


Acupuncture for Arthralgia Induced by Aromatase Inhibitors in Patients with Breast Cancer: A Systematic Review and Meta-analysis

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Abstract

Background: Aromatase inhibitor-induced arthralgia (AIA) is the most common side effect of aromatase inhibitors (AIs) used in breast cancer patients and is related to the rate of adherence to AIs. The clinical effects of acupuncture on AIA have been assessed by some randomized controlled trials (RCTs). However, some studies reported that acupuncture was effective, while others claimed that it was ineffective. To clarify the clinical and placebo effects of acupuncture in treating AIA, we conducted this meta-analysis. **Methods:** Two reviewers (XL and GW) independently searched for RCTs in 5 English databases (PubMed, Web of Science, Embase, Springer, Cochrane Library) and 4 Chinese databases (China National Knowledge Infrastructure Database (CNKI), SinoMed, VIP and Wanfang Database) from their inception to 30 November 2019. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, this meta-analysis was performed by fixed or random-effects models, and data were pooled with mean differences (MDs). **Results:** Seven trials involving 603 patients were reviewed. The primary outcome, the Brief Pain Inventory (BPI) score, significantly differed between the acupuncture and control groups [pain-related interference: MD = -1.89, 95% confidence interval (CI) [-2.99, -0.79], Z = 3.36 ($P = .008 < .05$), pain severity: MD = -1.57, 95% CI [-2.46, -0.68], Z = 3.45 ($P = .0006 < .05$), worst pain: MD = -2.31, 95% CI [-3.15, -1.48], Z = 5.47 ($P < .0001 < .05$)]. No severe adverse events were reported in any study. **Conclusion:** This meta-analysis showed that acupuncture is a safe and effective treatment for breast cancer patients with AIA. Additional research with improved blinding methods is warranted to further explore the nature of non-specific and placebo effects in true and sham acupuncture.

Keywords

acupuncture, aromatase inhibitor-induced arthralgia, breast cancer, meta-analysis

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Background

Breast cancer is the most widespread cancer and is the second leading cause of death among women.¹ Aromatase inhibitors (AIs), the standard treatment for early-stage breast cancer, can reduce the risk of recurrence in postmenopausal and hormone receptor-positive patients.² The types of AIs include steroidal inhibitors (exemestane) and nonsteroidal inhibitors (anastrozole and letrozole). The American Society of Clinical Oncology (ASCO) Clinical Practice Guideline recommends that women with node-positive breast cancer are offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.³

Nevertheless, side effects caused by AIs, such as severe aromatase inhibitor-induced arthralgia (AIA), may cause poor adherence to AIs. One study⁴ revealed that up to 50% of patients terminated the use of AIs within the first year of use. Another prospective study⁵ including 1916 patients receiving upfront anastrozole concluded that AIA was related to treatment noncompliance.

At present, the interventions for relieving AIA include drugs and exercise. A review⁶ suggested that exercise, weight loss, vitamin D and bisphosphonate can be beneficial for mild arthralgia. However, their clinical effects are still unclear. In addition, some drugs, such as bisphosphonate, have nonnegligible side effects, including acute-phase



reactions, gastrointestinal sequelae and nephrotoxicity.⁷ Some experts have suggested that prednisolone or nonsteroidal anti-inflammatory drugs are taken for AIA,^{6,8,9} but clinicians have argued that these drugs are associated with a risk of heart attack and stroke.¹⁰

Considering these unfavorable side effects, alternative approaches, such as acupuncture, yoga or exercise, have been used to treat AIA in recent years. Acupuncture has been confirmed to have a positive effect on AIA by some randomized controlled trials (RCTs).¹¹⁻¹⁷ The Clinical Practice Guidelines¹⁸ also recommended that acupuncture is used to relieve side effects caused by conventional treatments for breast cancer. However, the effect of acupuncture on AIA still needs to be further confirmed by high-quality studies or related meta-analyses.

By November 2019, 4 meta-analyses¹⁹⁻²² on the effect of acupuncture on AIA had been published. However, they did not assess the inconsistent placebo effects of acupuncture, and they did not include articles published in China, where acupuncture originated. In addition, a multicenter study¹¹ with 226 patients suggested the effect of acupuncture on AIA, which may affect the results of previous meta-analyses. Therefore, it was necessary to perform additional research to comprehensively assess the effect of acupuncture on AIA.

In general, the primary aim of this study was to clarify the clinical and placebo effects of acupuncture with respect to those of a control intervention. In addition, we aimed to provide suggestions for the design of future studies. The comprehensive searches and rigorous eligibility criteria strengthened the validity and generalizability of our review.

Methods

Study Eligibility Criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines²³ to perform this meta-analysis. The inclusion criteria consisted of RCTs that evaluated the effects of acupuncture on AIA in patients with breast cancer. The participants were (1) aged 18 years or older; (2) patients diagnosed with breast cancer on the basis of pathology, cytology, or histological features; and (3) patients taking AIs for more than 1 month. For the

interventions of the experimental group, all types, doses, and regimens of acupuncture, such as electroacupuncture and auricular acupuncture, were included. For the control intervention, sham acupuncture, drugs and the absence of treatment were included. The primary outcome was the severity of joint pain, as assessed by the Brief Pain Inventory (BPI), and the secondary outcomes were the scores for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS), functional assessment of cancer therapy (FACT), and other assessment tools. Nonrandomized studies, review articles, repeated publications, commentaries, letters, case reports, meeting abstracts, guidelines and nonpeer-reviewed articles were excluded.

Search Strategy

Two reviewers (XL and GW) independently searched for articles in 5 English databases (PubMed, Web of Science, Embase, Springer, Cochrane Library) and 4 Chinese databases (China National Knowledge Infrastructure Database (CNKI), SinoMed, VIP, and Wanfang) from their inception to 30 November 2019. The following English search terms were used for titles, abstracts and keywords: (“acupuncture” or “acupressure” or “acupoint” or “electroacupuncture” or “ear acupuncture” or “auricular acupuncture” or “warm needling” or “moxibustion”) and (“aromatase inhibitor”). The following Chinese medical subject heading (MeSH) terms were used for the electronic searches: (“acupuncture (针灸)” or “acupuncture (针刺)” or “electroacupuncture (电针)” or “ear acupuncture (耳针)” or “scalp acupuncture (头针)” or “moxibustion (艾灸)” or “acupoint (穴位)” or “acupoint (腧穴)”) and MeSH (“aromatase inhibitor (芳香化酶抑制剂)”). All searches were performed by two independent reviewers, and disagreements were resolved by consensus or, if necessary, by consulting with a third party (LJ). All the search strategies were developed and adapted for each database. The search strategies used for PubMed were as follows:

#1 Aromatase Inhibitor [MeSH Terms] OR Aromatase Inhibitor [Title/Abstract]

#2 Acupuncture [MeSH Terms] OR Electroacupuncture [MeSH Terms]

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#3 Acupuncture [Title/Abstract] OR acupressure [Title/Abstract] OR acupoint [Title/Abstract] OR Electroacupuncture [Title/Abstract] OR ear acupuncture [Title/Abstract] OR auricular acupuncture [Title/Abstract] OR warm needling [Title/Abstract] OR moxibustion [Title/Abstract] OR stimulat [Title/Abstract] OR electrostimulat [Title/Abstract] OR neurostimula [Title/Abstract] OR Zhen Jiu [Title/Abstract] OR meridian [Title/Abstract] OR Jing Luo [Title/Abstract]

#4 #2 OR #3

#5 #1 AND #4.

Selection of Studies and Data Extraction

Two authors (XL and GW) independently evaluated all titles and abstracts to identify all eligible studies. The full texts of candidate articles were subsequently screened to determine whether the articles were relevant to AIA. Discrepancies in this process were settled by discussion, with a third party (JL) if necessary. JL did not participate in the screening or data extraction processes. The study selection process was documented with a flow diagram according to the Cochrane handbook. XL and GW collected the data and recorded the data in Microsoft Excel. The data included the study design, sample size, age of the patients, eligibility criteria, details of the acupuncture and control groups (methods, acupoints, session, etc.), outcomes such as the BPI and WOMAC scores, side effects and conclusions. We emailed study authors if data were missing or unclear.

Quality Assessment

The risk of bias of the articles selected was independently assessed by 2 reviewers (XL and GW) based on the Cochrane Collaboration's risk of bias tool.²⁴ Any discrepancies were discussed with a third party (JL). This tool addressed sequence generation, allocation concealment, the blinding of the participants and personnel, the blinding of the outcome assessment, incomplete outcome data, selective reporting, and other bias. Each type of bias was graded as having a low, high or unclear level or risk by those 2 reviewers for all articles.

Statistical Analyses

We used Review Manager software (version 5.3, Cochrane Collaboration, UK) to statistically analyze the data and generate forest plots.²⁵ The severity of AIA in the included studies was measured by several scales with continuous data (eg, BPI and WOMAC). The changes in the continuous variables were measured by mean differences (MDs) and standard deviations (SDs). MDs were used to pool the measurement data. Statistical heterogeneity was examined with

the Cochrane Q statistic and I^2 statistic. The overall effect differences were considered statistically significant when $P \leq .05$. If $P \geq .10$ and $I^2 \leq 50\%$, we adopted a fixed-effects model to account for expected heterogeneity; otherwise, a random-effects model was used.²⁶ If the level of heterogeneity was substantial, post hoc subgroup analyses were performed according to the characteristics of different studies or patients. If it was inappropriate to pool data because of heterogeneity, only descriptive analyses were performed.

Results

Study Selection

We extracted 628 studies from 5 English databases and 4 Chinese databases. A total of 531 articles were excluded after the titles and abstracts were screened. We excluded 44 articles according to the eligibility criteria by reading the full texts. Of the remaining 53 articles, 12 were single-arm studies, 9 were commentaries, 16 did not have full-text versions available, and 7 articles were not related to our study. After 46 duplicate articles were excluded, 7 articles¹¹⁻¹⁷ were included in the final meta-analysis (Figure 1).

Among these 7 articles, the study by Oh et al.¹³ had incomplete data, and we failed to make contact with the author to retrieve the missing data. Bao et al.¹⁵ used medians to describe the results, while other articles used averages and standard deviations. Li et al.¹⁷ used the VAS to evaluate the severity of AIA, while other articles used the BPI. Because of these inconsistencies, it was difficult to analyze these 3 articles together with the other 4 articles, so we only described their results and did not perform meta-analyses.

Study Characteristics

Basic characteristics. The 7 articles included a total of 603 patients. The study characteristics are shown in Table 1. Four articles^{13-15,17} had 2 arms, 2^{11,12} had 3 arms, and 1¹⁷ had 4 arms. Only 1 study¹¹ had a sufficient sample size of over 50 in each group. The average age of the included participants ranged from 41 to 85 years. All patients were diagnosed with breast cancer stages I-III and hormone receptor-positive cancer and took AIs for more than 1 month. The drop-out rate was less than 12% in all 7 articles.

Interventions

The interventions included acupuncture (auricular acupuncture,¹⁶ body acupuncture^{11-15,17}), sham acupuncture,¹¹⁻¹⁵ drugs^{16,17} and no treatment.^{11,12}

Auricular acupuncture was administered in 1 study¹⁶ for 3 minutes 18 times a week for 12 weeks. In the body acupuncture groups, the duration of each session ranged from

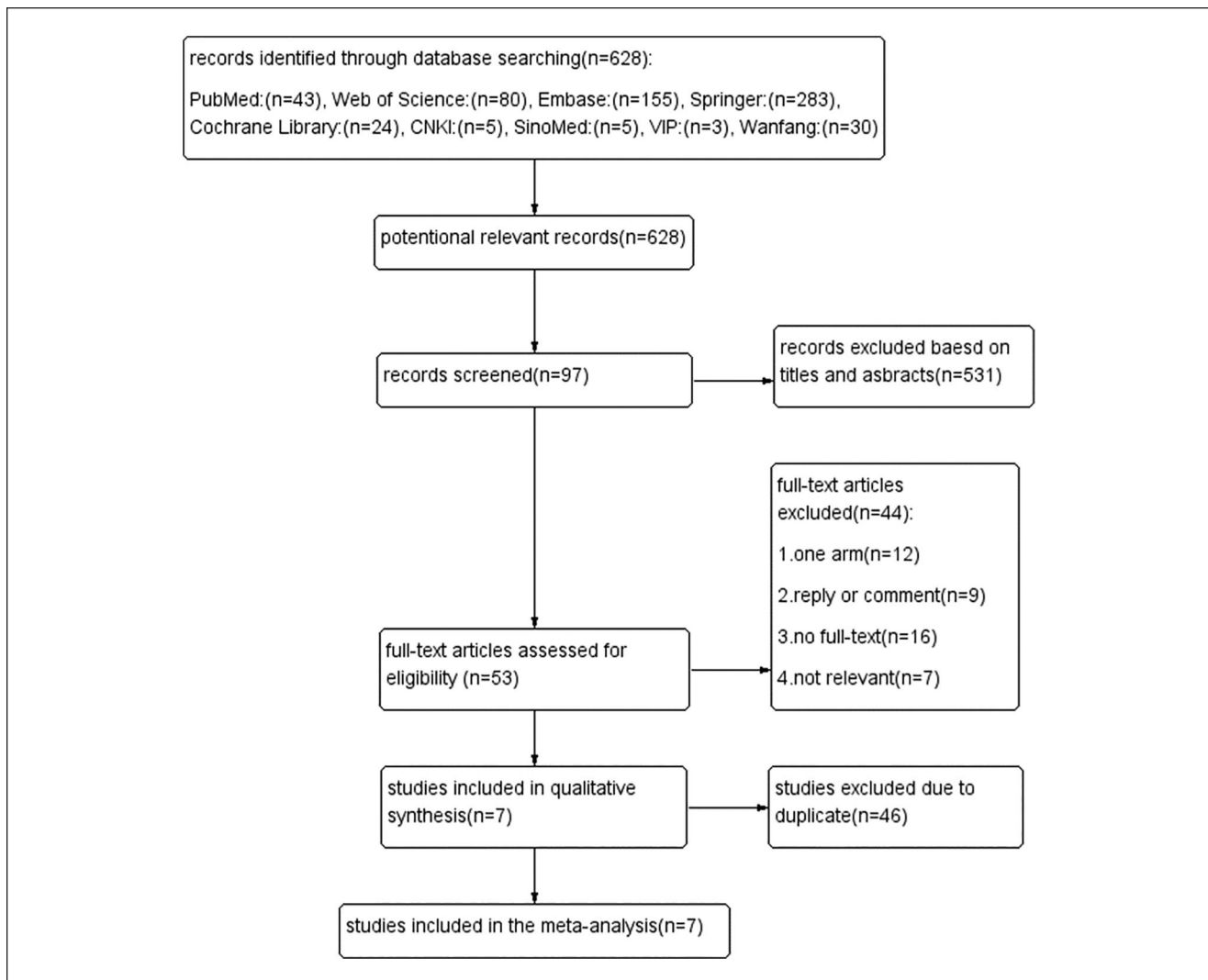


Figure 1. Flow chart.

20 to 45 minutes, the frequency of treatment ranged from twice to 8 times each week, and the entire study lasted for 6 to 12 weeks. Standard acupoints were used in 4 studies.^{11,13-15} Li et al.¹⁷ used the “Ashi Point (阿是穴)” in the most painful area, while Mao et al.¹² used 4 local points around the most painful joint and 4 distant points to regulate the whole body. In the sham-acupuncture groups, needles were inserted into the skin in 2 studies^{11,14} and were not inserted in 3 studies.^{12,13,15}

Outcomes

The severity of joint pain was mainly assessed by the BPI in 5 articles,^{11-14,16} by the WOMAC in 4 articles¹¹⁻¹⁴ and by the VAS in 2 articles.^{15,17} Five articles¹¹⁻¹⁵ evaluated functional ability with the FACT,^{11,13,14} quick disabilities of the arm, shoulder, hand (DASH) scale,¹² physical performance test

(PPT),¹² modified score for the assessment and quantification of chronic rheumatoid affections of the hands (M-SACRAH)^{11,14} and health assessment questionnaire (HAQ).¹⁵ Laboratory indices, including the C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), estradiol level, cytokine profile, β -endorphin level, and interferon- γ (IFN- γ) and interleukin 4 (IL-4) levels, were detected in 3 articles.^{13,15,17}

The BPI was used to assess the worst pain, worst stiffness and pain severity associated with AIA in breast cancer patients. The WOMAC was used to evaluate the severity of osteoarthritis in the knees or hips. The VAS is a standard measure of clinical musculoskeletal disorder severity than ranges from 0 (no pain) to 100 (severe pain). For assessing hand pain, stiffness, and functional status, the M-SACRAH was used. The FACT was used to assess physical ability and endocrine symptoms. The DASH scale was used to assess

Table 1. Study characteristics.

	Sample size		Age		Inclusion criteria	Drop out rate (%)	Outcome Measurement tool	Conclusion
	Study design	Acupuncture	Control	Acupuncture				
Oh et al. ¹³	Two arms	15	14	<45 12 (86%) ≥45 2 (14%)	<45 14 (93%) ≥45 1 (7%) Postmenopausal; stage I, II or IIIa; hormone receptor-positive; third generation AI ≥ 6 months; BPI-SF ≥ 3;	9.4	(1) Pain: BPI, WOMAC. (2) Functional ability: FACT-G, Grip test. (3) Inflammation biomarker: CRP, ESR	TA versus SA: non-significant findings. TA was well tolerated and potential
Mao et al. ¹²	Three arms	22	SA: 22 WLC:23	SA: 60.9 ± 6.5 WLC:60.6 ± 8.2	Stages I-III; AI ≥ 3 months; numerical rating scale ≥ 3	11.9	(1) Pain: BPI, WOMAC. (2) Functional ability: DASH, PPT. (3) Global Impression of Change	(1) TA > WLC: significantly effective. (2) SA > WLC: significantly effective. (3) TA versus SA: nonsignificant
Hershman et al. ¹¹	Three arms	110	SA: 59 WLC: 57	SA: 57.0 (40.6-77.5) WLC: 60.6 (27.1-76.0)	Postmenopausal or premenopausal with gonadotropin-releasing hormone agonist; stages I-III; primary invasive estrogen receptor-positive; third generation AI ≥ 30 days to continue for at least one additional year; Zubrod performance 0-1; BPI-SF ≥ 3	11.9	(1) Pain: BPI, WOMAC, PROMIS PLSF. (2) Functional ability: M-SACRAH, FACT-ES	joint pain at 6 weeks. (1) TA > WLC: statistically significant reduction. (2) TA vs SA: statistically significant reduction. (3) Uncertain clinical importance
Crew et al. ¹⁴	Two arms	20	18	57(37-77)	Postmenopausal; Stage I-III; Third-generation AI ≥ 3 months; BPI-SF ≥ 3	11.6	(1) Pain: WOMAC, BPI-SF. (2) Functional ability: M-SACRAH, FACT-G	TA > SA: significant
Bao et al. ¹⁵	Two arms	23	24	61 (44-82)	Postmenopausal; Stage 0-III; ER and/or PR positive; Third-generation AI ≥ 1 month; HAQ-DI ≥ 0.3 and/or VAS ≥ 20	7.8	(1) Pain: VAS. (2) Functional ability: HAQ-DI. (3) Serum: estradiol, cytokine profile, and b-endorphin	(1) TA versus SA: nonsignificant. (2) Positive trends were observed.
Ye et al. ¹⁶	Four arms	①:30, ②:31	③:33, ④:30	①:44-84, ②:41-78, ③:50-80, ④:41-77	Postmenopausal; Stage I-III; ER and/or PR positive; Third-generation AI ≥ 1 month; BPI-SF ≥ 3	11.4	(1) Pain: BPI-SF. (2) BMD of lumbar vertebrae	BPI-SF: (1) ① versus ②: nonsignificant. (2) ① Versus ③: significant after 6 weeks but nonsignificant after 12 weeks. BMD T-score: nonsignificant
Li et al. ¹⁷	Two arms	36	36	57 (45-68)	postmenopausal or ovariectomy; stage I-III; third-generation AI ≥ 1 month; VAS ≥ 3	0	(1) Pain: VAS. (2) Activity of daily living: BI. (3) BMD of lumbar vertebrae. (4) Serum: estradiol, IFN-γ, IL-4	VAS, BI, BMD T-score, IFN-γ, IL-4: Ganggui Tanxue > Caltrate: significantly effective. E2: Ganggui Tanxue versus Caltrate nonsignificant

(continued)

Table 1. (continued)

	Acupuncture group					Control group						
	Methods of acupuncture group	Acupoints	Session	Frequency	Course	Adverse effects	Methods of control group	Acupoints	Session	Frequency	Course	Side effects
Oh et al. ¹³	Electroacupuncture + Usual medication	Standard acupuncture points	30 minutes	2/week	6 weeks	minor-bruising	Sham electroacupuncture + usual medication; Streitberger sham needles do not penetrate the skin and no electrical current	Real standard acupuncture points	30 minutes	2/week	6 weeks	Minor bruising (n=4)
Mao et al. ¹²	Electroacupuncture	At least four local points around the joint with the most pain and four distant points for constitutional symptoms	30 minutes	2/week × 2 weeks 1/week × 6 weeks	8 weeks	Pain at the needling site (n=5)	SA: Streitberger sham needles do not penetrate the skin without receiving the electricity. WLC: no treatment and 10 real acupuncture treatments after follow-up	Nonacupuncture, non-trigger points	SA: 30 minutes	2/week × 2 weeks 1/week × 6 weeks	SA: 8 weeks	SA: Pain at the needling site (n=4)
Hershman et al. ¹¹	Body acupuncture and auricular acupuncture	Standard acupuncture points + three joint-specific points	30-45 minutes	2/week × 6 weeks 1/week × 6 weeks	1/ 12 weeks	Bruising (47%) presyncope(n=1)	SA: full body sham and auricular sham acupuncture: minimally invasive, shallow needle insertion using thin and short needles at nonacupuncture points and application of adhesives to nonacupuncture points on the ear. WLC: no treatment and 10 true acupuncture between 24-52 weeks.	SA: standard nonacupuncture points and joint-specific sham points	SA: 30-45 minutes	2/week × 6 weeks 1/week × 6 weeks	SA: 12 weeks	Bruising (25%) Presyncope(n=1)
Crew et al. ¹⁴	Body acupuncture and auricular acupuncture	Standard acupuncture points and most painful joint (up to 3) specific points	20-25 minutes	2/week	6 weeks	not report	SA: superficial needles insertion at nonacupuncture points	Standard nonacupuncture points	20-25 minutes	2/week	6 weeks	Not report
Bao et al. ¹⁵	Body acupuncture	Standard acupuncture points	20 minutes	8/week	8 weeks	No	SA: nonpenetrating retractable needles at the midpoint of the line connecting two real acupuncture points	Standard nonacupuncture points	20 minutes	8/week	8 weeks	No
Ye et al. ¹⁶	①: auricular acupuncture (AA) + zoledronic acid intravenous drip (ZA). ②: auricular acupuncture	AA: Standard acupuncture points ZA: ×	AA: 3 min. ZA: ×	AA: 18/week. ZA: 1/6 months	AA: 12 weeks. ZA: ×	not report	③: Intravenous drip zoledronic acid (ZA). ④: Caltrate D3 + alfalcidol per os	×	×	③: 1/6 months. ④: 1/day	③: ×. ④: 2 weeks	Not report
Li et al. ¹⁷	Caltrate D3 per os + Cangguai Tanxue at ashi point	Ashi point	20 minutes	5/week	3 months	No	Caltrate D3 per os	×	×	0.5 µg/day	3 months	No

Abbreviations: SA: sham acupuncture group; WLC: waitlist control group; TA: true acupuncture group; BPI: Brief Pain Inventory; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; DASH: Quick Disability of Arm, Shoulder, Hand scale; PPT: Physical Performance Test; FACT: Functional Assessment of Cancer Therapy; M-SACRAH: Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; VAS: Visual Analogue Scale; HAQ: Health Assessment Questionnaire.

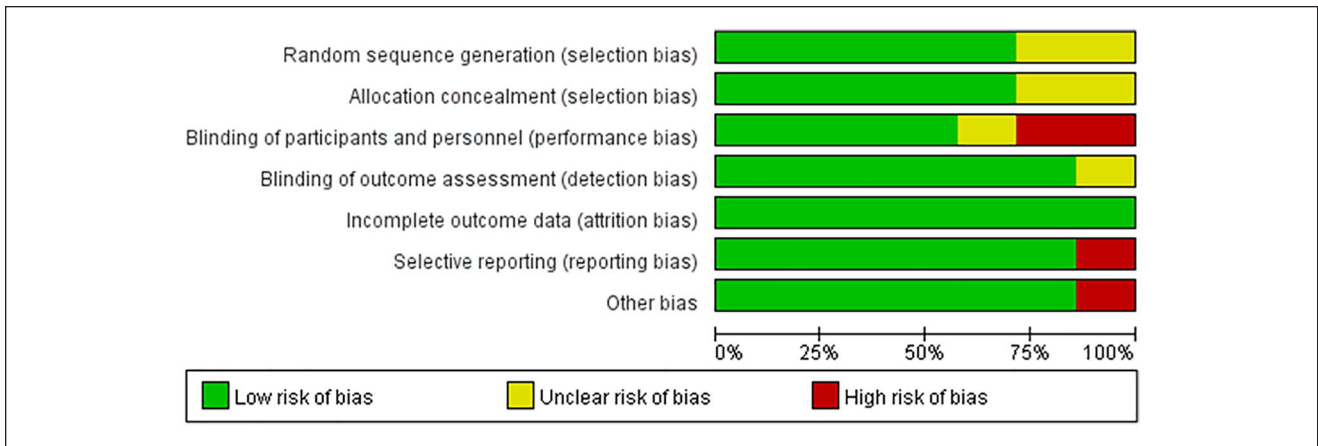


Figure 2. Risk of bias summary.

upper extremity function. The PPT included assessments of both lower and upper extremity function, as well as balance and endurance. In the HAQ-DI, dressing, rising, eating, walking, grooming, reaching gripping, and performing errands were assigned scores of 0 (no difficulty), 1 (some difficulty), 2 (much difficulty), or 3 (unable to do).

Results

In total, 5 studies¹¹⁻¹⁵ compared the effect of acupuncture and sham acupuncture; 3 of these studies^{12,13,15} showed that the difference was statistically significant. Two studies^{11,12} showed that the difference between the acupuncture group and the no treatment group was significant. Two studies^{16,17} compared the effect of acupuncture with that of drugs. One study¹⁶ showed a significant difference after 6 weeks but no significant difference after 12 weeks, while the other showed a significant difference during treatment. Seven articles¹¹⁻¹⁷ reported few and minor adverse reactions that did not severely harm patients.

Risk of Bias Assessment

The risk of bias assessment for all studies is shown in Figure 2. Figure 3 shows the risk of bias for each RCT according to the Cochrane risk of bias tool.

Adequate sequence generation. Five studies¹¹⁻¹⁵ reported the methods used for randomization clearly; studies that used computer-generated randomization tables were judged to have a low risk of bias, whereas the remaining 2 studies^{16,17} did not report how random numbers were generated and were judged to have an unclear risk of bias.

Allocated concealment. Three studies¹²⁻¹⁴ achieved concealment by using sealed, opaque envelopes, and 2 studies^{11,15} achieved concealment by using a central trial center.

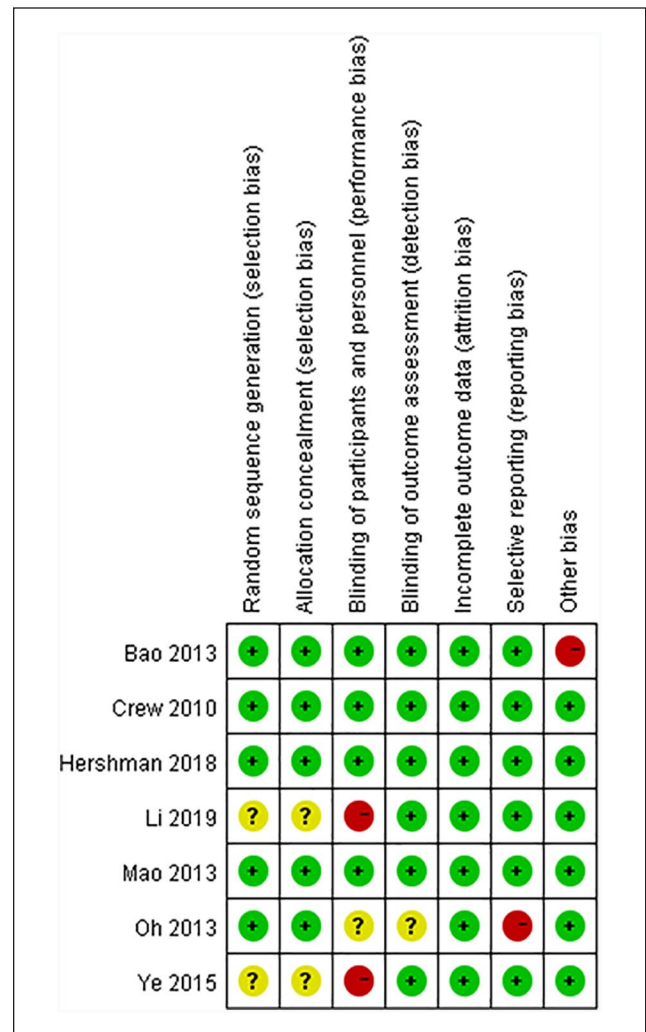


Figure 3. Risk of bias.

Therefore, these 5 studies were judged to have a low risk of bias. The remaining 2 studies^{16,17} did not report whether

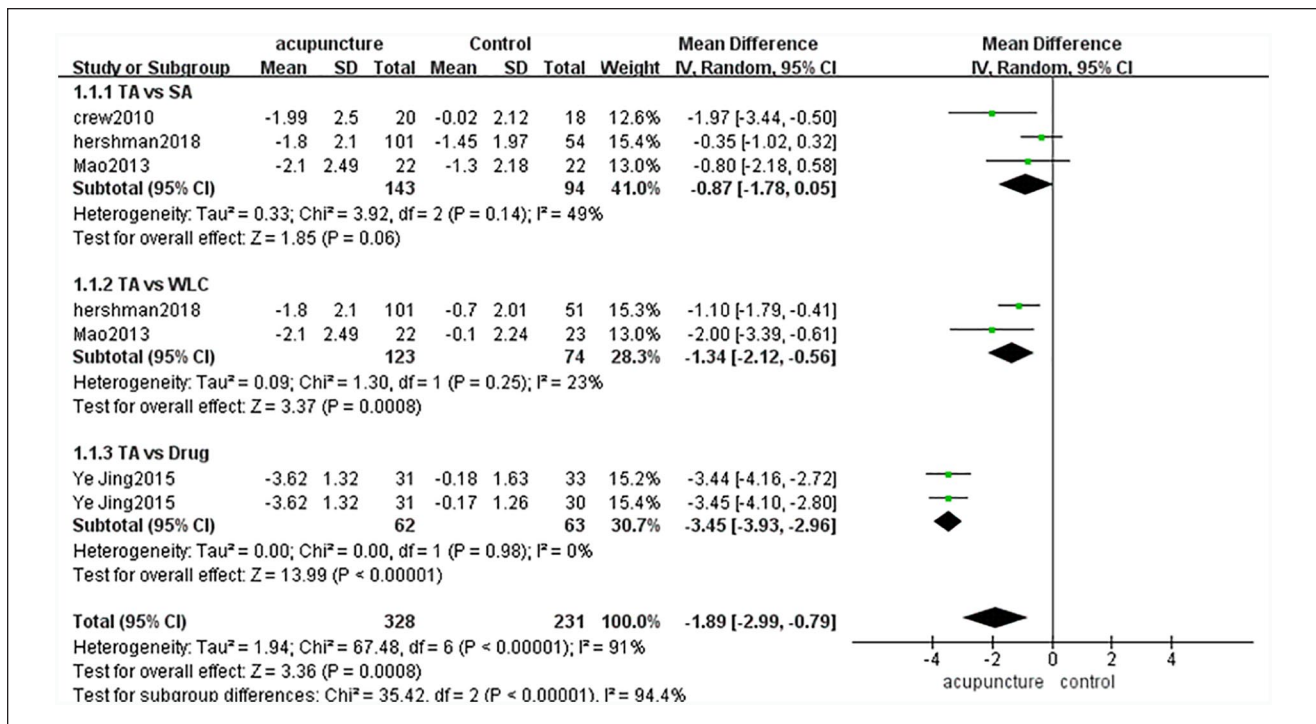


Figure 4. BPI pain-related interference.

group allocation was adequately concealed and were judged to have an unclear risk of bias.

Blinding methods. Because of the specificity of acupuncture, it is difficult to blind acupuncturists. Therefore, four studies^{11,12,14,15} performed blinding for patients and were judged as having a low risk of bias. Two studies^{16,17} compared the effect of acupuncture with that of drugs, and the included patients were definitely aware which group (acupuncture group or drug group) they belonged to; these studies were judged as having a high risk of bias. The level of risk was unclear for 1 study.¹³

Five studies^{11,12,14-16} performed blinding for the investigator or outcome assessor and were judged as having a low risk of bias, whereas the remaining 2 studies^{13,17} did not mention this type of blinding and were judged as having an unclear risk of bias.

Incomplete outcome data and selective outcome reporting. Only 1 study¹³ provided insufficient data and was judged as having a high risk of bias. The remaining six^{11,12,14-17} studies were judged as having a low risk of bias.

Other bias. The baseline HAQ score in the real acupuncture group was significantly higher than that in the sham-acupuncture group in 1 study,¹⁵ which was judged as having a high risk of bias. The remaining six studies^{11-14,16,17} were judged as having a low risk of bias.

Outcomes

BPI. The BPI consists of 3 subscales: pain-related interference, pain severity, and worst pain. In this part, we analyzed each subscale. In 5 articles^{11-14,16} that used the BPI to assess the severity of pain, the study by Oh et al.¹³ stated that there were no significant differences in pain severity or interference with daily functioning only between the sham and real electroacupuncture groups, and complete data were not provided, so it was difficult to include this article in the meta-analyses. Finally, 4 eligible articles^{11,12,14,16} were included in this part.

BPI Pain-Related Interference

There were 174 cases in the acupuncture group and 231 cases in the control group (sham-acupuncture group, waitlist group or drug group).^{11-14,16} The heterogeneity of these 4 articles was high ($P < .00001$, $I^2 = 91\%$), so we used a random-effects model in combined-effect analyses. The acupuncture group was superior to the control group [MD = -1.89, 95% CI [-2.99, -0.79], $Z = 3.36$ ($P = .008 < .05$)] (Figure 4).

Because of the high heterogeneity among these 4 studies, we divided them into 3 subgroups according to the control method used. There were no significant differences between the acupuncture group and sham-acupuncture group [MD = -0.87, 95% CI [-1.78, 0.05], $Z = 1.85$ ($P = .06 > .05$)], while there were significant differences

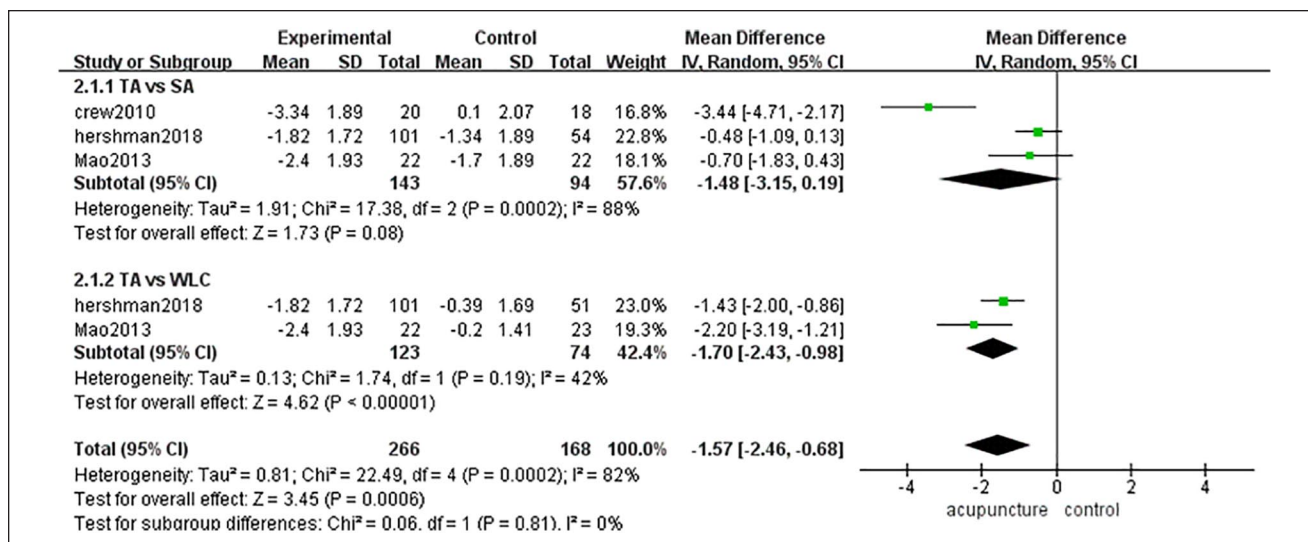


Figure 5. BPI pain severity.

between the acupuncture group and waitlist group [MD=-1.34, 95% CI [-2.12, 0.56], $Z=3.37$ ($P=.008 < .05$)] and between the acupuncture group and drug group [MD=-3.45, 95% CI [-3.93, 2.96], $Z=3.36$ ($P < .00001$)]. Subgroup analyses showed that the heterogeneity among subgroups was high ($P < .00001$, $I^2=96.8\%$) (Figure 4).

BPI Pain Severity

There were 143 cases in the acupuncture group and 168 cases in the control group (sham-acupuncture group or waitlist group).^{11,12,14} The heterogeneity among these 3 articles was high ($P=.0002$, $I^2=82\%$), so we used a random-effects model in combined-effect analyses. Acupuncture was more effective than sham acupuncture or the placebo [MD=-1.57, 95% CI [-2.46, -0.68], $Z=3.45$ ($P=.0006 < .05$)] (Figure 5).

Because of the high heterogeneity among these 3 studies, we divided them into 2 subgroups according to the control method used. There were no significant differences between the acupuncture group and sham-acupuncture group [MD=-1.48, 95% CI [-3.15, 0.19], $Z=1.73$ ($P=.08 > .05$)], while there were significant differences between the acupuncture group and waitlist group [MD=-1.70, 95% CI [-2.43, -0.98], $Z=4.62$ ($P < .00001$)]. Subgroup analyses showed that the heterogeneity among subgroups was low ($P=.81$, $I^2=0\%$) (Figure 5).

BPI Worst Pain

There were 152 cases in the acupuncture group and 186 cases in the control group (sham-acupuncture group, waitlist group or drug group).^{11,14,16} The heterogeneity among these 3 articles was high ($P=.00001$, $I^2=83\%$), so we used a random-effects model in combined-effect analyses. There

were significant differences between the acupuncture group and control group [MD=-2.31, 95% CI [-3.15, -1.48], $Z=5.47$ ($P < .0001 < .05$)] (Figure 6).

Because of the high heterogeneity among these 3 studies, we divided them into 3 subgroups according to the kind of control method used. There were no significant differences between the acupuncture group and sham-acupuncture group [MD=-2.13, 95% CI [-4.86, 0.60], $Z=1.53$ ($P=.13 > .05$)], while there were significant differences between the acupuncture group and waitlist group [MD=-2.12, 95% CI [-2.76, 1.48], $Z=6.45$ ($P < .00001$)] and between the acupuncture group and drug group [MD=-2.73, 95% CI [-3.22, 2.24], $Z=10.94$ ($P < .00001$)]. Subgroup analyses showed the heterogeneity among subgroups was low ($P=.32$, $I^2=11\%$) (Figure 6).

WOMAC

The WOMAC consists of 4 subscales: the pain, stiffness, function and normalized subscales. In this part, we planned to analyze the subscores respectively. However, in the 4 articles¹¹⁻¹⁴ that used the WOMAC as an assessment tool, Hershman et al.¹¹ reported only a total score, and Oh et al.¹³ did not report the specific WOMAC results. Therefore, two eligible articles^{12,14} were included in this part.

There were 42 cases in the acupuncture group and 40 cases in the control group (sham acupuncture). There were no significant differences between the 2 groups in the pain score [MD=-84.93, 95% CI [-254.49, 84.63], $Z=0.98$ ($P=.33 > .05$)], stiffness score [MD=-42.66, 95% CI [-114.73, 29.40], $Z=1.16$ ($P=.25 > .05$)], functional score [MD=-173.59, 95% CI [-518.03, 170.86], $Z=0.99$ ($P=.32 > .05$)] or normalized score [MD=-50.43, 95% CI [-143.20, 42.35], $Z=1.07$ ($P=.29 > .05$)] (Figure 7).

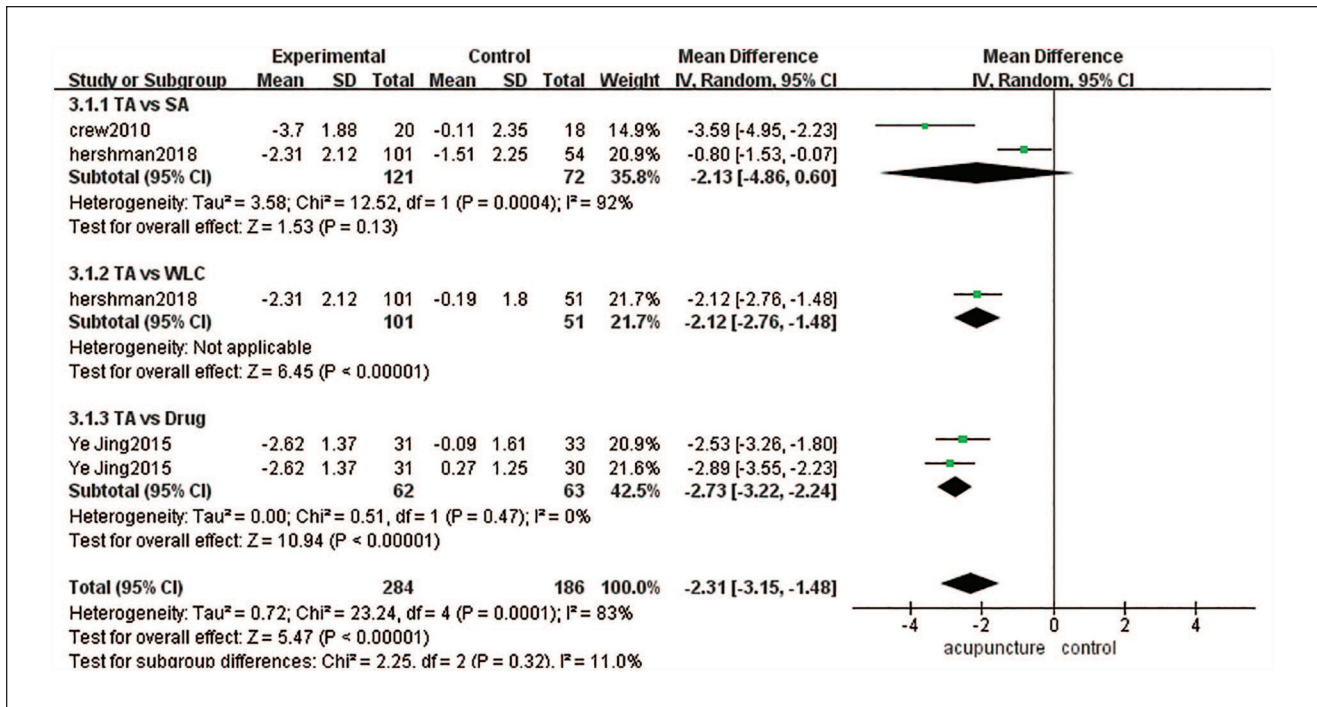


Figure 6. BPI worst pain.

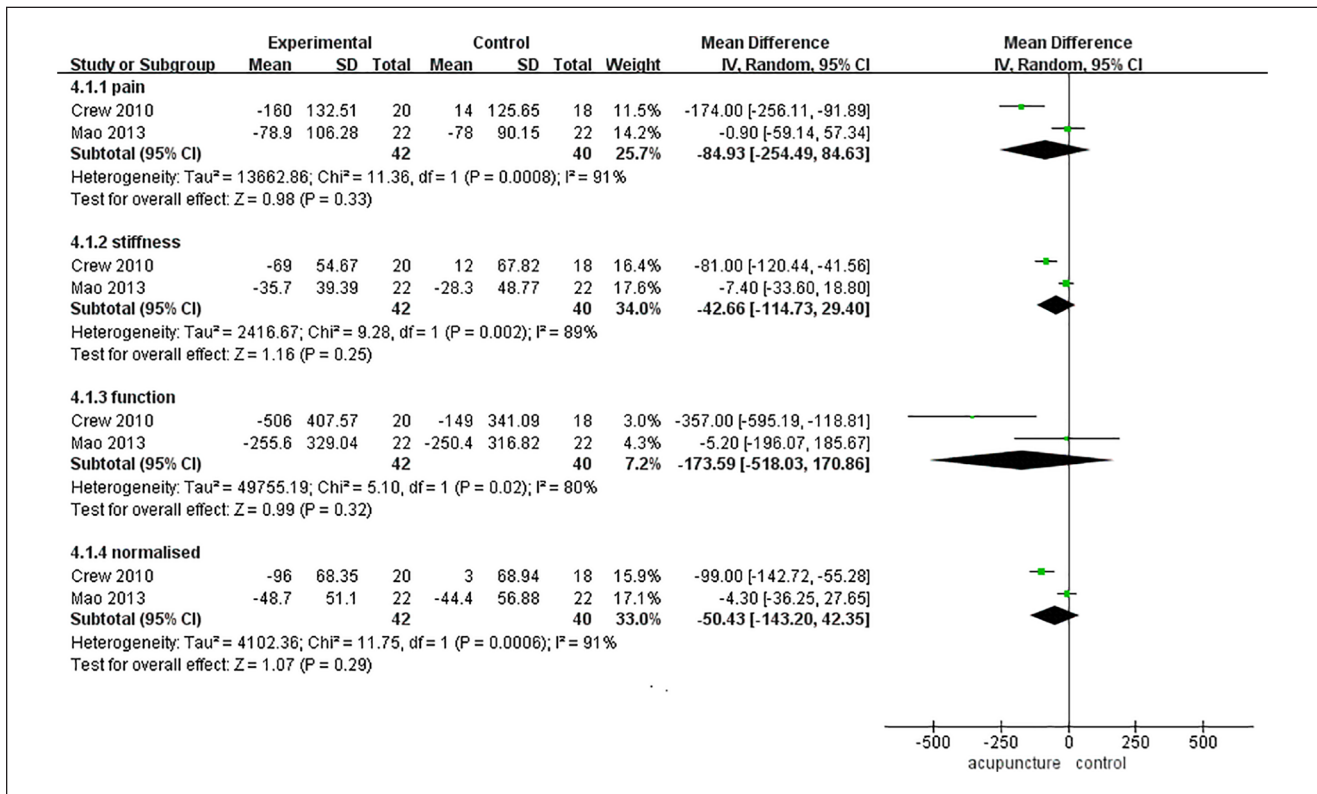


Figure 7. WOMAC.

Adverse Effects

No severe adverse events were reported in any study. Three studies reported adverse events, such as bruising and pre-syncope,¹¹ pain,¹² and minor bruising.¹³ Two studies reported there were no adverse events.^{15,17} However, the other 2 studies did not mention adverse events^{14,16} (Table 1).

Discussion

This meta-analysis assessed the effect of acupuncture on AIA in breast cancer patients. The results showed that acupuncture can significantly improve the pain-related interference score, pain severity score and worst pain score for the BPI compared with drugs and no treatment. Furthermore, no severe adverse events were reported in any of the studies. Therefore, we conclude that acupuncture can be an effective and safe treatment for AIA.

The effect of acupuncture on AIA has been preliminarily confirmed, but the mechanism is still unclear. The main cause of arthralgia is the lack of estrogen,²⁷ which may decrease the generation of endogenous opioids, thereby leading to a lowered pain threshold.²⁸ Acupuncture has been demonstrated to enhance endogenous opiates, such as dynorphin, endorphin, and enkephalin. In addition, polymodal receptor hypothesis,²⁹ purinergic signaling³⁰ and other mechanotransduction-based responses³¹ to acupuncture may also contribute to pain relief.

In the eligible studies in this meta-analysis, 3 studies tested blood samples from patients to explore the mechanism of acupuncture. Mao et al.¹² and Li et al.¹⁷ reported that there were no significant changes in the serum estrogen level between the acupuncture and control groups. As mentioned above, Bao et al.¹⁵ showed a significant reduction in the interleukin 17 (IL-17) level in both the real and sham-acupuncture groups. The IL-17 pathway is associated with the development of AIA.³² Therefore, we hypothesize that acupuncture may treat AIA by modulating IL-17.

Compared with drugs and no treatment, acupuncture is effective in treating AIA. However, when we compared acupuncture with sham acupuncture, there were no significant differences in the pain-related interference score, pain severity score or worst pain score for the BPI. According to the pain, stiffness, functional and normalized WOMAC scores (Figure 7), compared with sham acupuncture, acupuncture did not significantly improve the symptoms.

In 5 articles that used sham acupuncture as a control method, Mao et al.,¹² Oh et al.,¹³ and Bao et al.¹⁴ used sham needles that did not penetrate the skin. All the authors found that compared with sham acupuncture, acupuncture does not statistically significantly improve the symptoms of AIA. Hershman et al.¹⁴ and Crew et al.¹⁷ used minimally invasive needles to penetrate the skin in the sham-acupuncture groups. The authors found that the effects of acupuncture

were statistically significantly better than those of sham acupuncture.

The purpose of including a sham-acupuncture group in a clinical trial on acupuncture is to reduce the differences in outcomes that are caused by non-specific effects.³³ However, as the analyses above show, whether the effect of acupuncture is better than that of sham acupuncture is still unclear and controversial.

Acupuncture has been used in China and many other countries for several decades. Some clinical experts argue that acupuncture is definitely effective according to their experiences. However, if we want to demonstrate the effects of acupuncture scientifically to a broad audience, we need to follow the basic guidelines³⁴ of how to conduct scientific clinical research. The placebo group is necessary.

As mentioned before, sham acupuncture is considered a placebo intervention. However, how to perform sham acupuncture correctly to successfully reduce the placebo effect or psychological effects of acupuncture remains unclear. Some experts who used sham needles that do not penetrate the skin^{12,13,15} indicated that the effect of sham acupuncture is equivalent to that of acupuncture; others who used slightly more invasive needles that penetrate the skin when performing sham acupuncture^{11,14} showed that the effect of acupuncture is better than that of sham acupuncture. In other studies, a systematic review reported that sham acupuncture may be as effective as real acupuncture.³⁵ Other studies have indicated that both real and sham acupuncture can result in the binding of μ opioids to receptors in the brain³⁶ and activate the pain-related neuromatrix.³⁷

Given that this meta-analysis has shown that acupuncture is effective, perhaps in the future, all clinical and methodological experts should focus on finding a proper sham-acupuncture intervention to be used in acupuncture trials to concretely and scientifically show the effects of acupuncture; then, the medical community would have evidence that acupuncture is an acceptable and effective treatment for some symptoms such as pain and disorders such as insomnia and mood disorders.

Before this study, a previous meta-analysis¹⁸ assessed the double-blinded studies (Mao et al.,¹² Crew et al.,¹⁴ and Bao et al.¹⁵). The assessment is worth considering.

In double-blind studies, both the patients and doctors are unaware of which group the patient belongs to,³⁸⁻⁴⁰ which makes it easier to carry out a pharmaceutical trial. However, in interventional clinical trials, such as those on operations and acupuncture, the operator will definitely know which kind of intervention he or she should perform for a given participant,⁴¹ which means he or she knows the group allocation of the patient. Therefore, these studies are single-blind rather than double-blind studies.

Therefore, in our meta-analysis, we assessed 5 articles^{11,12,14-16} that were blinded rather than double blinded

and 2 articles^{13,16} that did not clearly report a method of blinding.

Blinding is critical for acupuncture trials.⁴² We suggest that the acupuncturist talks to the patient as little as possible, preventing the patient from knowing which group he or she belongs to, and an “acupuncture robot”⁴³ can be used in the future to ensure that the acupuncturist is blinded.

The level of heterogeneity was high among all 7 studies. Although subgroup analyses were carried out, the heterogeneity level was still high. We considered that different kinds of control interventions may be the reason for heterogeneity [the heterogeneity among subgroups ($P < .00001$, $I^2 = 94.4\%$)] (Figure 4). In addition, differences in factors such as the acupoints, needle type, number of treatment sessions, and period between treatments may contribute to heterogeneity. The BPI scores, WOMAC scores and other scores are patient-reported outcomes (PROs). Although an increasing number of clinical trials regard PROs as the most important outcomes in clinical trials,⁴⁴ the subjectivity of PROs can reduce the consistency of results.

Limitations

First, the number of included RCTs was small, and there were only 603 patients in our meta-analysis. Second, the results of PROs, which were the primary outcomes of all the articles, were not as objective as some experimental results. This subjectivity may reduce the accuracy of the results of each article. Finally, the heterogeneity of the studies was high, which prevented us from drawing a clear conclusion.

Conclusion

Compared with drugs and no treatment, acupuncture significantly improved BPI scores in breast cancer patients with AIA. However, there were no significant differences between the acupuncture group and sham-acupuncture group in the BPI scores or WOMAC scores. No significant side effects were associated with acupuncture treatment. Therefore, this meta-analysis showed that acupuncture is a safe and effective treatment for breast cancer patients with AIA. Future studies with better blinding methods are warranted to further explore the nature of non-specific and placebo effects in true and sham acupuncture.

Abbreviations

AIA: aromatase inhibitor-induced arthralgia; AIs: aromatase inhibitors; RCTs: randomized controlled trials; CNKI: China National Knowledge Infrastructure Database; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MD: mean difference; ASCO: American Society of Clinical Oncology; BPI: brief pain inventory; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; SD: standard deviation; VAS: visual analog scale; DASH: quick disability of arm,

shoulder, hand scale; PPT: physical performance test; FACT: functional assessment of cancer therapy; M-SACRAH: modified score for the assessment and quantification of chronic rheumatoid affections of the hands; VAS; HAQ: health assessment questionnaire; PROs: patient-reported outcomes.

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Authors' Contributions

XL, GW, and JL conceived the study together, analyzed and interpreted the data, and drafted the manuscript. They contributed equally to the work. HX, JH and XC revised the manuscript. MX and JT supervised the development of the work, reviewed the manuscript and served as corresponding authors. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

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Competing Interests

The authors declare that they have no competing interests.

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Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

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