

Cochrane Corner



What are the effects of systemic therapies for the prevention and treatment of aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer? - A Cochrane Review summary with commentary

Ekin Ilke Sen

Department of Physical Medicine and Rehabilitation, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

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The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review “Systemic therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer”¹ by Roberts et al.^a, published by the Cochrane Breast Cancer Group. This Cochrane Corner is produced in agreement with Journal of Musculoskeletal and Neuronal Interactions by Cochrane Rehabilitation with views* of the review summary author in the “implications for practice” section.

Background

Despite major achievements in diagnosis and management, breast cancer remains a worldwide public health problem. Aromatase inhibitors (AIs) have established benefits in the prevention and management of hormone receptor-positive breast cancer². However, approximately 50% of the patients who receive this therapy experience AI-induced

musculoskeletal symptoms (AIMSS)³. Individuals suffering from AIMSS experience arthralgias, myalgias, joint stiffness, and tendinopathy, which may lead to limited physical activity and restricted daily living activities, resulting in diminished quality of life (QoL) and frequent therapy discontinuation⁴⁻⁶. Therefore, the prevention and treatment of AIMSS in early breast cancer is considered an important research area. A recent Cochrane Review by Roberts et al.¹ studied the effectiveness of systemic therapies for the prevention and treatment of AIMSS in patients with early breast cancer.

Systemic therapies for preventing or treating aromatase inhibitor-induced musculoskeletal symptoms in early breast cancer^a

(Roberts KE, Adsett IT, Rickett K, Conroy SM, Chatfield MD, Woodward NE, 2022)

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*Corresponding author: Ekin Ilke Sen, MD, Assistant Professor, Istanbul University Istanbul Faculty of Medicine, Department of Physical Medicine and Rehabilitation, 34093 Capa, Istanbul, Turkey
E-mail: ekinozgorgu@gmail.com*

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* The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.



What is the aim of this Cochrane Review?

The aim of this Cochrane Review was to determine whether systemic therapies had any effects on the prevention and treatment of AIMSS in early hormone receptor-positive breast cancer.

What was studied in the Cochrane Review?

The population addressed in this review included women receiving AIs, with stage I to III oestrogen and/or progesterone receptor-positive breast cancer. The interventions studied were randomized controlled trials (RCTs) that assessed the effects of systemic therapies, including pharmacological therapies, dietary supplements, and complementary and alternative medicines, on the prevention or management of AIMSS. These interventions were compared to a placebo treatment and/or standard of care. The main outcomes studied were symptoms of AIMSS (i.e. pain, stiffness, and grip strength), safety, AI discontinuation, QoL [health-related quality of life (HRQoL) and breast cancer-specific quality of life (BCS-QoL)], and the incidence of AIMSS.

Search methodology and up-to-dateness of the Cochrane Review

The authors of the review extensively searched for RCTs in any language that had been published up to September 2020 on the CENTRAL, MEDLINE, Embase, CINAHL, World Health Organization International Clinical Trials Registry Platform (ICTRP), and Clinicaltrials.gov registries, as well as those published up to March 2021 on the Cochrane Breast Cancer Group (CBCG) Specialised Register.

What are the main results of the Cochrane Review?

The review included 17 studies, with a total of 2034 randomized participants. Of these studies, 13 had data on the treatment of AIMSS, while four reported on the prevention of AIMSS. All other outcome data were synthesized using novel methods outlined in Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions⁷. The findings were as follows.

Prevention studies relevant to aromatase inhibitor-induced musculoskeletal symptoms

- Two studies (one on vitamin D and one on omega-3 fatty acids) involving 183 people assessed pain. It is unclear whether these therapies had a positive or negative effect on pain. The evidence was considered very low certainty because certain studies showed no evidence of clinically important differences for these therapies.
- One study (on vitamin D) involving 137 people assessed grip strength and one study (on vitamin D) involving 147 people assessed discontinuation of AI. Systemic therapies may make little to no difference in grip strength (RR 1.08, 95% CI 0.37 to 3.17) or AI discontinuation (RR 0.16, 95% CI 0.01 to 2.99). The evidence was considered low certainty.

- A single study (on omega-3 fatty acids) involving 44 participants assessed QoL. Systemic therapies may make little to no difference in HRQoL and BCS-QoL from baseline to end of intervention. The evidence was considered low certainty.
- Two studies (both on vitamin D) involving 240 participants assessed incidence of AIMSS. It is uncertain whether these therapies had a positive or negative effect on the incidence of AIMSS (RR 0.82, 95% CI 0.63 to 1.06). The evidence was considered very low certainty.
- Four studies involving 344 participants assessed the safety of systemic therapies in AIMSS. It is unclear whether any of these studies found a positive or negative effect on the safety of systemic therapies because of the very low certainty evidence. No serious adverse events were reported in any of the studies.
- Stiffness was not assessed in the included studies.

Treatment studies relevant to aromatase inhibitor-induced musculoskeletal symptoms

- Ten studies involving 1099 participants assessed pain. Four studies (on calcitonin, bionic tiger bone, Yi Shen Jian Gu granules, and vitamin D) showed minimal clinically important differences for this outcome. However, six studies (on testosterone, vitamin D, duloxetine, omega-3 fatty acids, emu oil, and Cat's claw) showed no evidence of clinically important benefits. It is uncertain whether systemic therapies had a positive or negative effect on pain as the certainty of the evidence has been assessed as very low.
- Four studies involving 295 participants assessed stiffness. Two studies (one on bionic tiger bone and one on Yi Shen Jian Gu granules) showed minimal clinically important differences for this outcome. However, two studies (one on vitamin D and one on emu oil) showed no evidence of clinically important benefits. It is uncertain whether systemic therapies had a positive or negative effect on stiffness. The certainty of the evidence was very low.
- A single study (on vitamin D) involving 107 participants investigated grip strength. Systemic therapies likely result in little to no difference in grip strength, because of the low certainty of the evidence.
- Two studies (one on bionic tiger bone and one on Yi Shen Jian Gu granules) involving 147 participants and three studies (on bionic tiger bone, Yi Shen Jian Gu granules, and Cat's claw) involving 208 participants were assessed BCS-QoL and HRQoL, respectively. It is unclear whether systemic therapies had a positive or negative effect on QoL. The evidence was considered very low certainty.
- Ten studies involving 1250 participants assessed the safety of systemic therapies. It is uncertain whether systemic therapies are safe for the treatment of AIMSS because of the very low certainty evidence. No grade four or five adverse events were reported.
- The incidence of AIMSS and AI discontinuation were not assessed in the included studies.

How did the authors conclude?

The authors of the review were uncertain as to whether systemic therapies reduce the pain levels and incidence of AIMSS, as very low-certainty evidence was found for the prevention of AIMSS. Additionally, systemic therapies may make little to no differences in grip strength, QoL, or AI discontinuation. The review authors were also uncertain as to whether systemic therapies improve pain, stiffness, or QoL, as the certainty of the evidence has been assessed very low for the treatment of AIMSS. Evidence regarding the safety of systemic therapies was very uncertain for the prevention and treatment of AIMSS. Furthermore, the authors stated that these results should be interpreted with caution, as many of the included studies had small sample sizes, heterogeneous systemic therapy interventions, and significant methodological limitations and imprecision. Consequently, the meta-analysis was limited.

What are the implications of the Cochrane evidence for practice in rehabilitation?

This review provides a contemporary appraisal of the recent literature on systematic therapies for the prevention and treatment of AIMSS¹. However, there is currently very low-quality evidence to support or refute the use of any systemic therapies for the prevention and treatment of AIMSS in women with early breast cancer. Given that the quality of the currently available evidence is very low, there is also a need for better quality, adequately powered clinical trials with long-term follow-up to determine if pharmacological therapies, dietary supplements, or complementary and alternative medicines are effective for the prevention or treatment of AIMSS.

Despite these inconclusive findings, multiple approaches including patient education, weight management, exercise, omega-3 fatty acids, vitamin D supplementation, and pharmacological agents, such as duloxetine have been used in clinical practice for preventing and managing AIMSS⁸. Among these approaches, exercise interventions seem to be a safe and useful strategy to improve musculoskeletal symptoms and QoL in breast cancer survivors taking AIs⁹. However, the results of a Cochrane Review of exercise for the treatment of AIMSS indicate that there was very low-certainty evidence regarding the overall effect of exercise on pain, grip strength, HRQoL, cancer-specific QoL or adherence to AIs¹⁰. Additionally, exercise may improve cardiorespiratory fitness and muscle strength, and reduce pain and fatigue among breast cancer patients during adjuvant therapy^{10,11}. It should be highlighted that physical therapy interventions, which were not considered to be systemic therapies, were not investigated in the studies evaluated by this review. Moreover, future research should clarify the role of the combination of systemic therapies and rehabilitative interventions in women receiving AIs for the treatment of early breast cancer, as this approach seems to be effective in terms of musculoskeletal symptom relief and improved QoL.

From a rehabilitation perspective, the prevention and

treatment of AIMSS is very important due to its consequences resulting in disability with activity limitations and participation restrictions. A better understanding of the underlying mechanisms and the risk factors for the development of AIMSS is needed to develop effective therapeutic strategies for this condition^{4,12}. Furthermore, it may not be appropriate to generalize the results of studies conducted in heterogeneous populations. Thus, tailored interventions targeting specific impairments may be necessary to enable the prevention and treatment of AIMSS in breast cancer survivors.

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