

Acupuncture therapy for fibromyalgia: a systematic review and meta-analysis of randomized controlled trials

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Purpose: Fibromyalgia (FM) can cause chronic widespread pain and seriously affect the quality of patient lives. Acupuncture therapy is widely used for pain management. However, the effect of acupuncture on FM is still uncertain. The aim of this review was to determine the effect and safety of acupuncture therapy on the pain intensity and quality of life in patients with FM.

Materials and methods: We searched PubMed, the Cochrane Library, Embase, the China National Knowledge Infrastructure, the Chinese Science and Technology Periodical Database, and the Chinese Biomedical Literature Database to collect randomized controlled trials (RCTs) of acupuncture for FM published before May 2018. A meta-analysis was performed according to the Cochrane systematic review method by using RevMan 5.3 software, and GRADE was used to evaluate the quality of the evidence.

Results: We identified 12 RCTs that compared acupuncture therapy to sham acupuncture or conventional medication. Meta-analysis showed that acupuncture was significantly better than sham acupuncture for relieving pain (MD = -1.04, 95% CI [-1.70, -0.38], $P=0.002$, $I^2=78\%$) and improving the quality of life (MD = -13.39, 95% CI [-21.69, -5.10], $P=0.002$, $I^2=82\%$), with low- to moderate-quality evidence in the short term. At follow-up in the long term, the effect of acupuncture was also superior to that of sham acupuncture. No serious adverse events were found during acupuncture.

Conclusion: Acupuncture therapy is an effective and safe treatment for patients with FM, and this treatment can be recommended for the management of FM.

Keywords: acupuncture, fibromyalgia, pain, quality of life, meta-analysis

Introduction

Fibromyalgia (FM) is characterized by widespread musculoskeletal pain,¹ is present in as much as 0.4% to 9.3% of the population,² and is often accompanied by fatigue, sleep difficulties, cognitive dysfunction, depressed mood, or depressive episodes.^{3,4} FM can occur in all populations at every age, especially involving more middle-aged females than males.⁵ A recent study reported that the annual medical cost of FM was more than 12,993 million euros (32.5% corresponded to health care costs and 67.5% to indirect costs attributable to productivity losses) in Spain.⁶ Therefore, it is imperative to find effective therapies relieving pain and reducing social and economic burden.

The management of FM requires a multidimensional approach that includes patient education, behavioral therapy, exercise, and pain management.⁷ Unfortunately, no effective treatments for FM are presently available. The most common pharmacological therapies for the pain management of FM include amitriptyline, anticonvulsants,

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and serotonin noradrenaline reuptake inhibitors,⁸ or their combination.⁹ However, recent European guideline indicates that the effect size for most treatments is relatively modest and that all pharmacological therapies are only weak recommendations for FM.¹⁰ Moreover, the guideline suggests that initial management should focus on nonpharmacological therapies.¹⁰

There are different types of nonpharmacological interventions for FM. Acupuncture therapy is a significant component of nonpharmacological therapies. Modern medical researches indicate that the analgesic effects of acupuncture are known to activate peripheral and central pain control systems by releasing various endogenous opioids or nonopioid compounds, such as beta-endorphins, enkephalins, dynorphins, serotonin, norepinephrine, gamma-aminobutyric acid, or ATP.^{11–13} Excitingly, clinical studies of acupuncture therapy for FM showed promising results that acupuncture is effective in relieving symptoms of FM.¹⁴ However, the available systematic reviews published a few years ago indicated that there was no sufficient evidence to confirm the efficacy of acupuncture therapy for FM, mainly due to the small number of studies.^{15–17} Therefore, more randomized controlled trials (RCTs) were conducted to address this issue after demonstrating controversial results,^{18–20} which prompted us to conduct a meta-analysis of these primary studies to generate the pooled treatment effect of acupuncture on FM and offer suggestions for future studies and treatments.

Materials and methods

Protocol and registration

The protocol registration number is PROSPERO 2018 CRD42018094636 and is available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018094636. This review was reported in compliance with the PRISMA statement.²¹

Search strategy

We searched for RCTs in the following electronic databases, without language restriction, from their inceptions until May 2018: PubMed, the Cochrane Library, Embase, the China National Knowledge Infrastructure, the Chinese Science and Technology Periodical Database, and the Chinese Biomedical Literature Database. The search words were fibromyalgia (eg, fibromyalgia, fibrositis, fibromyositis, and FM) and acupuncture (eg, acupuncture, acupressure, acupoint, electroacupuncture, and electro-acupuncture [EA]). In addition, all the available reviews related to FM treatments were manually checked for any additional possibly relevant RCTs.

Inclusion and exclusion criteria

Types of studies: Only RCTs of acupuncture therapy for FM were included. Observational studies, cross-over studies, animal studies, conference abstracts, and letters were excluded, and the sample size of every study must be more than ten patients. The studies of unavailable data were excluded. There were no language restrictions.

Types of participants: Participants with FM must be diagnosed with a standard description of the diagnostic criteria (1990 American College of Rheumatology criteria).²² There are no limits to the age, gender, race, condition, duration, or intensity of the research subjects.

Types of interventions: Acupuncture therapy only included manual acupuncture and EA, regardless of different acupoints or needle materials. However, dry needling not based on traditional Chinese medicine (TCM) theory was excluded. Acupoint injections, laser acupuncture, moxibustion, cupping, herbal medicine, and any combination of the above were excluded. In addition, studies that compared different acupuncture therapies were also excluded.

Types of control groups: Sham acupuncture or conventional pharmacological therapies will be included. There were two types of sham acupuncture: a needling insertion into nonacupoints or ~1–2 cm from acupoints and nonpenetration by a blunt or retractable needle that contacts the skin without inserting the needle. Conventional pharmacological therapies do not contain herbal medicine.

Types of outcome measures: The primary outcome measures include a change in pain intensity and quality of life. The change in pain intensity was measured by using a VAS, a numerical rating scale (NRS), the Multidimensional Pain Inventory (MPI), or the McGill Pain Questionnaire (MPQ). Quality of life was evaluated using the fibromyalgia impact questionnaire (FIQ). The secondary outcome was an adverse event of acupuncture therapy to assess acupuncture safety.

Study selection and data extraction

According to the search strategy, one author (XCZ) performed the searches. Two investigators (XCZ and HC) reviewed the titles and abstracts of the references and screened eligible studies according to inclusion and exclusion criteria. Then, we downloaded the full text of the eligible studies to determine the final selection.

Two authors (XCZ and HC) independently extracted data from each study using a predesigned form. The information extracted included study design, patient characteristics, sample size, diagnostic criteria, interventions, treatment sessions, clinical outcome results, follow-up period, and

adverse events. If there were any unclear or missed data, we attempted to contact authors for the details by phone or email. If we could not obtain access to the data by contacting the authors, then we would exclude the studies. Any disagreements were resolved by rechecking the primary papers and further consultation with the third author (WTX).

Assessment of risk of bias

Two independent investigators (XCZ and HC) evaluated the risk of bias (ROB) in each included trial according to the Cochrane risk of bias assessment tool. This tool contains seven items of ROB: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias.²³ For each item, ROB was graded as high, low, or unclear. Discrepancies were resolved by further discussion with the third author (WTX).

Quality of evidence

For each comparison in the meta-analysis, we assessed the quality of evidence by using the Grading of Recommendations assessment, Development and Evaluation (GRADE) Guideline Development Tool (GRADEpro GDT, <https://gradepro.org/>).²⁴ In this online system, the quality of RCTs was initially graded as high and then downgraded as moderate, low, or very low because of any limitations with respect to ROB, inconsistency, indirectness, imprecision, or publication bias. Two authors (XCZ and HC) independently evaluated the quality of evidence according to the GRADE handbook,²⁵ and consensus was adapted to resolve any disagreement.

Statistical analyses

The meta-analysis was performed using RevMan 5.3 software provided by the Cochrane Collaboration. Continuous outcomes were calculated with mean difference (MD) and 95% CI. Dichotomous outcomes were calculated with the risk ratio (RR) and 95% CI. The overall effect was evaluated by the *Z* test, and a *P*-value of <0.05 was considered statistically significant. Considering the clinical heterogeneity of different acupuncture therapies, we performed subgroup analysis based on EA and manual acupuncture (MA). Statistical heterogeneity between studies was quantified by the *I*² statistic. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions (version 5.10), we defined *I*² >50% as representing substantial heterogeneity, and the random effects model was used for meta-analysis.²³ Sensitivity analyses were performed to explore potential

sources of heterogeneity. Publication bias was estimated by funnel plot analysis if sufficient studies were included.

Results

Study selection

A total of 744 studies were identified from all the initial searches; 441 studies were retained after screening and removing duplications, and 393 studies were excluded according to the title and abstract. Then, 48 full-text studies were further assessed for eligibility. Of these, 36 studies were excluded because of not RCTs, inappropriate intervention, data duplication, or data unusable (Table S1). Finally, 12 RCTs^{14,18–20,26–33} were eligible and included in the systematic review. The flow chart of the study selection process is shown in Figure 1.

Description of the included studies

In 12 studies, all FM patients were diagnosed by the 1990 American College of Rheumatology criteria. The sample size ranged from 20 to 164 participants. Nine articles were published in English,^{14,18–20,27,29,30,32,33} two in Chinese,^{28,31} and one in Portuguese.²⁶ Two studies used EA,^{14,30} and the other ten studies used MA.^{18–20,26–29,31–33} The main characteristics of the included studies are presented in Table 1.

Risk of bias within studies

Most of the studies were rated as low ROB, except for four studies.^{19,26,28,31} Eight studies used computer software or a random number table for random sequence generation.^{14,18,19,26,27,29,32,33} Two studies reported that participants were divided randomly according to the order of admission, and they did not perform allocation concealment.^{28,31} Eight studies performed allocation concealment by opaque sealed envelopes or central allocation.^{14,18,20,27,29,30,32,33} The acupuncturists in all studies were not blinded. Nine studies performed blinding of participants and outcome assessment.^{14,18,20,26,27,29,30,32,33} There were no missing data in five studies,^{19,26,28,29,31} and seven other studies reported dropout numbers and reasons.^{14,18,20,27,30,32,33} Six studies did not report any details about adverse events.^{26–29,31,32} The ROB summary is presented in Figure 2.

Effects of interventions

Real acupuncture vs sham acupuncture

Pain changes after treatment

The data regarding pain changes were reported in all studies. Eight studies compared real MA with sham MA,^{18–20,26,27,29,32,33} and two studies compared real EA with sham EA.^{14,30} We

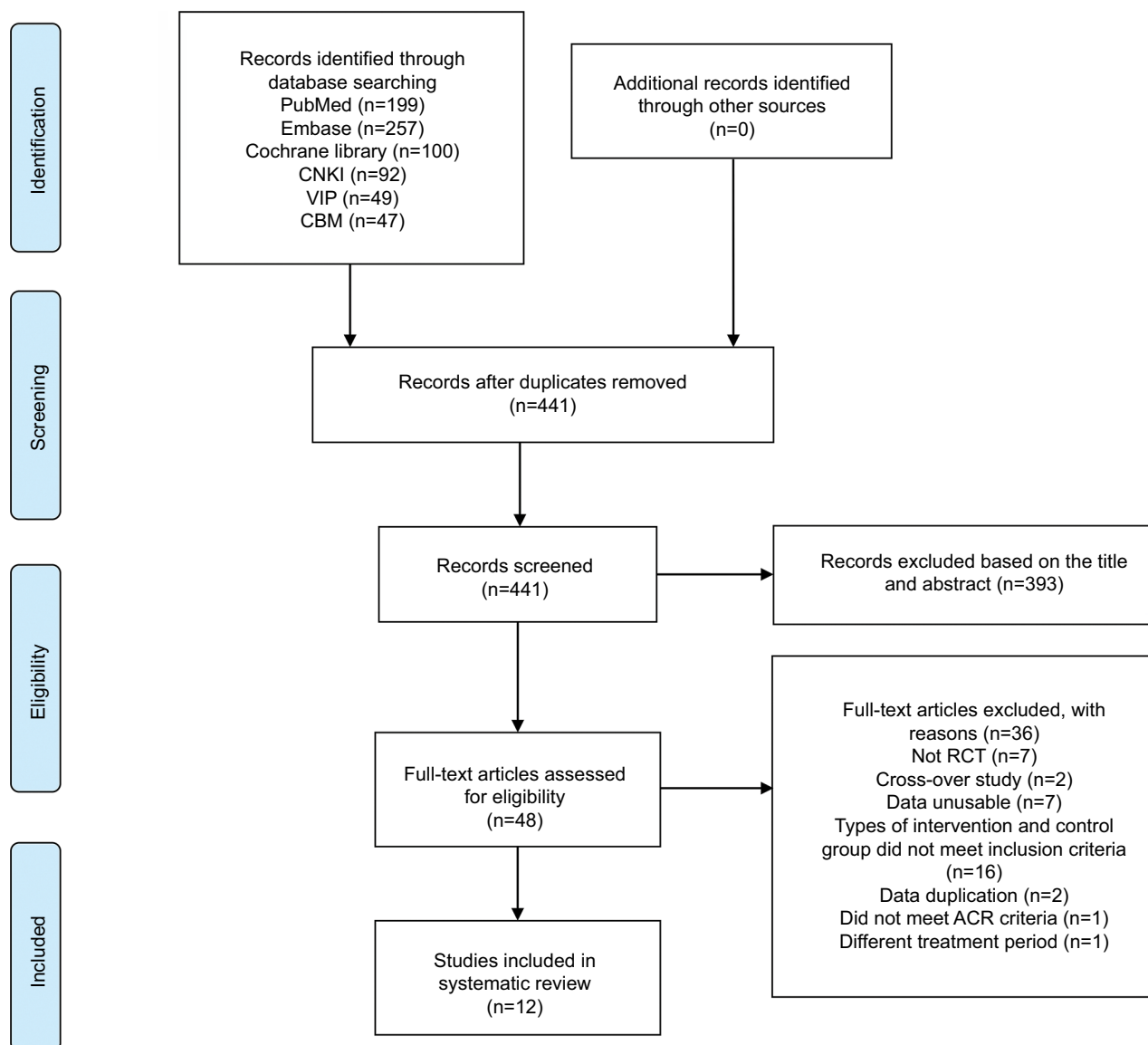


Figure 1 Review flow diagram.

Abbreviations: ACR, American College of Rheumatology; CBM, Chinese Biomedical Literature Database; CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial; VIP, Chinese Science and Technology Periodical Database.

performed a meta-analysis of pain changes (VAS, 0–10 cm scale). The overall meta-analysis of nine studies showed that real acupuncture was significantly better than sham acupuncture in reducing pain after treatment (MD =−1.04, 95% CI [−1.70, −0.38], $P=0.002$, $I^2=78\%$; Figure 3A). The quality of evidence was downgraded because of inconsistency and evaluated as moderate (Table 2). The subgroup analysis indicated that both real MA (MD =−1.14, 95% CI [−2.18, −0.09], $P=0.03$, $I^2=82\%$; Figure 3A) and real EA (MD =−0.94, 95% CI [−1.17, −0.72], $P<0.00001$, $I^2=0\%$; Figure 3A) were statistically significantly better than sham

acupuncture in reducing pain after treatment. The quality of evidence was moderate for the comparison of real MA vs sham MA and low for the comparison of real EA vs sham EA (Table 2).

Only two studies measured pain intensity by using a short form of MPQ (SF-MPQ).^{27,29} The pooled results indicated that there were no statistically significant differences in pain reduction between real MA and sham MA (MD =−1.23, 95% CI [−4.74, 2.27], $P=0.49$, $I^2=0\%$; Figure 3B). The quality of evidence was evaluated as low (downgraded because of imprecision and publication bias, Table 2)

Table 1 Characteristics of included studies

Study	Country	Diagnostic criteria	Sample size (AG/CG)	Interventions	Treatment period	Outcomes	Measurement time points (weeks)	Adverse events
Karatay et al 2018 ²⁰	Turkey	ACR 1990 criteria	25/25/25 (all female)	AG: real MA CG1: sham acupuncture CG2: simulated acupuncture CG1 was selected as sham acupuncture group	8 sessions for 4 weeks, each session lasting 30 minutes	VAS FIQ	0, 4, 8, 16	NO
Ugurlu et al 2017 ¹⁹	Turkey	ACR 1990 criteria	25/25 (all female)	AG: real MA CG: sham acupuncture	12 sessions for 8 weeks, each session lasting 30 minutes	VAS FIQ	0, 4, 8	NO
Vas et al 2016 ¹⁸	Spain	ACR 1990 criteria	80/82 (all female)	AG: real MA CG: sham acupuncture	9 sessions for 9 weeks, each session lasting 20 minutes	VAS FIQ	0, 10, 24, 48	Not serious, mild
Stival et al 2014 ²⁶	Brazil	ACR 1990 criteria	21/15 (female: 14/17)	AG: real MA CG: sham acupuncture	1 session for 20 minutes	VAS	Before and immediately after treatment	NR
Harte et al 2013 ²⁷	USA	ACR 1990 criteria	22/28 (all female)	AG: real MA CG: sham acupuncture	9 sessions for 4 weeks, each session lasting 30 minutes	VAS SF-MPQ	0, 4	NR
Gong et al 2010 ²⁸	China	ACR 1990 criteria	30/30 (female: 21/19)	AG: real MA CG: amitriptyline	AG: 36 sessions for 3 months, each session lasting 30 minutes CG: every day for 3 months	VAS	0, 12, 24	NR
Harris et al 2009 ²⁹	USA	ACR 1990 criteria	10/10 (all female)	AG: real MA CG: sham acupuncture	9 sessions for 4 weeks	SF-MPQ	0, 4	NR
Martin et al 2006 ³⁰	USA	ACR 1990 criteria	25/25 (female: 25/24)	AG: real EA CG: sham EA	6 sessions for 2-3 weeks	MPI FIQ	0, 3, 7, 31	Not serious, mild
Guo et al 2005 ³¹	China	ACR 1990 criteria	19/19 (female: 16/15)	AG: real MA CG: amitriptyline	AG: 28 sessions for 30 days, each session lasting 30 minutes CG: every morning for 30 days	VAS	0, 4	NR
Harris et al 2005 ³²	USA	ACR 1990 criteria	29/30/28/27 (female: 29/27/24/26)	AG: traditional site with stimulation CG1: traditional site without stimulation CG2: nontraditional site with stimulation CG3: nontraditional site with no stimulation CG3 was selected as sham acupuncture group	18 sessions for 9 weeks, each session lasting 20 minutes	NRS	0, 3, 4, 8, 9, 10, 13, 15	NR
Assefi et al 2005 ³³	USA	ACR 1990 criteria	25/25/24/25 (female: 22/24/24/24)	AG: real MA CG1: needling for unrelated condition CG2: sham needling CG3: simulated acupuncture CG2 was selected as sham acupuncture group	24 sessions for 12 weeks, each session lasting 30 minutes	VAS	0, 1, 4, 8, 12, 24, 36	Not serious, mild
Deluze et al 1992 ¹⁴	Switzerland	ACR 1990 criteria	36/34 (female: 33/21)	AG: real EA CG: sham EA	6 sessions for 3 weeks	VAS	0, 3	Not serious, mild

Abbreviations: ACR, American College of Rheumatology; AG, acupuncture group; CG, control group; EA, electro-acupuncture; FIQ, fibromyalgia impact questionnaire; MA, manual acupuncture; MPI, Multidimensional Pain inventory; NR, not reported; NRS, numeric rating scale; SF-MPQ, short form of McGill Pain Questionnaire.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Assefi 2005	+	+	-	+	+	+	+
Deluze 1992	+	+	-	+	+	+	+
Gong 2010	-	-	-	?	+	-	+
Guo 2005	-	-	-	?	+	-	+
Harris 2005	+	+	-	+	+	-	+
Harris 2009	+	+	-	+	+	-	+
Harte 2013	+	+	-	+	+	-	+
Karatay 2018	?	+	-	+	+	+	+
Martin 2006	?	+	-	+	+	+	+
Stival 2014	+	?	-	+	+	-	+
Ugurlu 2017	+	?	-	-	+	+	+
Vas 2016	+	+	-	+	+	+	+

Figure 2 Risk of bias summary.

Quality of life: FIQ changes after treatment

Four studies evaluated quality of life by using the FIQ score.^{18-20,30} The pooled results indicated that real acupuncture was significantly better than sham acupuncture in improving quality of life after treatment (MD = -13.39, 95% CI [-21.69, -5.10], *P*=0.002, *I*²=82%; Figure 3C). The quality of evidence was evaluated as low (downgraded because of inconsistency and imprecision, Table 2). The subgroup analysis showed that the real MA of three studies was sig-

nificantly better than sham MA for improving quality of life after treatment (MD = -16.72, 95% CI [-22.51, -10.94], *P*<0.00001, *I*²=46%; Figure 3C), and the quality of evidence was evaluated as moderate (Table 2). However, there was no statistically significant difference between real EA and sham EA based on one study (MD = -2.7, 95% CI [-9.06, 3.66], *P*=0.41; Figure 3C), and the quality of evidence was evaluated as low (Table 2).

Long-term effect of acupuncture

There were three studies that followed-up long-term (more than three months after treatment) to assess the effect of acupuncture, and the data can be obtained.^{18,20,30} Because more than one follow-up result was measured among the studies (Table 1), we included the last follow-up result in our pooled analysis.

Two studies compared real MA with sham MA, and one study compared real EA with sham EA. The pooled results indicated that real acupuncture had a superior long-term effect on reducing pain and improving the quality of life compared with sham acupuncture (MD = -1.58, 95% CI [-2.72, -0.44], *P*=0.006, *I*²=67%, Figure 3D; MD = -12.92, 95% CI [-24.92, -0.93], *P*=0.03, *I*²=81%; Figure 3E). Because of inconsistency and imprecision, the quality of evidence was downgraded and evaluated as low (Table 2). The subgroup analysis showed that real MA was significantly better than sham MA for reducing pain and improving the quality of life in the long term (MD = -2.06, 95% CI [-3.49, -0.63], *P*=0.005, *I*²=68%, Figure 3D; MD = -18.96, 95% CI [-26.69, -11.23], *P*<0.00001, *I*²=0%, Figure 3E), and the quality of evidence was evaluated as very low and low, respectively (Table 2). However, there were no statistically significant differences between real EA and sham EA for reducing pain and improving the quality of life in the long term (MD = -0.6, 95% CI [-1.78, 0.58], *P*=0.32, Figure 3D; MD = -3.0, 95% CI [-8.98, 2.98], *P*=0.33; Figure 3E), and the quality of evidence was evaluated as low (Table 2).

Adverse events

Six studies reported no serious adverse events,^{14,18-20,30,33} of which four studies observed mild adverse events, such as bruising, soreness, nausea, discomfort of needle insertion, and aggravation of symptoms.^{14,18,30,33} These mild adverse events were more common in the real acupuncture group than in the sham acupuncture group. The other four studies did not provide any details about adverse events.^{26,27,29,32}

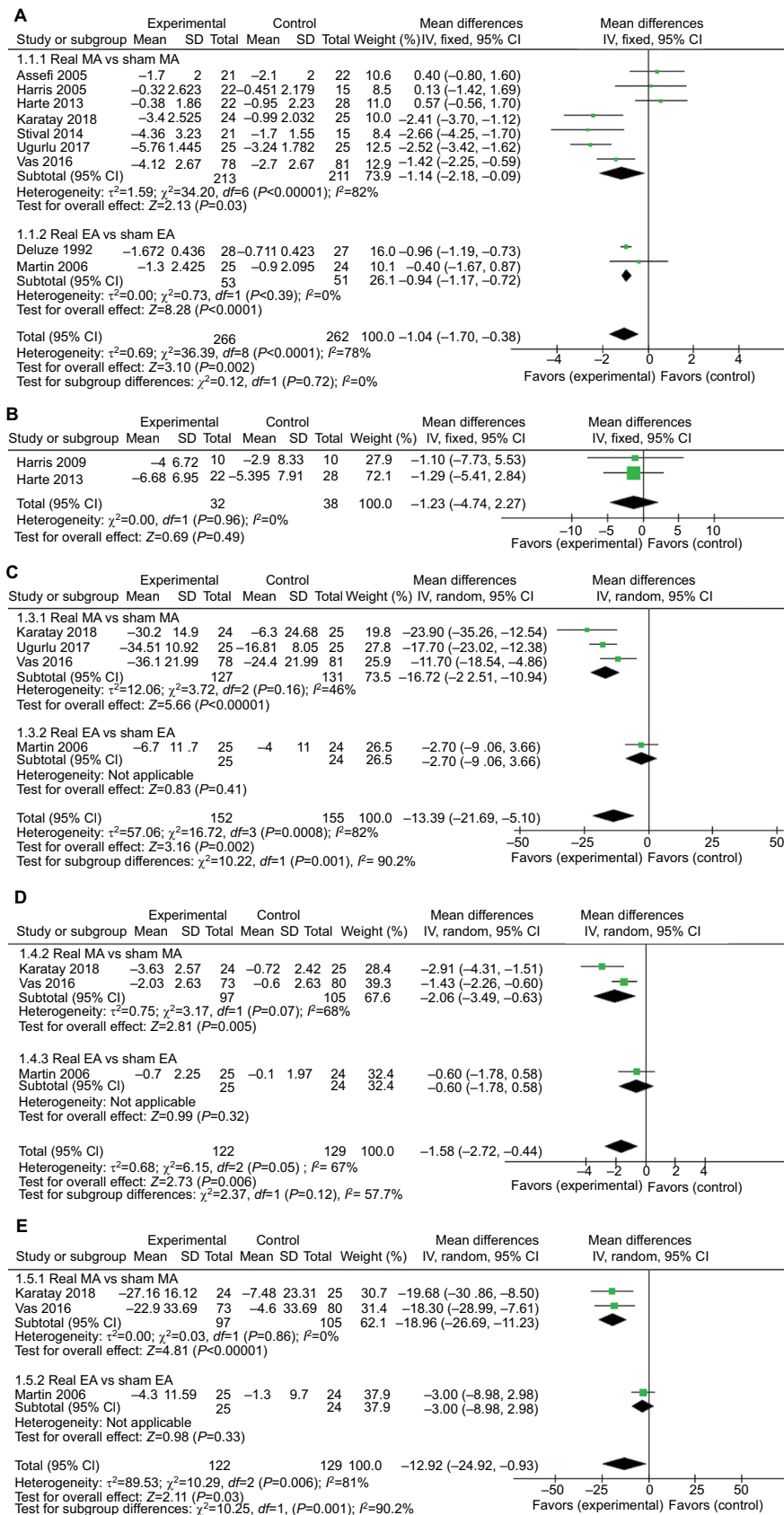


Figure 3 Forest plot comparing real acupuncture vs sham acupuncture.

Notes: (A) Outcome: pain changes after treatment (VAS, 0–10 cm scale). (B) Outcome: pain changes after treatment (SF-MPQ). (C) Outcome: FIQ changes after treatment. (D) Outcome: long-term effect of pain changes (VAS, 0–10 cm scale). (E) Outcome: long-term effect of FIQ changes.

Abbreviations: EA, electro-acupuncture; FIQ, fibromyalgia impact questionnaire; MA, manual acupuncture; SF-MPQ, short form of McGill Pain Questionnaire.

Table 2 Effect size and GRADE quality of evidence

Certainty assessment		No. of patients					Effect	Certainty	Importance		
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Real acupuncture	Sham acupuncture	Absolute (95% CI)		
Pain changes after treatment (VAS, 0–10 cm scale) – real acupuncture vs sham acupuncture											
9	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Not serious ^d	None ^e	266	262	MD 1.04 lower (1.70 lower to 0.38 lower)	⊕⊕⊕⊕ Moderate	Critical
Pain changes after treatment (VAS, 0–10 cm scale) – real MA vs sham MA											
7	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Not serious ^d	None ^e	213	211	MD 1.14 lower (2.18 lower to 0.09 lower)	⊕⊕⊕⊕ Moderate	Critical
Pain changes after treatment (VAS, 0–10 cm scale) – real EA vs sham EA											
2	Randomized trials	Not serious ^a	Not serious ^f	Not serious ^c	Serious ^g	Publication bias strongly suspected ^h	53	51	MD 0.94 lower (1.17 lower to 0.72 lower)	⊕⊕⊕⊕ Low	Critical
Pain changes after treatment (SF-MPQ scale) – real MA vs sham MA											
2	Randomized trials	Not serious ^a	Not serious ^f	Not serious ^c	Serious ^g	Publication bias strongly suspected ^h	32	38	MD 1.23 lower (4.74 lower to 2.27 higher)	⊕⊕⊕⊕ Low	Critical
FIQ changes after treatment – real acupuncture vs sham acupuncture											
4	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Serious ^g	None ^e	152	155	MD 13.39 lower (21.69 lower to 5.1 lower)	⊕⊕⊕⊕ Low	Critical
FIQ changes after treatment – real MA vs sham MA											
3	Randomized trials	Not serious ^a	Not serious ^f	Not serious ^c	Serious ^g	None ^e	127	131	MD 16.72 lower (22.51 lower to 10.94 lower)	⊕⊕⊕⊕ Moderate	Critical
FIQ changes after treatment – real EA vs sham EA											
1	Randomized trials	Not serious ^a	Not serious ^f	Not serious ^c	Serious ^g	Publication bias strongly suspected ^h	25	24	MD 2.7 lower (9.06 lower to 3.66 higher)	⊕⊕⊕⊕ Low	Critical

(Continued)

Table 2 (Continued)

Certainty assessment										
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Real acupuncture	Sham acupuncture	Effect	Importance
Long-term effect of pain changes (VAS, 0–10 cm scale) – real acupuncture vs sham acupuncture										
3	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Serious ^d	None ^e	122	129	MD 1.58 lower (2.72 lower to 0.44 lower)	⊕⊕○○ Low Critical
Long-term effect of pain changes (VAS, 0–10 cm scale) – real MA vs sham MA										
2	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Serious ^d	Publication bias strongly suspected ^h	97	105	MD 2.06 lower (3.49 lower to 0.63 lower)	⊕○○○ Very low Critical
Long-term effect of pain changes (VAS, 0–10 cm scale) – real EA vs sham EA										
1	Randomized trials	Not serious ^a	Not serious ^b	Not serious ^c	Serious ^d	Publication bias strongly suspected ^h	25	24	MD 0.6 lower (1.78 lower to 0.58 higher)	⊕⊕○○ Low Critical
Long-term effect of FIQ changes – real acupuncture vs sham acupuncture										
3	Randomized trials	Not serious ^a	Serious ^b	Not serious ^c	Serious ^d	None ^e	122	129	MD 12.92 lower (24.92 lower to 0.93 lower)	⊕⊕○○ Low Critical
Long-term effect of FIQ changes – real MA vs sham MA										
2	Randomized trials	Not serious ^a	Not serious ^b	Not serious ^c	Serious ^d	Publication bias strongly suspected ^h	97	105	MD 18.96 lower (26.69 lower to 11.23 lower)	⊕⊕○○ Low Critical
Long-term effect of FIQ changes – real EA vs sham EA										
1	Randomized trials	Not serious ^a	Not serious ^b	Not serious ^c	Serious ^d	Publication bias strongly suspected ^h	25	24	MD 3.0 lower (8.98 lower to 2.98 higher)	⊕⊕○○ Low Critical
Pain changes after treatment (VAS, 0–10 cm scale) – real acupuncture vs conventional medication										
2	Randomized trials	Serious ^a	Not serious ^b	Not serious ^c	Serious ^d	Publication bias strongly suspected ^h	49	49	MD 1.81 lower (2.43 lower to 1.18 lower)	⊕○○○ Very low Critical

Notes: ^a<25% of studies had high risk of bias. ^bI² is >50%. ^cDirect comparison and outcomes. ^dTotal sample size is >400. ^eNo clear publication bias was detected. ^fI² is <50%. ^gTotal sample size is <400. ^hOnly one study or two studies consider potential publication bias. ⁱThe study had low risk of bias. ^jOnly one study and no inconsistency. ^kTwo studies had high risk of bias.

Abbreviations: EA, electro-acupuncture; FIQ, fibromyalgia impact questionnaire; MA, manual acupuncture; MD, mean difference; SF-MPQ, short form of McGill Pain Questionnaire.

Real acupuncture vs conventional medication

Pain changes after treatment

Two studies compared real acupuncture with conventional medication and reported the data on pain changes (VAS, 0–10 cm scale).^{28,31} The pooled results showed that real acupuncture was statistically significantly better than conventional medication in reducing pain after treatment (MD =−1.81, 95% CI [−2.43, −1.18], $P<0.00001$, $I^2=0\%$; Figure 4A). However, the quality of evidence was downgraded because of ROB, imprecision and publication bias and was evaluated as very low (Table 2).

Long-term effect of acupuncture

Two studies^{28,31} included follow-up observations at 6 months after treatment, but only one study provided data on pain changes (VAS, 0–10 cm scale). The result indicated that real acupuncture yielded significantly more pain reduction than conventional medication at follow-up (MD =−2.11, 95% CI [−2.97, −1.25], $P<0.00001$; Figure 4B).

Adverse events

There were no details about any adverse events reported.

Heterogeneity and sensitivity analyses

There was considerable heterogeneity ($I^2=78\%$) in the comparison of real acupuncture vs sham acupuncture on pain changes after treatment. We conducted sensitivity analyses by omitting potential heterogeneous studies to observe their influence on the pooled effect size. Two studies were omitted

because their ROB was high.^{19,26} The third study was omitted because the mean data were measured from the published article and SD was taken from baseline.³³ The fourth study was omitted because the data in the meta-analysis were transformed from NRS.³² All studies omitting either of the four mentioned studies were then recalculated to determine the pooled effect size. Sensitivity analyses indicated that the pooled effect was not changed when omitting either of the four mentioned studies. The result of sensitivity analyses on studies with low ROB was consistent with the result of all studies (Table S2). However, the heterogeneity was not resolved and may be caused by various acupoints, different measurement time points, and sham acupuncture methods. The sensitivity analyses of other outcomes were not conducted due to the low number of corresponding included studies.

Publication bias

The funnel plot for pain changes after treatment demonstrated that visual inspection of the funnel plot was symmetric and no clear publication bias was detected (Figure 5).

Discussion

Summary of the main findings

We included 12 RCTs that compared acupuncture therapy to sham acupuncture or conventional medication. With respect to reducing pain (VAS 0–10 cm scale), there was moderate-quality evidence showing that real acupuncture was more effective than sham acupuncture in the short term, and similar

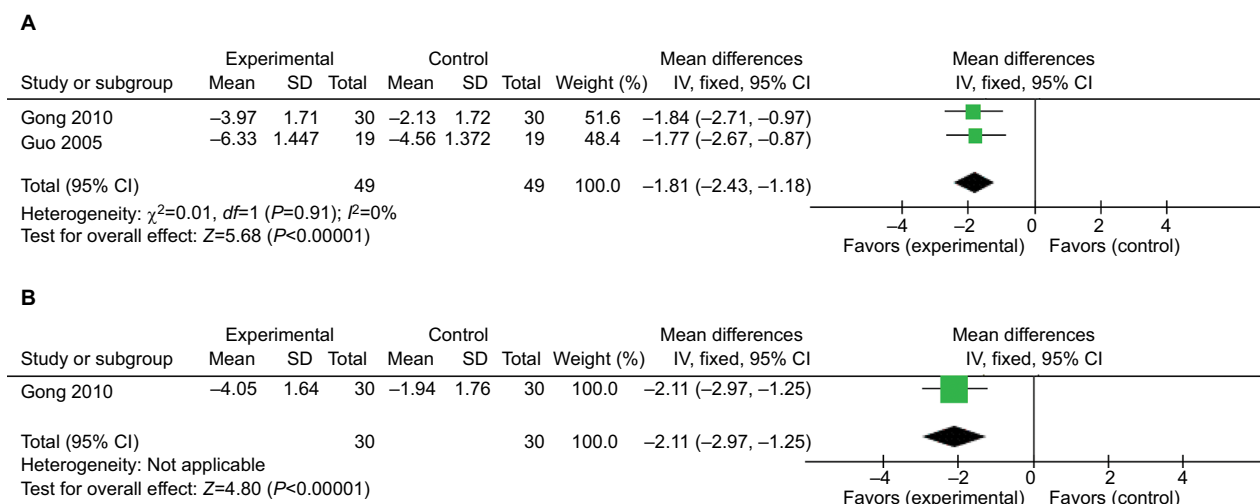


Figure 4 Forest plot comparing real acupuncture vs conventional medication.

Notes: (A) Outcome: pain changes after treatment (VAS, 0–10 cm scale). (B) Outcome: long-term effect of pain changes (VAS, 0–10 cm scale).

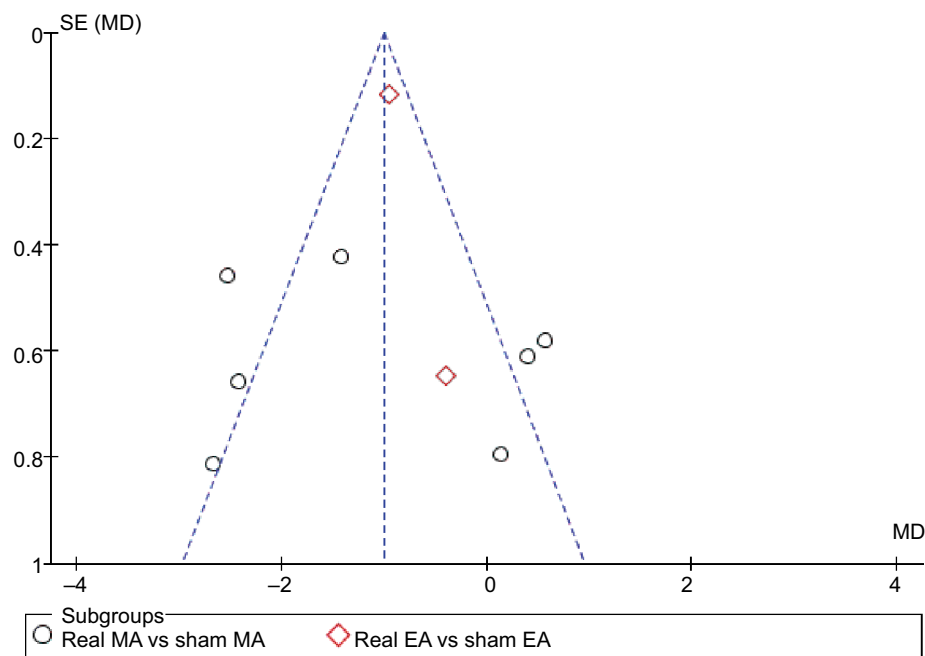


Figure 5 Funnel plot comparing real acupuncture vs sham acupuncture.

Note: Outcome: pain changes after treatment (VAS, 0–10 cm scale).

Abbreviations: EA, electro-acupuncture; MA, manual acupuncture; SE, standard error; MD, mean difference.

results were obtained with low-quality evidence in the long term. With respect to improving the quality of life, there was low-quality evidence showing that real acupuncture was more effective than sham acupuncture in both the short and long term. In the comparison of acupuncture vs conventional medication, we found very low-quality evidence showing that acupuncture was more effective in relieving pain in both the short and long term.

Subgroup analyses demonstrated that real MA was superior to sham MA in reducing pain (VAS, 0–10 cm scale) and improving the quality of life, with moderate-quality evidence in the short term and low- to very low-quality evidence in the long term. There were two studies that compared real EA with sham EA. The results indicated real EA was superior to sham EA in reducing pain in the short term with low-quality evidence, but no significant difference was observed in the long term with low-quality evidence. Only one study compared real EA with sham EA and reported the effect on improving the quality of life. The results demonstrated no significant difference between real EA and sham EA in both the short and long term with low-quality evidence.

According to the TCM theory, FM is categorized as Bi Syndrome; the invasion of pathogenic wind, cold, and dampness can affect imbalance in the flow of Qi and blood, and then cause pain, stiffness, and other symptoms in the body's

muscles, tendons, and joints.³⁴ Therefore, the TCM mechanism of acupuncture for FM is to regulate the circulation of Qi and blood, combined with expelling cold and removing dampness. A modern medical study indicated that acupuncture can significantly increase blood flow in the skin and muscles of patients with FM,³⁵ which is very important for reducing pain symptoms. As a primary mechanism of FM, the central sensitization of nervous system can decrease the pressure pain threshold, elicit hyperalgesia, and as a result, a noxious stimulus can cause more severe pain than in normal individuals.^{36,37} One recent animal study found that the upregulation of transient receptor potential vanilloid 1 and the phosphoactivation of extracellular signal regulated kinase were associated with mechanical hyperalgesia in FM model mice. EA at the bilateral Zusanli (ST36) acupoints can reverse the upregulation of these receptors and reduce mechanical hyperalgesia significantly.³⁸ Another animal study showed that acid-sensing ion channel 3 and the ERK pathway participated in FM pain attenuated by EA.³⁹ Additionally, acupuncture can regulate the central nervous system to release endogenous opioids and nonopioid compounds, such as endorphin, serotonin, enkephalins, dynorphin, norepinephrine, oxytocin, neuropeptide, and ATP. These substances are essential to decrease the hypersensitivity of pain and reduce pain symptoms.^{12,13,40,41} However, the specific mechanism of

acupuncture therapy for FM is very complex and remains unknown. Therefore, more studies are needed in the future.

Comparison with previous systematic reviews

Previous meta-analyses have drawn various conclusions depending on the inclusion criteria and the number of included studies.^{15–17,42} One review⁴² published in 2010 included seven RCTs. The pooled analysis found strong evidence for the reduction of pain (standardized mean difference (SMD) = -0.25, 95% CI [-0.49, -0.02]) at posttreatment compared to control acupuncture, which contained sham and simulated acupuncture. However, sensitivity analysis indicated that this small analgesic effect of acupuncture was only present in studies with ROB. Therefore, this review concluded that acupuncture cannot be recommended for the management of FM. In 2013, one systematic review¹⁶ included 16 RCTs that compared acupuncture alone or combined with other interventions (cupping therapy, point injection, point catgut embedding, or moxibustion) to no treatment, sham, or conventional medication. The conclusion indicated that acupuncture alone or combined with cupping therapy was superior to conventional medications. However, acupuncture had no better effect than sham acupuncture on pain reduction. Another Cochrane review of acupuncture for FM was also published in 2013 and included nine RCTs.¹⁷ Pain severity measured with VAS, NRS, MPI, and MPQ was pooled in six studies, and the results indicated that acupuncture was no better than sham acupuncture in reducing pain (SMD = -0.14, 95% CI [-0.53, 0.25]). Therefore, the available systematic reviews demonstrated controversial conclusions about whether acupuncture was more effective than sham acupuncture in relieving pain.

Compared with previous systematic reviews, our review focused mainly on observing the efficacy of acupuncture alone, so we did not involve studies with mixed therapies. We included an additional five new RCTs published after 2013 in our review, three with low ROB and two with high ROB. Since the pain severity of patients was measured with VAS, NRS, MPI, or MPQ, this analysis may produce greater heterogeneity if the results of different measurement tools are directly pooled. Therefore, we extracted the results of the same tool as much as possible. Because most of the included studies used VAS as a measurement tool and FIQ contained VAS, we extracted the results of VAS to pool the analysis. Because one study data of the meta-analysis were transformed from NRS, we conducted sensitivity analyses by excluding this study and found that the pooled effect was not changed. We included nine RCTs, and the results indicated

that real acupuncture was superior to sham acupuncture in reducing pain (VAS, 0–10 cm scale) in the short term with moderate-quality evidence (MD = -1.04, 95% CI [-1.70, -0.38]). This new conclusion of our review was completely different from that of previous research and can provide a better reference for clinical decisions because we analyzed direct VAS results.

Limitations and implications

This systematic review has several limitations. First, a low number of studies were included in our review, and most of the studies had a relatively small sample size. This limitation may lead to imprecise evidence. Second, there was considerable heterogeneity in our meta-analysis. We attempted to decrease the heterogeneity by subgroup and sensitivity analyses, but it was not completely resolved. We considered that this heterogeneity possibly derived from methodological bias and differences in acupoint selection, sham acupuncture method, and the frequency and duration of treatment. Third, only a few studies followed-up the patients after treatment and reported adverse events; thus, studies with more details about follow-up and adverse events would better evaluate the long-term effect and safety of acupuncture.

Given the above limitations, more rigorous larger-scale and well-designed RCTs are needed to provide higher-quality evidence and evaluate the efficacy of acupuncture for FM. First, future RCTs should correctly conduct random sequence generation, allocation concealment, and blinding to avoid ROB. Simultaneously, the details about follow-up, dropout, and adverse events must be reported thoroughly. Second, many different kinds of acupuncture are used to treat FM in clinical practice. Therefore, future studies comparing different acupuncture interventions are needed to find the most effective acupuncture treatment. Furthermore, the optimal duration and frequency of treatment are also important for FM. Third, all RCTs must be registered in advance and reported using standards for reporting interventions in clinical trials of acupuncture (STRICTA) guideline⁴³ to improve the quality of future reports in this field.

Conclusion

In summary, real acupuncture was more effective than sham acupuncture in relieving pain (VAS, 0–10 cm scale) and improving the quality of life in both the short and long term. Both EA and MA were better than sham acupuncture in relieving pain in the short term. Furthermore, acupuncture was more effective in relieving pain in both the short and long term compared with conventional medication. No serious adverse events were found during acupuncture. In brief, acupuncture

therapy is an effective and safe treatment for patients with FM, and it can be recommended for the management of FM. However, more large-sample RCTs are needed to investigate the therapeutic effect of EA for FM in the long term.

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Author contributions

Study concept and design: GN, XZ. Acquisition of data: XZ, HC, WX. Analysis and interpretation of data: GN, XZ, HC, WX, YS, YG. Article drafting and critical revision of the manuscript for important intellectual content: GN, XZ, HC, WX, YS, YG. Administrative, technical, or administrative support: GN, XZ, HC. Study supervision: GN, XZ. All authors read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Reasons for excluded studies

Study	Reason for exclusion
Mist et al, 2018 ¹	Acupuncture vs education
Ma et al, 2018 ²	Article in Chinese; not an RCT
AM et al, 2017 ³	Dry needling vs cross tape
Iannuccelli et al, 2017 ⁴	Not an RCT
Zucker et al, 2017 ⁵	Secondary analysis of original article Harris et al, 2005 ³⁷
Li et al, 2016 ⁶	Article in Chinese; acupuncture + moxibustion vs Western medicine
Disa et al, 2016 ⁷	Acupuncture vs electro-acupuncture vs moxibustion
Yu et al, 2016 ⁸	Article in Chinese; acupuncture + herbal medicine vs Western medicine
Weber et al, 2015 ⁹	No acupuncture therapy
de Tommaso et al, 2014 ¹⁰	Cross-over study; only ten patients
Casanueva et al, 2014 ¹¹	Dry needling vs medical treatment
Collazo et al, 2014 ¹²	Article in Spanish; acupuncture vs moxibustion vs scalp acupuncture
Shao et al, 2013 ¹³	Article in Chinese; data unusable
Collazo et al, 2013 ¹⁴	Article in Spanish; acupuncture vs scalp acupuncture
Hadianfard et al, 2012 ¹⁵	Different treatment period. Acupuncture group received therapy for 2 weeks and control group received fluoxetine orally for 8 weeks
Iannuccelli et al, 2012 ¹⁶	Not an RCT
Collazo et al, 2012 ¹⁷	Article in Spanish; acupuncture vs traditional Chinese dietary therapy
Itoh et al, 2010 ¹⁸	Five acupuncture treatments vs ten acupuncture treatments
Jiang et al, 2010 ¹⁹	Article in Chinese; acupuncture + cupping + Western medicine vs acupuncture + cupping vs Western medicine
Collazo et al, 2010 ²⁰	Article in Spanish; not an RCT
Li et al, 2009 ²¹	Article in Chinese; lower Dan-Tian acupuncture vs conventional acupuncture
Zhao et al, 2009 ²²	Article in Chinese; moxibustion + Western medicine vs Western medicine
Targino et al, 2008 ²³	Acupuncture + tricyclic antidepressants + exercise vs tricyclic antidepressants + exercise
Harris et al, 2008 ²⁴	Data unusable; only ten patients
Sun, 2008 ²⁵	Article in Chinese; not an RCT
Li, 2007 ²⁶	Article in Chinese; not an RCT
Li et al, 2006 ²⁷	Article in Chinese; acupuncture + cupping + Western medicine vs vs Western medicine
Yao et al, 2006 ²⁸	Article in Chinese; not an RCT; data unusable
Harris et al, 2006 ²⁹	Secondary analysis of original article Harris et al, 2005 ³⁷
Guo et al, 2005 ³⁰	Data unusable
Wang et al, 2004 ³¹	Article in Chinese; not an RCT
Wang et al, 2002 ³²	Article in Chinese; data unusable
Liu et al, 2002 ³³	Article in Chinese; did not meet ACR criteria
Zhang et al, 2001 ³⁴	Article in Chinese; data unusable
Sandberg et al, 1999 ³⁵	Cross-over study; only ten patients
Spratt et al, 1998 ³⁶	Data unusable

Abbreviations: ACR, American College of Rheumatology; RCT, randomized controlled trial.

Table S2 Sensitivity analyses on pain changes after treatment

Real acupuncture vs sham acupuncture	Effect size	Heterogeneity
All studies	MD = -1.04, 95% CI (-1.70, -0.38)	I ² =78%
All studies except Ugurlu et al, 2017 ³⁸	MD = -0.83, 95% CI (-1.47, -0.19)	I ² =72%
All studies except Stival et al, 2014 ³⁹	MD = -0.90, 95% CI (-1.57, -0.22)	I ² =78%
All studies except Assefi et al, 2014 ⁴⁰	MD = -1.21, 95% CI (-1.89, -0.53)	I ² =77%
All studies except Harris et al, 2005 ³⁷	MD = -1.15, 95% CI (-1.84, -0.46)	I ² =80%
The studies with low risk of bias	MD = -0.65, 95% CI (-1.30, -0.01)	I ² =71%

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