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Comparison of the clinical effectiveness of treatments for aromatase inhibitor-induced arthralgia in breast cancer patients: a protocol for a systematic review and network meta-analysis

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ABSTRACT

Introduction Aromatase inhibitor-induced arthralgia (AIA) is a major adverse event of aromatase inhibitors (AIs) and leads to premature discontinuation of AI therapy in breast cancer patients. The objective of this protocol for a systematic review and network meta-analysis (NMA) is to provide the methodology to compare the change in pain intensity between different AIA treatments and demonstrate the rank probabilities for different treatments by combining all available direct and indirect evidence.

Methods and analysis PubMed, the Cochrane Controlled Register of Trials (CENTRAL), EMBASE, Web of Science and ClinicalTrials.gov will be searched to identify publications in English from inception to November 2019. We will include randomised controlled trials (RCTs) assessing the effects of different treatments for AIA in postmenopausal women with stage 0–III hormone receptor-positive breast cancer. The primary endpoints will be the change in patient-reported pain intensity from baseline to post-treatment. The number of adverse events will be presented as a secondary outcome.

Both pairwise meta-analysis and NMA with the Frequentist approach will be conducted. We will demonstrate summary estimates with forest plots in meta-analysis and direct and mixed evidence with a ranking of the treatments as the P-score in NMA. The revised Cochrane risk-of-bias tool for randomised trials will be used to assess the methodological quality within individual RCTs. The quality of evidence will be assessed.

Ethics and dissemination As this review does not involve individual patients, ethical approval is not required. The results of this systematic review and NMA will be published in a peer-reviewed journal. This review will provide valuable information on AIA therapeutic options for clinicians, health practitioners and breast cancer survivors.

PROSPERO registration number CRD42019136967.

Strengths and limitations of this study

- This systematic review and network meta-analysis will combine all available direct and indirect evidence.
- Where possible, the study will demonstrate the rank probabilities of different treatments for aromatase inhibitor-induced arthralgia.
- To ascertain the robustness of the findings, the primary network and the alternative network will be evaluated.
- The diverse details in the treatment classes may interfere with the transitivity assumption.

INTRODUCTION

Breast cancer has been estimated to account for 30% of all new cancer diagnoses in women and is the second leading cause of female cancer death in the USA in 2019. In Europe, breast cancer was estimated to be the most common cancer site and the most common cause of death from cancer among women in 2018.[1] The mortality rate for breast cancer rapidly dropped over 40% in the last 30 years in the USA, the UK, Canada and Australia.[2] In South Korea, while breast cancer is still the fifth leading cause of cancer death in women (8.5% of estimated deaths) in 2019,[3] a 2.4-fold increase in the breast cancer mortality was observed from 1985 to 2016.[2] Breast cancer mortality rates were also increasing in China, Japan and Thailand.[2 4] Survival from breast cancer results from advances in early detection and treatment.[4]

Third-generation aromatase inhibitors (AIs), anastrozole, letrozole and exemestane, are routinely administered to hormone receptor-positive breast cancer patients as endocrine treatment.[5] Primary and sequential AI therapy significantly improves disease-free survival,[6] and extended AI therapy for up to 10 years prevents distant recurrence and second breast cancer.[7]

The adverse events associated with AI are arthralgia, hot flashes, vaginal dryness, fatigue, bone pain, insomnia, night sweats, nausea and vomiting, and mood disturbance.[8 9] A

meta-analysis published in 2017 revealed that the overall pooled prevalence rate of AI-induced arthralgia (AIA) was 45.9% in postmenopausal hormone receptor-positive breast cancer patients.[10] AIA impairs quality of life in breast cancer survivors and leads to premature discontinuation of AIs.[8 11] While the use of AIs for hormone receptor-positive breast cancer patients for 5 or 10 years is firmly supported, with accumulated evidence,[12] a prior study found that 28% of AI-only users were non-adherent by 4.5 years.[13] Another study reported that more than 30% of AI users were non-adherent to AI by the third year after diagnosis and the non-adherence rate reached 53.33% after 5 years from diagnosis.[14]

Studies published from 2008 to 2012 suggested the use of omega-3 fatty acids, glucosamine sulphate, non-steroidal anti-inflammatory drugs (NSAIDs), codeine/acetaminophen and change to another AI therapy to manage AIA.[5 15] However, these AIA treatment algorithms were based on the management of peripheral pain[15] and information from literature and anecdotal experience of oncologists,[5] not randomised controlled trials (RCTs) on AIA. During the past decade, a number of RCTs evaluating the effects of AIA treatments have compared duloxetine with placebo,[16] omega-3 fatty acids with placebo,[17 18] acupuncture with sham acupuncture and wait-list control,[19] and natural products with placebo.[20]

A meta-analysis showed that acupuncture and exercise had no difference in the worst pain compared with control, whereas each RCT had heterogeneous results.[21] Another meta-analysis involving both RCTs and single-arm studies reported significant effects of acupuncture, relaxation techniques and pharmacological approaches involving duloxetine, prednisolone and thymalfasin. Nutritional supplementation and exercise also reduced pain in AIA, but no statistical significance was found.[22] To our knowledge, a systematic review of systematic reviews and network meta-analysis (NMA) comparing therapeutic options for AIA has been published.[23] This pilot NMA involving six RCTs demonstrated that omega-3 fatty acids, acupuncture and aerobic exercise significantly reduced pain severity compared with wait-list control group, but placebo also showed a significant improvement in pain compared with wait-list control group. However, the network geometry of this study only involved RCTs that measured a specific pain scale and were identified from existing systematic reviews and discarded considerable number of published RCTs.

NMA can produce more precise estimates and narrower measures of uncertainty than traditional pairwise meta-analysis by combining all available direct and indirect evidence. Also, NMA enables comparison of interventions that had never been directly compared in RCTs.[24]

Therefore, we will conduct a systematic review with NMA to compare the change in pain intensity between different treatments for AIA in hormone receptor-positive breast cancer patients by combining all available direct and indirect evidence. Also, this NMA aims to demonstrate the rank probabilities of different treatments for AIA. The purpose of this protocol is to clarify the rationale, methodology and analytic approach for this systematic review with NMA.

METHODS

Protocol design and study registration

This protocol was developed by following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 statement.[25] The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO). The record can be accessed on their website (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019136967).

Eligibility criteria

This systematic review and NMA will involve full-text articles which meet the eligibility criteria outlined below.

Types of study

This review will include RCTs published from inception to November 2019 in English. Cross-sectional studies, controlled trials that do not use random sequence to allocate interventions, prospective and retrospective cohort studies and case series will be excluded from the review.

Types of participants

We will include studies assessing the effects in postmenopausal women with stages 0–III hormone receptor-positive breast cancer whose musculoskeletal symptoms developed or worsened after initiation of AI therapy. Women who were premenopausal at the time of diagnosis and have become definitively postmenopausal after chemotherapy or tamoxifen therapy will be included. Male breast cancer patients and premenopausal women receiving ovarian suppression with luteinising hormone-releasing hormone agonists in addition to AI therapy will be excluded. This review has no age limits on eligibility.

Types of interventions and comparators

As the aim of this systematic review and NMA is to compare available interventions based on currently accumulated evidence; studies assessing the effects of any interventions for AIA will be included in this review. Studies comparing the interventions classified into 10 treatment classes will be selected for NMA (table 1). Specific treatments which have similar characteristics according to expert-based consensus or are classified under the prespecified treatment classes according to Medical Subject Headings descriptor hierarchy will be clustered into the same nodes in the network. Treatment classes were established based on previous systematic reviews on AIA.[21 22 26]

Sham acupuncture, which is designed to inactivate therapeutic effects, has been included as a control group in acupuncture trials.[27 28] However, a growing number of studies have reported that sham acupuncture has comparable effects over no treatment or pharmacological

Table 1 Ten treatment categorisation and common comparator included in the treatment network

Treatment classes	Type of treatment
Acupuncture	The stimulation of acupoints with or without skin penetration by needles; with or without *de qi* sensation, electric stimulation or thermal stimulation and so on: acupuncture, auricular acupuncture, electroacupuncture, warm needling, fire needling, pharmacopuncture, catgut embedding
Antidepressive agents	Duloxetine and other antidepressive agents
Physical therapy	Passive physical therapy: transcutaneous electric nerve stimulation, musculoskeletal manipulations, massage, kinesiology and application of athletic tape (Kinesio tape)
Biological product	Natural product and herbal medicine
Bisphosphonates (diphosphonates)	Risedronic acid, zoledronic acid and other diphosphonates
Exercise	Any types of isometric, mobilising and strengthening exercises: aerobic exercise, resistance exercise, aquatic exercise, yoga, Tai Chi, walking
Nonopioids	Conventional pain or anti-inflammatory medication: Non-steroidal anti-inflammatory drugs and acetaminophen
Omega-3 fatty acids	A group of unsaturated fatty acids occurring mainly in fish oils
Sham acupuncture	Sham acupuncture designed to inactivate therapeutic effects by manipulating needle insertion location, depth of needle insertion, needle stimulation and components of patient–practitioner interactions.
Vitamin D	High dose of vitamin D
Common comparator	**Type of comparator**
Inactive control	Usual care, wait-list control, no treatment and any type of placebo

placebo.[28–31] Sham acupuncture will be included as a treatment lump to compare its effects with other available treatments in this review.

As comparators, studies comparing the effects with inactive control and with active intervention will be both selected. The duration of treatment will not be limited. If no RCT on prespecified treatment classes exists or RCTs on AIA intervention not categorised into 10 classes are found, different treatment categorisation can be considered. The rationale for any post hoc decisions on treatment classes of the network will be reported.

Types of outcomes

Studies evaluating the change in patient-reported pain intensity from baseline (pre-treatment) to post-treatment, which is the primary endpoint of this review, measured by using any pain measurement scales will be included in the review. The pain measurement scales will not be specified to exploit all available evidence.

Electronic search

PubMed, the Cochrane Controlled Register of Trials (CENTRAL), EMBASE, Web of Science and ClinicalTrials.gov will be searched to identify relevant publications in English from inception to November 2019. Also, available references from relevant reviews will be handsearched to find additional studies.

The following search terms will be combined by Boolean operators: 'breast neoplasms', 'aromatase inhibitors', 'arthralgia' 'joint pain' and 'randomised controlled trial'. Search terms relevant to interventions for AIA will not be combined to find all available evidence for current treatments (table 2). The retrieved articles will be managed by EndNote V.X9 (Clarivate Analytics, Philadelphia, Pennsylvania, USA), and the search results will be recorded in a pre-defined Excel sheet.

Study selection

At first, two independent reviewers will conduct an electronic search from five databases according to the search strategy described above. Additionally, potentially eligible studies will be retrieved from references of relevant reviews. Duplicate studies will be excluded from yielded articles by the 'find duplicate' function in EndNote V.X9 software. Two reviewers will screen titles and abstracts independently and select the articles that meet the predefined inclusion criteria for full-text evaluation. After evaluating full texts, studies that satisfy the inclusion criteria will be included in the systematic review. Studies which include relevant data for the synthesis of effect estimates will be included in the meta-analysis and NMA (figure 1).We will record the reasons for excluding trials. As the interest of this review is a study, not a report, the primary report of a particular study will be selected, and additional data from secondary reports will be collected when multiple publications of the same study present.[32] All discrepancies will be solved by consensus.

Data extraction and management

Two independent reviewers will extract data from included RCTs and input data into a pre-designed electronic spreadsheet. Descriptive information involving the author's name, title, publication year, trial setting location, location of the corresponding author, study design,

Table 2 Search strategy sample for PubMed

#1	Search Breast Neoplasms[Mesh]
#2	Search (((“Breast Neoplasm”) OR “Breast Cancer”) OR “Breast Carcinoma”) OR “Breast Tumor”
#3	#1 OR #2
	Search (Breast Neoplasms[Mesh]) OR ((((“Breast Neoplasm”) OR “Breast Cancer”) OR “Breast Carcinoma”) OR “Breast Tumor”)
#4	Search “Aromatase Inhibitors”[Mesh]
#5	Search (((((((“Aromatase Inhibitors”) OR AI) OR exemestane) OR anastrozole) OR letrozole) OR Aromasin) OR Arimidex) OR Femara
#6	#4 OR #5
	Search (“Aromatase Inhibitors”[Mesh]) OR (((((((“Aromatase Inhibitors”) OR AI) OR exemestane) OR anastrozole) OR letrozole) OR Aromasin) OR Arimidex) OR Femara)
#7	Search “Arthralgia”[Mesh]
#8	Search ((((((Arthralgia) OR “Joint Pain”) OR “Joint Stiffness”) OR “Musculoskeletal symptom”) OR AIA) OR AIMSS) OR Arthr*
#9	#7 OR #8
	Search (“Arthralgia”[Mesh]) OR (((((((Arthralgia) OR “Joint Pain”) OR “Joint Stiffness”) OR “Musculoskeletal symptom”) OR AIA) OR AIMSS) OR Arthr*)
#10	Search “Randomized Controlled Trial” [Publication Type]
#11	Search (((“Randomized Controlled Trial”) OR “Randomised Controlled Trial”) OR RCT) OR Random*
#12	#10 OR #11
	Search (“Randomized Controlled Trial” [Publication Type]) OR ((((“Randomized Controlled Trial”) OR “Randomised Controlled Trial”) OR RCT) OR Random*)
#13	#3 AND #6 AND #9 AND #12
	Search (((((Breast Neoplasms[Mesh]) OR ((((“Breast Neoplasm”) OR “Breast Cancer”) OR “Breast Carcinoma”) OR “Breast Tumor”))) AND ((“Aromatase Inhibitors”[Mesh]) OR (((((((“Aromatase Inhibitors”) OR AI) OR exemestane) OR anastrozole) OR letrozole) OR Aromasin) OR Arimidex) OR Femara))) AND ((“Arthralgia”(Mesh)) OR (((((((Arthralgia) OR “Joint Pain”) OR “Joint Stiffness”) OR “Musculoskeletal symptom”) OR AIA) OR AIMSS) OR Arthr*))) AND ((“Randomized Controlled Trial”[Publication Type]) OR ((((“Randomized Controlled Trial”) OR “Randomised Controlled Trial”) OR RCT) OR Random*))

participants, intervention and comparator assessed, outcome measurements, method of statistical analysis (intention-to-treat analysis vs per-protocol analysis) and funding source will be collected for descriptive analysis.

The following primary outcomes data will be collected: sample size, mean and SD of pain intensity before and after treatments, mean change and change-from-baseline SD, or estimated treatment effect and SE of the pooled estimate. When observed results and adjusted results are both reported in an RCT, the observed results will be extracted. In cases where only adjusted results are available, the adjusted results will be extracted, and they will be specified as the adjusted estimates. If the above data are not reported in the RCT publication, the reviewers will conduct the following procedures.

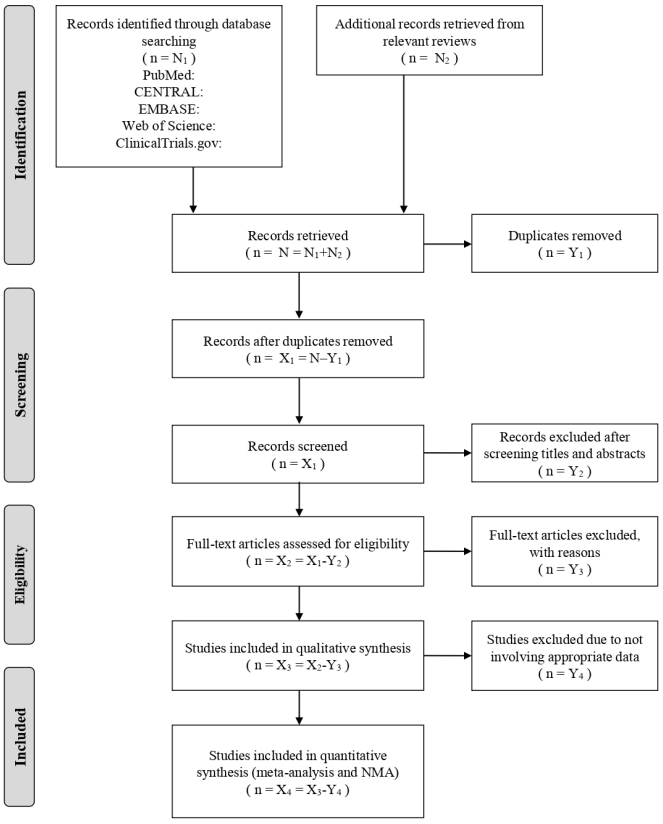

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection

1. Available numerical data such as median, 95% CI, the correlation coefficient between pre-treatment and post-treatment, range (maximum–minimum), IQR and binary outcomes will be collected to calculate the effect size.
2. The corresponding author of the RCT publication will be contacted to request data by email twice. Data collected from response email by March 2020 will be included in the quantitative study.
3. If only figures are presented without numerical data, reviewers will extract the numerical data from figures in the original publication by using WebPlotDigitizer V.4.2 (Ankit Rohatgi, San Francisco, CA, USA).
4. If no data are available despite the above procedures, the corresponding RCT will be excluded from meta-analysis and NMA.

From the RCTs reporting multiple outcome measurements on pain intensity, we will extract all available data on pain intensity. Considering some pain assessment tools such as Brief Pain Inventory, which is extensively used for a broad range of pain symptoms, are composite measures,[33] both composite and subitem results on pain intensity will be extracted as reported. When composite outcomes involve pain intensity, joint stiffness, functional score and different symptoms’ scores, components only corresponding to pain intensity will be recorded. In the case of multiple time points reported, data at baseline and on follow-up elucidated as primary analysis in the RCT will be extracted. If the primary analysis’s time

points are not elucidated, the data from the follow-up close to completion of the intervention will be extracted.

Additionally, the frequency, type and grade of adverse events will be extracted. The information on the randomisation process, deviations from intended interventions, missing outcome data, measurement of outcome data and the selection of the reported results will be collected to assess the risk of bias (ROB). When multiple publications of the same study present, additional information not reported in the primary report will be collected from multiple reports and entered into a single-data collection form.[32] Any disagreement will be resolved by discussion.

ROB assessment

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2)[34] will be used to assess the ROB within individual RCTs. The Cochrane Collaboration's tool for assessing the ROB in randomised trials[35] was updated to RoB 2 in 2018. RoB 2 contains five domains which cover all types of bias that can arise from RCTs: (1) bias arising from the randomisation process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome and (5) bias in selection of the reported result.[34] Unlike the previous version of the Cochrane risk-of-bias tool in which reviewers could modify the domains as necessary, the domains must not be added or modified in RoB 2. RoB 2 presents signalling questions relevant to each domain's information. The response options for the signalling questions are: (1) Yes; (2) Probably yes; (3) Probably no; (4) No and (5) No information. Using an algorithm based on the response to the questions, a judgement into 'low' ROB, 'high' ROB or 'some concerns' will be made. Finally, an overall ROB judgement will be generated according to the criteria presented in RoB 2. As the aim of this review is to assess the effect of assignment to intervention, the ROB due to deviations from the intended interventions will be evaluated in domain 2. Two independent reviewers will respond to signalling questions and judge ROB in five domains by the proposed algorithm. If disagreements cannot be solved by consensus between the two reviewers, a third reviewer will intervene as an arbitrator. The judgements for each domain and overall ROB will be tabulated graphically in the main text. We will incorporate the ROB assessment into the sensitivity analysis.

Outcomes

Primary outcomes

The primary outcome is the change of pain intensity from baseline to post-treatment. The change in the pain intensity score is less intuitive but more sensitive than dichotomous data such as response rate. In most pain assessment scales, a higher score means worse pain intensity. Therefore, the more negative the value for change in pain, the greater the reduction in pain intensity.

Secondary outcome

The secondary outcome is the number of adverse events or patients experiencing harm. If the RCT states 'no events reported', it will be treated as a 'zero events' rate.[36] The type and grade of adverse events will be evaluated descriptively.

Data synthesis

The assumption of transitivity and geometry of the networks

To combine direct and indirect comparisons, the assumptions of transitivity and consistency should be held. When the distributions of effect modifiers are balanced across studies comparing A versus B and B versu C, the transitivity assumption is held.[37] As the eligibility criteria for the types of studies and participants are clearly established, the plausibility of transitivity is predicted. Nonetheless, information regarding patient and study characteristics will be presented to describe adherence to the assumption of transitivity. Especially, patient characteristics will involve body mass index, prior chemotherapy status, stage of cancer and duration of menopause that may be predictors for the development of AIA, if information is available.[10]

To present how the evidence base is summarised, network graphs will be generated graphically. Nodes will indicate the treatment classes included in this review. A solid line means a direct comparison and line thickness indicates the number of comparisons between nodes. If the network contains closed loops of treatments, the figure made from connected lines will be marked with a shadow.

Conversion and combination of multiple effect sizes per study

If the RCTs does not report desired data including estimated treatment effect, SE of estimate or mean change, SD of mean change and sample size for each intervention group, data will be reconstructed from other available statistics based on the Cochrane handbook and estimation formulas from publications.[32 38 39] When a missing SD for changes from baseline to post-treatment needs to be imputed, correlation coefficient will be calculated, if possible.[32] If the actual correlation coefficient is unavailable for calculation, the conservative value 0.5 will be used.[40] When pain intensity change is reported in dichotomous scales, the data will be converted, rather than excluded, to continuous outcomes with the underlying assumption that continuous measurements in each group follow a logistic distribution.[32]

When applying the benefit of an NMA, which is to summarise all available data on outcomes of interest, the pain intensity measurement tool is not defined as a specific measurement tool in this review protocol. However, composite pain outcomes and pain intensity subitem outcomes are repetitive. Different pain intensity assessments can be dependent on multiple pain scores. Combining all multiple outcomes at once would violate the independence assumption. On the other hand, the involvement of one pain assessment tool induces data

loss. Therefore, we will average multiple effect sizes within a study to obtain a single independent effect size per study.[32 41] Standardised mean differences (SMDs) will be calculated for multiple pain intensity outcomes in a trial. The arithmetic mean of the SMDs will be computed. To obtain SE of a within-study averaged effect, the averaged variance of the effect estimates will be used as the variance of the averaged effect size.[41]

Statistical analysis

1. For direct comparisons, if study population, interventions, comparator and measurement time points are homogenous, a standard pairwise meta-analysis will be performed. The random effects meta-analysis will be conducted based on an expectation that intervention effects across studies are different.[32] I^2 will be calculated to assess heterogeneity. For pain intensity outcomes, results will be displayed using SMD with 95% CI. A p value of <0.05 will be considered statistically significant. Forest plots will be presented.
2. NMA with a Frequentist approach will be conducted to combine direct and indirect comparisons. To assess assumptions, design-based decomposition of Cochrane's Q for assessing the homogeneity in the whole network and split network estimates into the contribution of direct and indirect evidence to evaluate inconsistency will be performed. The estimate of effect size will be calculated by a random-effects model. Direct and mixed evidence will be estimated with SMD and 95% CI. Ranking of treatments will be presented as P-score, a Frequentist analogue to the surface under the cumulative ranking curve.

If independent subgroups are present within a study, effects will be combined across subgroups using the study as a unit of analysis.[42] Publication bias will be assessed using funnel plots and Egger's test when at least 10 RCTs are included. In cases where the desired data on pain intensity is not obtained from the RCTs, the results will be qualitatively reviewed instead of using quantitative analyses. Statistical analyses will be performed by using R V.3.5.2 with a 'netmeta' package.[43]

Sensitivity analyses and alternative formulation of the network

First, if the majority of RCTs are judged to have an overall low risk of bias, a sensitivity analysis excluding studies with some concerns and/or high risk of bias will be conducted. Second, if the effect size converted from binary outcomes or data extracted from figures is used to calculate effect estimates, a sensitivity analysis excluding these studies from the primary network will be performed. Graphical data extraction with software has been reported to be accurate between 73% and 75% compared with original data.[44] Conducting sensitive analysis of the original effect sizes by omitting studies with transformed effect sizes is recommended, as a transformation may involve approximations.[45]

In addition to primary network, the reviewers will evaluate alternative network to ascertain the robustness of the findings. The alternative network will include studies with data measured by the most frequently reported pain assessment scale.

Quality of evidence assessment

The quality of evidence will be assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system for grading evidence.[46] To rate quality of NMA estimates, a four-step approach for rating the quality of evidence from NMA developed by GRADE Working Group will be followed.[47] Certainty of evidence for all comparisons will be judged to be of 'high', 'moderate', 'low' or 'very low' quality.

Patient and public involvement

Patients or the public are not involved in the study.

DISCUSSION

AIA is considered one of the most severe adverse events of AI which impairs the quality of life.[10] The severity of AIA was significantly associated with anastrozole non-compliance from the onset of AI to 9 months.[8] Previous studies demonstrated that AIA generally started 1–6 months following the incipience of AI administration.[5 8 9 11 48–50] Actual patient-reported compliance with anastrozole therapy was lower than compliance assessed by investigators.[8] Since 5–10 years of AI use is strongly recommended for hormone receptor-positive breast cancer patients,[12] treatments to relieve AIA effectively are required.

One study indicated that 50% of AI users with joint pain used analgesia, and the analgesia used the most was NSAIDs.[9] Another study reported that patients suffering from AIA have tried various treatment modalities: herbals including fish oil, glucosamine and chondroitin, calcium, flaxseed, vitamins D and E, acetaminophen, NSAIDs, hydrocodone/acetaminophen, yoga and exercise.[5] Various therapeutic options have been applied to patients suffering from AIA in the real clinical world, however, the superiority of each treatment's effects and adverse events have not been ascertained.

We designed this systematic review with NMA to evaluate the effects of different treatments for AIA by synthesising all current evidence. This NMA will combine both direct and indirect evidence via a thorough search strategy, prespecified data extraction plan and statistical methods with the Frequentist approach. The result of this systematic review with NMA will provide valuable information on AIA therapeutic options for clinicians, health practitioners and breast cancer survivors.

ETHICS AND DISSEMINATION

This systematic review with NMA aims to compare the change in pain intensity between AIA treatments by summarising all direct and indirect evidence and suggest rank probabilities of different treatments. As this review

does not involve individual patients, approval from an ethics committee is not required. Incase the protocol is amended, protocol amendments will be updated in PROSPERO and will be documented clearly in the review publication. The results of this systematic review and NMA will be published in a peer-reviewed journal.

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Contributors KB contributed to conceptualisation, study design and funding acquisition; supervised the research. SYS contributed to investigation and visualisation of data. KB and SYS designed the risk of bias approach and statistical analysis plan; wrote original draft. Both the authors read the manuscript and approved the publication of the protocol. The research has not been conducted.

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