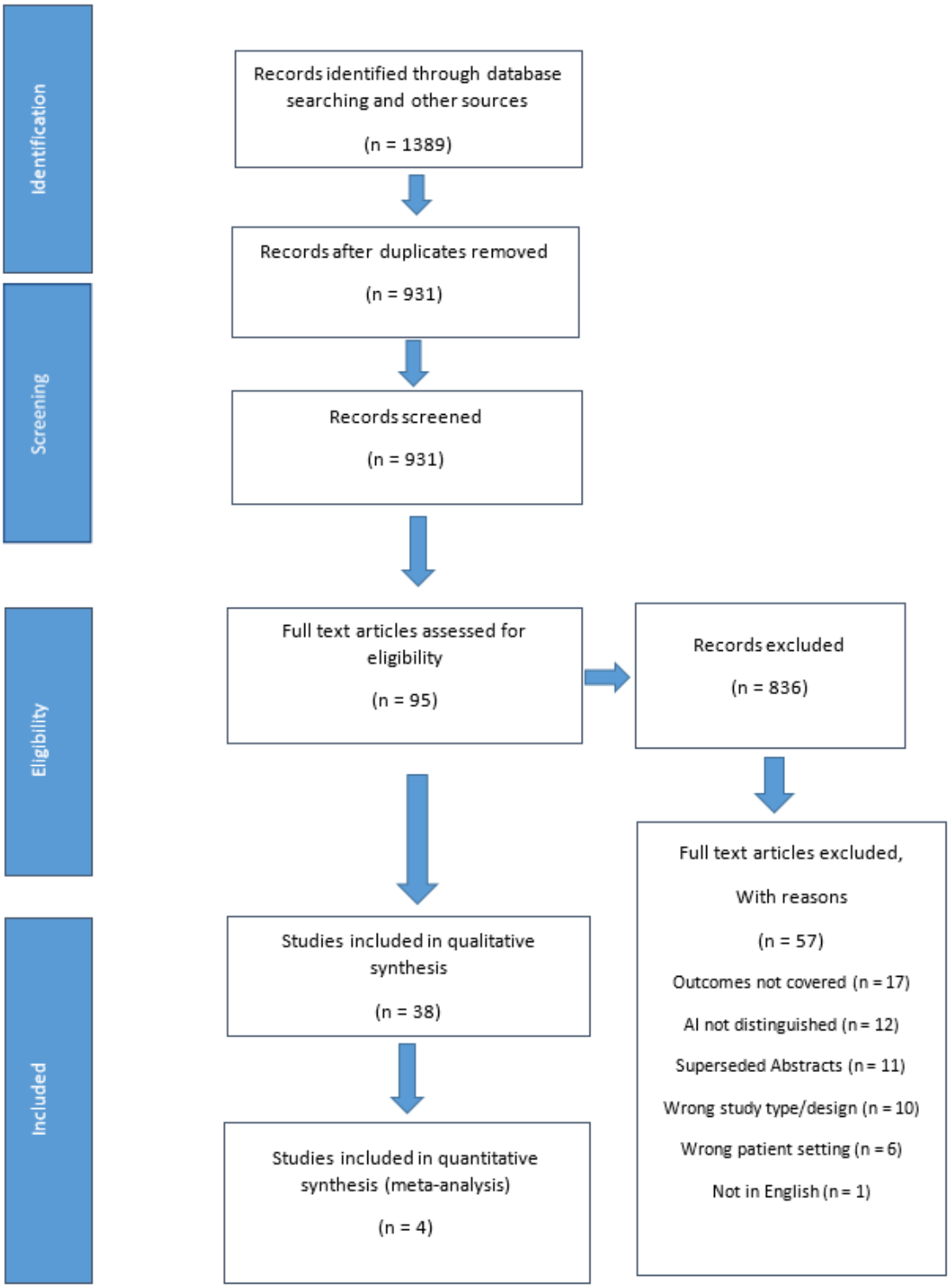

Figure 2: Effect of acupuncture on AIMSS using BPI-SF. SD, standard deviation; MD, mean difference; CI, confidence interval.

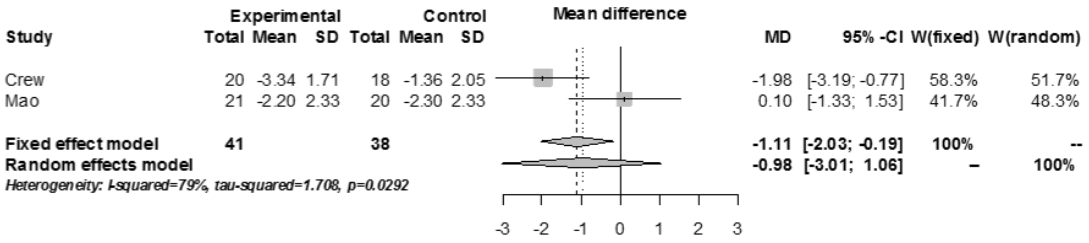

Figure 3: Effect of physical therapy on AIMSS using BPI-SF. SD, standard deviation; MD, mean difference; CI confidence interval.

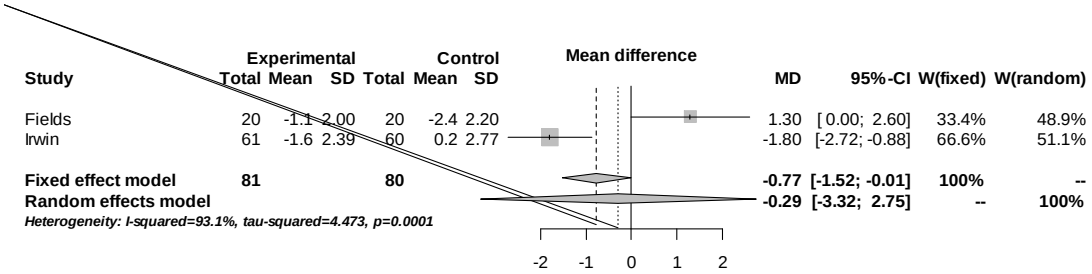

Table 1: All included studies in the analysis

Intervention & Author	Type	n	Arms	Significant Outcome
Acupuncture				
Acupuncture *Bao 2013 (32)*	RCT	51	Real vs Sham (8 weeks)	No. Similar VAS scores at 8 weeks between real and sham arms (p 0.31)
Acupuncture *Crew 2007(34)*	RCT	21	Real (RA) vs Sham (SA) 6 weeks then crossover	Yes, RA better at 6 weeks (values not given). Not sustained 12 weeks
Acupuncture *Crew 2010 (31)*	RCT	38	Real vs Sham (6 weeks)	Yes. Worst pain 3 vs 5.5 (p<0.001) at 6 weeks
Electroacupuncture *Oh 2013 (28)*	RCT	32	Real vs Sham (6 weeks)	No. No difference in pain between groups (no values given)
Electroacupuncture *Mao 2014 (29)*	RCT	67	Real vs Sham vs waitlist (8 weeks)	Yes. Decrease in pain severity in EA (-2.2) vs WLC (-0.2, p=0.0004), week 8. Benefits continue week 12.
Electroacupuncture *Mao 2009 (42)*	Pre/post	12	6 weeks	Yes. Decrease in pain severity (5.3 to 1.9; p<0.001)
Pharmacological				
Testosterone *Birrell 2010 (43)*	RCT	90	Placebo vs 40mg vs 80mg daily	Yes. VAS score decreased 70% in 80mg arm, compared to 35% decrease in placebo arm (p=0.04)
Etoricoxib *Rosati 2011 (44)*	RCT	182	Etoricoxib 60mg/day vs placebo	Yes. Improved pain. 31% MSS symptoms vs 76% (RR 2.1 p=0.002)
Calcitonin *Liu 2014 (36)*	RCT	82	200IU/day salmon calcitonin daily	Yes. Improvement in VAS scores in both groups (placebo -1.00; calcitonin -3.00). Difference between groups p<0.01.
Switch *Kadakia 2016 (45)*	Pre/post	83	Exemestane or letrozole; crossover if intolerant	62% continued second aromatase inhibitor at 6 months.
Switch *Briot 2010 (46)*	Pre/post	179	Anastrozole switched to letrozole	Yes. 19% decrease pain scores (p<0.001) 72% continued letrozole 6 months.
Duloxetine *Henry 2011 (47)*	Pre/post	29	30mg 7 days, then 60mg 21 days, then 60mg bid	Yes. Mean decrease pain severity 60% (p<0.001; 95% CI 49-73%)
Prednisolone *Kubo 2012 (48)*	pre/post	27	5mg prednisolone for 1 week.	Yes. 52% reported improved VAS at 2 months post prednisolone use. No p-values given
Thymosin *Zhang 2010 (49)*	Pre/post	16	Thymosin α1 1.6mg twice weekly for 4 weeks	Yes. Decreased BPI worst pain scores (5.7-3.4, p<0.001)
Bisphosphonates *Santa Maria 2014 (50)*	Cohort	59	Zoledronic acid 4mg baseline and 6 months	Yes. 37% on zoledronic acid had AIMSS, compare to 61% in historical cohort (p<0.001)
Bisphosphonates *Muslimani 2009 (40)*	Retrospective Cohort	316	Calcium and Bisphosphonate vs none	Yes. Associated between AIMSS symptoms and low bone mineral density (p<0.001)
Diuretic Therapy *Xepapadakis 2010 (41)*	Retrospective Cohort	288	Diuretic therapy vs no diuretics	Yes. 7% on diuretics had arthralgia, compared with 16% not on diuretics (p0.01)
Analgesics/ supplements *Presant 2007 (17)*	Retrospective Cohort	56	Chart review pain meds and effectiveness	50% obtained relief from NSAIDs
Complementary Therapies				
Blue Citrus Herbal (BCH) *Massimino 2011 (51)*	RCT	31	BCH vs Placebo (P) then crossover 90 days each	Yes. Both arms experienced decreased VAS (p<0.02). No p value given for BCH vs P
O3FA *Herschmann 2015 (30)*	RCT	249	O3FA vs placebo 24 weeks	Yes. Improved BPI worst pain in O3FA arm (-2.23, p<0.001) and placebo arm (-1.81, p<0.001). No difference between arms (p=0.52)
O3FA *Lustberg 2014 (52)*	RCT	44	O3FA vs placebo 24 weeks	No difference in mean BPI-SF pain scores. Less interference of pain in O3FA arm (-0.72, p=0.08)
Vitamin D *Khan 2012 (53)*	RCT	160	30000IU D3wkly vs placebo for 24 weeks	No. 51% in placebo arm vs 37% in vitamin D arm had MS event (p=0.069)

Vitamin D *Rastelli 2011 (27)*	RCT	60	Vit D2 50000IU vs placebo weekly 8-16 weeks then mthly for 4 months	Benefit in BPI worst pain in Vit D arm at 2 months (p=0.0045). No difference between groups in regards to pain at 4 or 6 months.
Vitamin D *Shapiro 2016 (26)*	RCT	113	600 IU Vit D3 vs 4000 IU Vit D3 daily for 6 months	No. Change in BCPT-MS scores at 6 months: -0.5 in 600IU D3 vs -0.2 in 4000 IU D3, p=0.38
Vitamin D *Khan 2010 (39)*	Cohort	51	Vit D3 50000IU weekly for 12 weeks if 25OHD <40ng/ml vs standard D3/Calcium	Yes. Difference in pain between Vit D <66ng/ml (52%) vs > 66ng/ml (19%; p=0.026).
Vitamin D *Prieto-Alhambra 2011 (37)*	Cohort	290	16000 IU Vit D3 q2wkly if 25(0H)D <30ng/ml vs Vit D3 800 IU daily	Joint pain less likely if 25(OH)D >40ng/ml (p<0.008). VAS scores increased in entire cohort (p<0.001)
Vitamin E *Kiyomi 2015 (54)*	Pre/post	62	Vit E (150mg/day) for 30 days	Yes. Mean osteoarthropathy scores (scoring 0-3) improved with Vitamin E (p=0.0178)
Glucosamine/ chondroitin *Greenlee 2013 (55)*	Pre/post	37	Glucosamine (1500mg) + chondroitin (1200mg) daily. 24 weeks	Yes. Benefit in BPI worst pain (-1.2, p=0.02); M-SACRAH pain (-13.8, p=0.0008) & WOMAC pain (-10.7, p=0.02).
Physical Therapies				
Aerobic/Resistance *Irwin 2015 (35)*	RCT	121	12/12 supervised vs usual care	Yes. Decreased pain by 1.6 points vs 0.2 points (p<0.001)
Aerobic/Resistance *Lohrisch 2011 (56)*	RCT	20	48/52. Step-down supervision vs UC	No. No difference between groups. No p values given for results.
Aerobic/Resistance *Lash 2011 (57)*	Pre/post	14	Supervised, 2-3 times/week, 8/52	Yes. Pain in multiple joints decreased (p<0.05). Scores not given.
Aerobic/Resistance *DeNysschen 2013 (58)*	Pre/post	26	8/52 home-based exercise	Yes. Improvement in pain by AIMS2, -2.7 (p=0.01).
Aquatic *Cantarero-Villanueva 2012 (38)*	CCT	40	2/12 hydrotherapy vs waitlist	Yes. Improved pressure pain threshold in treatment arm (p<0.05). No benefit in waitlist arm.
Nordic Walking *Fields 2015 (33)*	RCT	40	6/52 supervised followed by 6/52 self-managed walking vs waitlist control	No. Pain scores changed -1.1 Nordic walking vs -2.4 control group (p=0.10)
Walking *Nyrop 2014 (59)*	Pre/post	20	Self-directed walking program, 6/52	No. Mean joint pain decreased 10% (p0.63)
Tai Chi *Galantino 2013 (60)*	Pre/post	12	Supervised tai chi, 8/52	No. Difference in pain severity -1.04 (p=0.058)
Yoga *Jacobsen 2015 (61)*	Pre/post	10	Supervised yoga, 12/52	Yes. Improved BPI pain severity -1.35 (p=0.015)
Yoga *Galantino 2012 (62)*	Pre/post	10	Supervised, 8/52	Yes. BPI pain severity reduced (3.90 to 2.79; p<0.05)

VAS = visual analogue scale, EA = electroacupuncture, WLC = waitlist control, MSS = musculoskeletal symptoms, Vit = vitamin, BPI = brief pain inventory, AIMSS = Aromatase inhibitor-induced musculoskeletal symptoms, NSAIDs = non-steroidal anti-inflammatory drugs, O3FA = omega 3 fatty acids, BPI-SF = brief pain inventory, short-form, BCPT-MS = Breast Cancer Prevention Trial-Musculoskeletal Symptoms subscale, M-SACRAH = Modified Score for the assessment of Chronic Rheumatoid Affections of the Hands, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, AIMS2 = Arthritis Impact Measurement Scale