Author's response to reviews

Title: Acupuncture for ankle sprain: Systematic review and meta-analysis

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Author's response to reviews: see over
Dear Dr. Tom Rowl es,

We are pleased to submit the revised manuscript entitled “Acupuncture for ankle sprain: Systematic review and meta-analysis” for consideration for publication in BMC Complement Altern Med (Manuscript no. 162010349801865). We greatly appreciate the referees’ critical comments and have tried our best to incorporate their suggestions and recommendations into the revised manuscript.

Attached are the point-by-point detailed responses to the comments from the referees.

We thank you in advance for your consideration of this revised manuscript.

Yours faithfully,

Hyangsook Lee, KM D, PhD, associate professor
[Detailed responses to the referees]

Referee #1. Dr. Daniel Cheuk

We appreciate invaluable comments from Dr. Daniel Cheuk and tried our best to incorporate his suggestions in the revision. Also it should be noted that we accepted 2nd reviewer’s suggestion of using non-responder rate in the meta-analysis, and accordingly, the point estimates have been changed in the revision in the revised manuscript.

1. This is a meta-analysis of randomized controlled trials and hence at the top of the evidence-base hierarchy and therefore the results can potentially be practice-changing. So it is very important for the conclusion of the review to be accurately phrased so as not to be misleading. After I have read the whole review and evaluated the included studies, I think the conclusion should be that “there is no good evidence supporting the use of acupuncture for ankle sprain”, mainly due to high risk of bias in the included studies. The authors’ conclusion in the abstract that “the results from this review show the potential of acupuncture for ankle sprains” is misleading and should be deleted or rephrased.

ANSWER > We accepted the reviewer’s comment and revised the conclusion where relevant. The revised conclusion goes as follows; “Given methodological shortcomings and the small number of high-quality primary studies, the available evidence is insufficient to recommend acupuncture as an evidence-based treatment option, calling for further rigorous investigations”.

2. The authors included quasi-RCTs. How did they define quasi-RCTs? Which included studies were quasi-RCTs? The authors should show this in the tables and analyze them separately as they are more prone to bias compared to genuine RCTs.

ANSWER > We defined quasi-RCTs as RCTs using quasi-random methods of allocating participants to different intervention groups. Quasi-random methods are not truly random; for example, allocation by data of birth, medical record number, or alternation (http://www.medicine.ox.ac.uk/bandolier/booth/glossary/RCT.htm). In this review, our search identified no quasi-RCTs; instead, most of the trials (14 out of 17 trials) were given ‘unclear risk of bias’ for adequate sequence generation as they
poorly reported the method of randomisation. Three studies which were given high risk of bias for randomisation method in the original submission were again shown to two native Chinese researchers and one researcher who specialised in Chinese language in the university. They judged that these trials did not allocate participants according to the order of hospital visit, but gave these trials uncertain risk of bias as these studies lacked reporting of randomisation methods. Therefore, we deleted the word ‘quasi-RCTs’ in the study selection criteria for clarity as we actually had no quasi-RCTs. Please see page 10 in the revised manuscript with track changes. It reads as follows: “Types of studies: All randomised controlled trials (RCTs) evaluating acupuncture treatment for ankle sprains were considered.”

3. There should only be a single primary outcome and all others should be put in the secondary outcome category.
ANSWER: We left only one primary outcome of patient-reported global assessment, put the others to secondary outcomes and the results were revised accordingly.

4. Results derived from comparing acupuncture with different controls should not be pooled together as the effect size of different comparisons is conceptually very much different. For example, NSAID and herbal medicine should be separately analyzed.
ANSWER: We generally agree with the reviewer’s comment and did the analyses again. Basically, we used non-responder rate and divided the main analysis into acupuncture as an alternative treatment and acupuncture as an add-on treatment because we thought these two were fundamentally different and should not be pooled together – this was also recommended by the second reviewer. We also did the analysis separately according to the control types, i.e. NSAIDs and herbal medicine, as you commented and these analyses are shown in the subgroup analyses (see revised figure 3 and pages 28-29 in the revised manuscript with track changes).

5. In the 3rd paragraph of the discussion section, the authors mentioned that “it is not clear whether there is ‘no evidence of difference’ or ‘evidence of no difference’.
Actually these two are different conclusions. With small sample size, a statistically non-significant result clearly indicates no evidence of difference instead of evidence of no difference.

ANSWER: We newly analyzed the effect of acupuncture compared with NSAIDs. Because we expected the effect of acupuncture alone and as an add-on would differ, we analyzed them separately. Consequently, acupuncture, both as an alternative and as an add-on treatment, had no significant benefit for symptom improvement compared with NSAIDs. This was clearly put in the revision (see pages 37 and 42 in the revised manuscript with track changes). It reads as follows; (page 37) “In our review, acupuncture as an add-on or alternative treatment demonstrated no better effect than oral/topical NSAIDs...” / (page 42) “We have no convincing evidence supporting acupuncture compared with NSAIDs whether given as an alternative or add-on treatment.”

6. In the Discussion section, the authors should make specific suggestions on how future studies should be conducted so as to give a more definitive answer to the research question by reducing bias, e.g., how blinding may be achieved, etc.

ANSWER: We added ‘Implications for research’ in the last part of the discussion to suggest how we think future trials should be conducted (see pages 42-43 in the revised manuscript with track changes).

Quality of written English: Not suitable for publication unless extensively edited

ANSWER: We had the revised manuscript checked and edited for proper English language, grammar, punctuation, spelling, and overall style by the native English speaker in our university.

We sincerely thank again Dr. Daniel Cheuk for his invaluable criticisms and suggestions which we believe are quite valid and improved our revised manuscript.
We appreciate invaluable comments from Dr. Klaus Linde and tried our best to incorporate his suggestions in the revision. Also, it should be noted that we accepted his suggestion of using non-responder rate in the meta-analysis, and accordingly, the point estimates have been changed in the revision in the revised manuscript.

Major compulsory revision

1. While I do not think that this will change the conclusion a lot, I find it problematic that the authors analyze trials in which acupuncture is used as a treatment alternative (e.g. should I treat with acupuncture OR NSAIDs) together with trials where acupuncture is added (should I ADD acupuncture to NSAIDs or not). In my view these are fundamentally different questions which should not be analyzed together (although it does not seem to explain a lot of the heterogeneity). Also, you had several trials with more than two arms which addressed both questions.

Answer: We agree with the reviewer’s comment that these two are fundamentally different – add-on and alternative. Therefore, we newly analyzed the data of acupuncture as an alternative or as an add-on treatment, respectively, and it is shown in the revised Figure 2 and ‘Effects of acupuncture on primary outcome’ in pages 23-25 in the revised manuscript with track changes. Out of the 5 trials with more than two arms, 4 studies tested acupuncture both as an alternative and add-on treatment. In the original submission, we analyzed acupuncture + other treatment vs. other treatment alone pair as we thought add-on treatment was more common in practice. In the revised manuscript, we analyzed them in a separate meta-analysis; acupuncture as an alternative (e.g. acupuncture vs. NSAIDs) and acupuncture as an add-on (e.g. acupuncture plus NSAIDs vs. NSAIDs alone).

Minor comments (discretionary revisions)

1. page 2 line 6 to 7 and page 28 line 7 (“Acupuncture’s benefit was negated/nullified...”): (Although I am so skeptical about the primary studies) I do not think that this comes out of the data. In fact, the point estimate for the RR in adequately randomized studies is very similar to that for all studies. The confidence intervals are wide due to the small number of studies included. I would say “are not
significant” or something similar.

As we newly analyzed the results using non-responder rate, the results have been somewhat changed. And the effect of acupuncture remained significant when the analysis was limited to the studies with a low risk of bias. However, we understand and agree with the reviewer’s concern about poor-quality studies and tried to interpret the findings with caution.

2. Page 10, line 8 “considering countries in which acupuncture has been widely used”: I would suggest to delete this as other countries in which acupuncture is widespread (such as France and Germany) would be excluded (but authors from these countries often publish in English). You might argue that you cover relevant languages.

As we agreed with the reviewer and therefore deleted “considering countries in which acupuncture has been widely used”.

3. Page 10, selection criteria: I am surprised you considered quasi-RCTs.

We defined quasi-RCTs as RCTs using quasi-random methods of allocating participants to different intervention groups. Quasi-random methods are not truly random; for example, allocation by data of birth, medical record number, or alternation (http://www.medicine.ox.ac.uk/bandolier/book/glossary/RCT.html). In this review, our search identified no quasi-RCTs; instead, most of the trials (14 out of 17 trials) were given ‘unclear risk of bias’ for adequate sequence generation as they poorly reported the method of randomization. Three studies which were given high risk of bias for randomization method in the original submission were again shown to two native Chinese researchers and one researcher who specialised in Chinese language in the university. They judged that these trials did not allocate participants according to the order of hospital visit, but gave these trials uncertain risk of bias as these studies lacked reporting of randomisation methods. Therefore, we deleted the word ‘quasi-RCTs’ in the study selection criteria for clarity as we actually had no quasi-RCTs. Please see page 10 in the revised manuscript with track changes. It reads...
as follows; "Types of studies: All randomized controlled trials (RCTs) evaluating acupuncture treatment for ankle sprains were considered."

4. Page 17, selection process, “37 studies did not satisfy acupuncture and control group criteria”: this is somewhat unclear – give at least examples.
ANSWER: We added detailed information on these 37 excluded studies (see page 18 in the revised manuscript with track changes).

5. Page 20, control intervention: describe how many comparisons with acupuncture as add-on and as alternative.
ANSWER: There are 12 studies evaluating acupuncture as an add-on and 9 trials assessing acupuncture as alternative treatment (4 trials with more than 2 arms were included in both acupuncture as an add-on and alternative treatment) and details of control interventions are explained in the revised manuscript (see pages 21-22 in the revised manuscript with track changes).

6. Page 25, sensitivity analysis: in the largest study most studies were “responders”; this seems to apply to a number of other studies. This is somewhat tricky. Might it be better to use the OR or the number of non-responders?
ANSWER: We accepted the reviewer’s suggestion of using the number of non-responders and newly analyzed the data accordingly. The main analysis was still the effect of acupuncture on patient-reported global assessment where RR was expressed as RR of non-responders. It was also divided into two categories according to the acupuncture as an alternative or add-on as we agree with the reviewer that these two are fundamentally different questions (see the revised Figure 2 and ‘effect of acupuncture’ of the results part in the revised manuscript).

We sincerely thank again Dr. Klaus Linde for his invaluable criticisms and suggestions which we believe are quite valid and improved our revised manuscript.
(Revised MS for *BMC Complement Altern Med*)

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Abstract

Background: Ankle sprain is one of the most frequently encountered musculoskeletal injuries. However, the efficacy of acupuncture for treating ankle sprains remains uncertain. Therefore, we performed a systematic review to evaluate the evidence on acupuncture for ankle sprains.

Methods: We searched 15 data sources and two trial registries up to February 2012. Randomized controlled trials of acupuncture were included if they involved patients with ankle sprains and reported outcomes of symptom improvement including pain. A Cochrane risk of bias assessment tool was used. Relative risk (RR) or mean difference (MD) were calculated with 95% confidence intervals (CI) in a random effects model. Subgroup analyses were performed based on acupuncture type, grades of sprain, and control types. Sensitivity analyses were also performed with respect to risk of bias, sample size, and outcomes reported.

Results: Seventeen trials involving 1820 participants were included. Trial quality was generally poor, with three reporting adequate methods of randomization and only one a method of allocation concealment. Significantly more participants in the
acupuncture group reported global symptom improvement compared with no acupuncture group (RR of non-responder = 0.56, 95 % CI 0.42 to 0.77). However, this is probably an overestimate due to heterogeneity ($I^2 = 51\%$) and high risk of bias of the included studies. Acupuncture as an add-on treatment also improved global symptoms compared with other treatment only without significant variability (RR 0.61, 95 % CI 0.51 to 0.73, $I^2 = 1\%$). Acupuncture’s benefit remained significant when the analysis was limited to two studies with a low risk of bias. Acupuncture was more effective than various controls in relieving pain, facilitating return to normal activity, and promoting quality of life, but these analyses were based on only a small number of studies. Acupuncture does not appear to be associated with adverse events.

**Conclusion:** Given methodological shortcomings and the small number of high-quality primary studies, the available evidence is insufficient to recommend acupuncture as an evidence-based treatment option, calling for further rigorous investigations.
**Key words:** acupuncture; ankle sprain; systematic review; randomized controlled trial; meta-analysis.
Background

An acute ankle sprain is an acute injury of one or more of the ligaments of the ankle. Among the tendon and ligament injuries presenting to physicians, acute ankle sprain is one of the most commonly encountered musculoskeletal injuries in athletes and sedentary people. It has been estimated that ankle sprain occurs at a rate of one injury per 10,000 people every day in the US, accounting for an estimated 2 million injuries per year and 20 % of all sports injuries [1, 2].

Depending on the severity of injuries, ankle sprains are classified into three grades: grade I indicates mild stretching or partial tear of the anterior talofibular and/or calcaneofibular ligaments accompanied by mild tenderness and swelling but with slight or no functional loss; grade II is incomplete tear of ligaments with moderate pain, swelling and functional loss; and grade III is characterized by complete tear of ligaments that results in severe swelling, pain and loss of function and motion [3].

The main goals of treatment are to relieve pain, maintain range of motion (ROM), return to pre-injury level, and prevent recurrence of injury. Among many different...
treatment options used for ankle sprains, the three major treatments are conservative treatment, functional treatment and surgical treatment. Conservative treatment means plaster cast immobilization and functional treatment indicates early mobilization with using external supports (e.g. elastic bandage, tape or orthotic support), plus coordination training [4]. For patients with grade I or II, early use of PRICE (protection, rest, ice, compression and elevation), ankle support and keeping of ROM are necessary. For patients with grade III, surgical treatment is recommended [3]. In addition to these treatments, analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used as an adjunct. Therapeutic ultrasonography and short-wave diathermy are also commonly used, but there is little evidence to promote their use in terms of symptom relief [5, 6].

Acupuncture is one of the most frequently used complementary and alternative medicine modalities in Asian countries including Korea, ankle injury being the 3rd most common disease for patients to seek acupuncture treatment from Korean Medicine Doctors [7]. Clinical experience and some animal studies have reported
that ankle sprain responds rapidly to acupuncture, which achieves alleviation in pain intensity and duration, and also contributes to the prompt return to their pre-injury activity [8, 9]. However, the efficacy of acupuncture for treating ankle sprain remains unclear. Therefore, we decided to critically evaluate the evidence for or against acupuncture for ankle sprains.
Methods

Data sources

We searched the Cochrane Central Register of Controlled Trials, Pubmed (1975 to February 2012), Ovid EMBASE (1980 to February 2012), the Cumulative Index to Nursing and Allied Health Literature (CINAHL, 1996 to February 2012), SPORTDiscus (1982 to February 2012), the Allied and Complementary Medicine Database (AMED, 1990 to February 2012), Rehabilitation and Sports Medicine Source (2007 to February 2012) and China National Knowledge Infrastructure databases (CNKI, 1979 to February 2012). We also searched Korean databases including Oriental Medicine Advanced Searching Integrated System, Korean Studies Information Service System, RISS4U, Korea Institute of Science and Technology Information, KOREAMED, DBPIA, and Korea National Assembly Library. Ongoing trials were searched in trial registries of www.controlled-trials.com and www.clinicaltrials.gov. Reference lists of reviews and relevant articles were screened for additional studies.
Search terms used for Cochrane Central Register of Controlled Trials were as follows: ("ankle injuries"[MeSH] OR "sprains and strains"[MeSH] OR "sprain*"[ti, ab, kw] OR "strain*"[ti, ab, kw] OR "injur*"[ti, ab, kw] OR "ankle*"[ti, ab, kw]) AND ("acupuncture"[MeSH] OR "acupuncture therapy"[MeSH] OR "acupunc*"[ti, ab, kw] OR "electroacupunc*"[ti, ab, kw] OR "meridian*"[ti, ab, kw] OR "acupoint*"[ti, ab, kw] OR "moxibustion*"[ti, ab, kw] OR "moxa*"[ti, ab, kw]). These search terms were slightly modified for other databases. Trials published in English, Korean and Chinese were sought.

Study selection

Types of studies: All randomized controlled trials (RCTs) evaluating acupuncture treatment for ankle sprains were considered.

Types of participants: Studies enrolling patients who reported an ankle sprain regardless of duration were eligible for inclusion. The diagnosis could be based on any methods, e.g. physical examination (positive anterior drawer test, pain and swelling), an arthrogram or a stress radiograph of the injured ankle. Trials
including patients with congenital deformities, degenerative conditions, or fractures were excluded. Mixed population studies including adults and children were included.

*Types of intervention:* Acupuncture included needle acupuncture, ear acupuncture, electroacupuncture, pharmacopuncture (injection of herbal medicine into acupuncture points), bee-venom acupuncture, scalp acupuncture, warm acupuncture and moxibustion. Studies which assessed the combined effect of acupuncture plus other related treatments (e.g. acupuncture plus moxibustion) were also considered. We did not include trials testing non-penetrating acupuncture point stimulation (e.g. acupressure, transcutaneous electrical nerve stimulation (TENS), or magnets). Trials comparing different forms of acupuncture were excluded, because the efficacy of control intervention could not be determined.

Details of acupuncture interventions were extracted and tabulated based on the revised STAndards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [10].
Types of control: For control groups, we considered placebo, usual care and no interventions. Sham or placebo acupuncture interventions mean non-penetrating sham needle or superficial needling at non-acupuncture points. Usual care includes PRICE technique, analgesic drugs, functional exercise, and/or electrotherapy such as ultrasound or short-wave. When acupuncture was given with other usual treatment, we only included trials where the identical usual treatment was administered both to the acupuncture group and the control group.

Types of outcome measures:

The primary outcome of this systematic review was patient-reported global symptom improvement at the end of treatment. Pain intensity data were included in the review if data for global symptoms were not provided.

Secondary outcomes included time to achieve pre-injury level of work or sports, both subjective (e.g. giving way) and objective (e.g. inversion stress test, talar tilt, anterior drawer test, postural sway analysis) evaluations of ankle instability, dichotomous (e.g. yes or no) and continuous data (e.g. visual analog scale, VAS) of swelling, recurrence of ankle sprain, subsequent surgery or long-term treatment,
health-related quality of life (e.g. SF-36), and adverse events related to acupuncture treatment.

Data extraction and risk of bias assessment

Data extraction: Two reviewers (Jimin Park & Ji-Yeun Park) independently reviewed all searched articles to evaluate suitability for inclusion. If there was disagreement, it was resolved by discussion among reviewers and further information was sought from the original authors if necessary.

After selection of studies, the aforementioned two reviewers extracted data from the selected articles independently: author, year of publication, country, study design, participants (age, gender), duration of disease, acupuncture intervention, control intervention, outcome measures, main results and adverse events.

Risk of bias assessment: Two reviewers (Jimin Park & Ji-Yeun Park) independently evaluated risk of bias for the included studies according to the Cochrane Collaboration’s risk of bias assessment tool [11]. The evaluated items for risk of bias were as follows:
(1) Was the method of randomization sequence generation adequate?

(2) Was the treatment allocation adequately concealed?

(3) Was the patient blinded to the intervention?

(4) Was the outcome assessor blinded to the intervention?

(5) Were incomplete outcome data adequately addressed?

(6) Are reports of the study free of suggestion of selective outcome reporting?

Reviewers rated risk of bias for each item using ‘Yes, Unclear, or No’ as keys of judgments; the answer ‘Yes’ meant a low risk of bias (Y), ‘Unclear’ meant uncertain or unknown risk of bias (U), and ‘No’ meant a high risk of bias (N). If there were disagreements, it was resolved by discussion among reviewers.

**Analyses**

*Statistical analysis:* Review Manager software (version 5.1 for Windows; The Nordic Cochrane Centre, Copenhagen, Denmark) was used to perform statistical analysis. Studies were classified and combined in the main analysis according to the purpose of acupuncture intervention, i.e. acupuncture as an alternative or as
an add-on treatment. Data were pooled using a random effects model. The impacts of acupuncture on dichotomous data were expressed as a risk ratio (RR) of non-responders of global symptom improvement compared with control with 95% confidence intervals (CIs). To define non-responders, patient-reported global symptoms in ordinal assessments were divided into two groups (e.g. ‘poor or good’ as non-responder vs. ‘very good or excellent’ as responder). If different strata were used to define improvement, the cut-off point with the least improvement was taken (e.g. if the ordinal assessment was poor, good, and excellent, we utilized a poor vs. good or excellent comparison). For continuous outcomes, the mean difference (MD) with a 95% CI was calculated.

Visual inspection of the forest plots and a $\chi^2$ test with a significance level of $p < 0.1$ was used to assess heterogeneity among studies. To quantify inconsistencies among the included studies, the $I^2$ test was used and the $I^2$ value of 50% or more was considered to be indicators of a substantial level of heterogeneity [12]. Subgroup analyses were conducted in terms of different acupuncture interventions (e.g. manual acupuncture, electroacupuncture), different grades of ankle sprain,
and control types (e.g. usual care, sham acupuncture). Sensitivity analyses were also planned by including studies with low risk of bias only, or by including studies with sample size ≥ 40 per arm, and by differently grouping the outcome measures. We analyzed the trials with a low risk of bias for randomization and/or allocation concealment only [13, 14] and examined if the estimate of the intervention effect was affected. Studies with ≥ 40 participants per arm were analyzed separately to see whether there emerges any difference in the estimate [15]. For outcome measures, as it is common for Chinese trials to report outcomes based on an ordinal assessment (e.g. ‘excellent’, ‘very good’, ‘good’, ‘poor’), we also performed a sensitivity analysis by re-analyzing the dichotomous outcomes; we compared the ‘excellent, very good vs. good, poor’ scenario which was our original analysis to the ‘excellent (very) good vs. poor’ scenario to ascertain any discrepancies.

**Results**

**Selection of eligible studies**

Our search terms yielded 387 records: 5 in the Cochrane Central Register of Controlled Trials, 21 in the EMBASE, 42 in the CINAHL, 10 in the SPORTDiscus,
10 in the AMED, 2 in the Rehabilitation and Sports Medicine Source, 175 in the CNKI, 90 in the Pubmed, and 32 in the relevant Korean journals. After duplicate studies were removed, 380 records were screened. Based on the title and abstract, 322 records were excluded; 162 articles were not specific to the topic of this review and 160 were not clinical studies or were non-randomized trials. Out of the remaining 58 studies, 37 studies did not satisfy the inclusion criteria for acupuncture or control intervention; comparison of different acupuncture styles (n = 9), acupuncture vs. Chinese herbal medicine or bee venom of which the efficacy has not been established (n = 8), trials where acupuncture was given with other therapies so that the effect of acupuncture per se cannot be isolated (n = 9), and trials comparing the effect of other therapy given with acupuncture to acupuncture alone (n = 11). One study published in French was excluded; we failed to obtain full texts of three studies. Finally 17 studies were included in our review and 16 studies reporting patient-reported global assessment outcome were pooled in the main analysis. Figure 1 shows a flow diagram of literature searching as recommended in
the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16].

**Characteristics of the included studies**

Details of the included studies are summarized in Tables 1, 2 and supplementary table 1.

*Participants*: Seventeen studies involving 1,820 participants were included in our review. All of them were conducted in China and they were published in Chinese. When divided into acute, chronic and mixed ankle sprains based on 6 months after onset cutoff [17, 18], 12 studies [19-30] involved participants with acute ankle sprains, three studies [31-33] involved mixed participants, no study involved participants with chronic ankle sprains only, and one study [34] did not report disease duration but it was assumed that the participants had acute ankle sprain. Another study [35] mentioned ‘acute’ in the title but 326 participants had sprained ankles for less than two days while the other 12 did so for more than three days. Regarding the severity of the sprain, only 4 trials clearly reported that the participants had grade I or II injuries [19, 23, 26, 34].
Acupuncture intervention: Highly variable acupuncture interventions were given either alone or as an add-on treatment to control intervention. Out of the included 17 studies, 9 [19-21, 26-30, 35] tested manual acupuncture, 4 [22, 25, 33, 34] used electroacupuncture, three [23, 31, 32] used warm acupuncture and one [24] used warm acupuncture in addition to manual acupuncture. Among 5 trials that assessed the effect of acupuncture alone, three studies evaluated electroacupuncture [22, 25, 34]; one each evaluated warm acupuncture [23] and manual acupuncture [21]. Fixed (i.e. all participants received the same treatment), partially individualized (using a fixed set of points to be given with a set of points flexibly to be used) and individualized acupuncture treatment (each participant received a tailored treatment) were given; out of the 17 studies, 7 used fixed [19, 20, 24, 25, 28-30], 6 used partially individualized [21, 22, 26, 33-35] and 4 used individualized acupuncture treatment [23, 27, 31, 32]. The number of acupuncture sessions ranged from three to 15 over three days to 4 weeks. De-qi, acupuncture-evoked specific sensations such as numbness, heaviness, soreness, or distention, was sought in 11 studies [19-22, 24-26, 31-34]. Regarding acupuncture points used in the studies, 14 studies
[19-22, 24-26, 28-30, 32-35] used 12 meridian points and/or extra points while the other two studies [23, 31] used tender points and one study [27] did not report acupuncture points. Details of acupuncture interventions are summarized in Table 2 based on the revised STRICTA [10].

Control intervention: A range of control interventions were used including ice pack, exercise, bandage, analgesic drugs, herbal medicine, infrared radiation, tuina massage, hot pack or TENS. No study adopted sham acupuncture as a control group (Table 1). More than one comparison groups were used in 5 trials [28-31, 35]. For 9 trials evaluating the effect of acupuncture alone, usual care [21, 22, 25, 28-30] or infrared radiation [21, 23, 34] were used as a control. Two studies adopted hot pack [21, 25] or herbal medicine [21, 30] as a control treatment, respectively. Only one study [35] adopted tuina massage. Among the other 12 trials testing acupuncture as an add-on treatment, 7 trials [19, 20, 24, 28-31] used usual care, three trials used herbal medicine [26, 27, 30] or tuina massage [32, 33, 35], respectively. One each adopted infrared radiation [33] or TENS [32].
*Outcome measures:* Outcome measures reported in the included studies were patient-reported global assessment (in 16 trials) [19-22, 24-30, 32-35], pain (one trial) [31], time to return to pre-injury level of work or sports (4 trials) [19-21, 24], recurrence rate (one trial) [33], health-related quality of life (one trial) [31] and adverse events (two trials) [29, 30]. For patient-reported global assessment outcomes, a range of definitions were used to assess efficacy. We thus used the proportion of participants who had less than 50 % symptom improvement, i.e. non-responders, in the analysis.

**Risk of bias in the included studies**

The majority of the included trials were assessed as having a high risk of bias. Three out of the 17 studies reported adequate method of sequence generation such as using a random number table or coin tossing [19, 26, 31], and among them, group assignment was adequately concealed using sealed opaque envelopes in only one trial [19]. For participant and personnel blinding, not a single trial was rated as having a low risk of bias because there was no sham-controlled trial. Except three studies where outcome measure was assessed by non-blinded
participants [24, 27, 33], the other 14 studies were rated as having an unclear risk of bias as we could not completely exclude the possibility that the blinded 3rd party assessor might have evaluated global symptom improvement. Regarding incomplete outcome data addressing, all but one trial were assessed as having a low risk of bias as they had no missing outcome data; one study [19] did not report the number of participants analyzed in the outcome measure. As to selective outcome reporting, we could not locate and compare the protocol of any included studies, hence we judged a risk of bias based on the described methods in each study. Six studies had a high risk of bias for selective outcome reporting because they were reporting unplanned outcome measurements [19-21, 24, 32, 33] (Table 3).

**Effects of acupuncture on primary outcome**

The key outcomes from the included studies are provided in Table 1 and Figure 2. We evaluated primary outcomes of patient-reported global assessment. Pain was considered if global assessment was not available.

1. Effects of acupuncture as an alternative treatment
Nine trials with 797 participants [21-23, 25, 28-30, 34, 35] reported global symptom improvement as a dichotomous outcome. Approximately 9 sessions of acupuncture were given over 11.5 days of period. Acupuncture had a statistically significant effect in reducing global symptoms of ankle sprain (RR of non-responder = 0.56; 95 % CI 0.42 to 0.77, Figure 2 (A)). However, there was substantial heterogeneity among trials ($\chi^2 = 16.38$, degrees of freedom (df) = 8, $p = 0.04$, $I^2 = 51\%$).

2. Effects of acupuncture as an add-on treatment

Eleven trials with 926 participants reported the add-on effect of acupuncture [19, 20, 24, 26-30, 32, 33, 35]. Median 10 sessions of acupuncture over 9 days of period was provided. When added to other treatment, acupuncture statistically significantly improved global symptoms compared with other treatment only (RR of non-responder = 0.61; 95 % CI 0.51 to 0.73, Figure 2 (B)). There was no significant heterogeneity among studies ($\chi^2 = 10.08$, df = 10, $p = 0.43$, $I^2 = 1\%$).

3. Effects of acupuncture for pain intensity

One study reported pain intensity on VAS immediately and over two years after treatment [31]. At immediately after treatment, warm needling significantly
alleviated pain compared with the control group (1.32 ± 0.42 vs. 6.55 ± 1.76, MD -5.23, 95 % CI -5.61 to -4.85). At the long-term follow up of 28.8 months on average, the analgesic effect was maintained (1.01 ± 0.15 vs. 5.89 ± 1.93, MD -4.88, 95 % CI -5.29 to -4.47).

**Effects of acupuncture on secondary outcomes**

1. Time to achieve pre-injury level of work or sports

Four studies reported time to cure [19-21, 24]. Of them, one study [19] reported that acupuncture in addition to functional exercise shortened the time to return to normal activity by 3.4 days than the functional exercise only group (5.2 ± 0.7 vs. 8.6 ± 1.4, MD -3.40, 95 % CI -3.88 to -2.92). In the other three studies [20, 21, 24], participants were not more likely to have recovered within a week than those in the control group whether they were given acupuncture as an add-on (two trials, RR 2.49, 95 % CI 0.60 to 10.29, I² = 0 %) or alternative treatment (one trial, RR 1.21, 95 % CI 0.99, 1.47).

2. Ankle instability & swelling
No study reported on ankle instability and/or swelling as a separate outcome measure because the majority of the included studies reported a composite measure of patient-reported global symptom assessment.

3. Recurrence of ankle sprain

One study [33] reported that one participant in the acupuncture group had a re-injury while 5 in the control group did so at 6-month follow-up (RR 0.17, 95 % CI 0.02 to 1.33).

4. Health-related quality of life

One study [31] reported quality of life using SF-36 at immediately and over two years after treatment. At immediately after treatment, the acupuncture group reported significantly better quality of life than the control group (91.25 ± 10.16 vs. 76.53 ± 5.24, MD 14.72, 95 % CI 12.32 to 17.12). At 2-year follow up, the effect remained significant (93.62 ± 9.05 vs. 62.31 ± 6.67, MD 31.31, 95 % CI 28.95 to 33.67).

5. Adverse events

Two studies [29, 30] reported mild adverse events such as mild allergic response
to drug which was recovered at stopping (three participants).

**Subgroup analyses**

We conducted subgroup analyses based on the pre-defined characteristics, i.e., types of acupuncture interventions, different grades of ankle sprain, and control types.

1. Acupuncture types

Manual acupuncture [19, 20, 26-30, 35] has an additional effect on symptom improvement compared with control groups (8 trials, RR 0.62, 95 % CI 0.50 to 0.77, $I^2 = 0 \%$). When given as an alternative [21], the RR of non-responder was 0.20 (95 % CI 0.06 to 0.65). Electroacupuncture as a sole treatment [22, 25, 34] had no significant benefit compared with oral/topical NSAIDs or infrared radiation (three trials, RR 0.50, 95 % CI 0.20 to 1.22, $I^2 = 76 \%$). When added to massage and infrared radiation [33], the effect of electroacupuncture was statistically significantly better than the massage and infrared radiation only (one trial, RR 0.11, 95 % CI 0.01 to 0.82).

2. Grades of ankle sprain
There were insufficient data for subgroup analyses on the severity of the sprain; only 4 trials [19, 23, 26, 34] clearly reported that the participants had grade I or II injuries and the RR of non-responder was 0.39 (two trials, 95 % CI 0.18 to 0.88, $I^2 = 0 \%$) when acupuncture was given as an add-on treatment and 0.35 (two trials, 95 % CI 0.17 to 0.71, $I^2 = 0 \%$) when it was an alternative treatment.

3. Control types

1) Acupuncture vs. oral/topical NSAIDs

(1) Acupuncture vs. NSAIDs

Two trials with 122 participants tested the effect of acupuncture on global symptom improvement against oral/topical NSAIDs [22, 25]. There was no statistical difference between groups (Figure 3 (A1), RR 0.64, 95 % CI 0.29 to 1.39, $I^2 = 67 \%$).

(2) Acupuncture plus NSAIDs vs. NSAIDs

Acupuncture had no additional effects on global symptom improvement compared with oral/topical NSAIDs only [28, 29] (Figure 3 (A2), RR 0.72, 95 % CI 0.50 to 1.05, $I^2 = 22 \%$).
2) Acupuncture plus herbal medicine vs. herbal medicine

When added to oral/topical herbal medicine [26, 27, 30], significantly less participants remained with symptoms in the acupuncture group (Figure 3 (B), RR 0.56, 95 % CI 0.40 to 0.78, \( I^2 = 0 \) %).

**Sensitivity analyses**

We also performed sensitivity analyses by excluding studies with pre-defined less desirable characteristics;

1. Risk of bias

When the analysis was limited to two studies with a low risk of bias for random sequence generation and/or allocation concealment [19, 26], the add-on effect of acupuncture on patient-reported global assessment remained significant (RR 0.39, 95 % CI 0.18 to 0.88, \( I^2 = 0 \) %).

2. Sample size

Combining 4 studies which had \( \geq 40 \) participants per group [19, 21, 28, 35] resulted in no significant difference between acupuncture and control group (RR 0.50, 95 % CI 0.24 to 1.05, \( I^2 = 55 \) %).
3. Outcome measures

For 16 studies reporting the dichotomous outcome based on the ordinal assessment, we compared ‘excellent, very good’ vs. ‘good, poor’ scenario (16 trials, RR 0.55, 95% CI 0.45 to 0.69, I² = 40 %) with ‘excellent, (very) good vs. poor’ scenario (RR 0.26, 95% CI 0.18 to 0.38, I² =0 %); the estimate remained significant without variability.
Discussion

Summary of main findings

This systematic review aimed at establishing the evidence of acupuncture treatment for ankle sprains. There were a total of 17 RCTs included in this review. They investigated the effect of acupuncture as an alternative or as an add-on to other treatment on global symptom improvement of ankle sprain. When evaluating acupuncture compared with other treatment, acupuncture has a therapeutic benefit in improving global symptoms of ankle sprain (RR of non-responder = 0.56, 95 % CI 0.42 to 0.77). However, this is probably an overestimate due to heterogeneity ($I^2 = 51 \%$) and high risk of bias of the included studies. Compared with other treatment alone, acupuncture as an adjunct to other treatment significantly alleviated global symptoms of ankle sprain without significant variability (RR of non-responder = 0.61, 95 % CI 0.51 to 0.73). A sensitivity analysis of the trials with a low risk for selection bias suggested that the beneficial effect of acupuncture was maintained while the effect of acupuncture was not any more significant when the analysis was limited to studies
with adequate sample size. Acupuncture was more effective than various controls in relieving pain, facilitating return to normal activity, and promoting quality of life, but these analyses were based on only a small number of studies. Acupuncture does not appear to be associated with serious adverse events but the evidence is limited.

**Applicability of evidence**

Although this systematic review seems to show that acupuncture may be effective in symptom improvement in ankle sprain, the true intervention effects estimated are likely to be inflated due to poor methodological design and conduct.

There are several issues worth considering before we make any judgments on acupuncture for ankle sprain in practice. First of all, tested acupuncture interventions were diverse across trials in terms of acupuncture types, acupuncture points, number of sessions, and duration of treatment. So it is difficult to determine adequate or optimal acupuncture intervention.

Secondly, control interventions used in the included studies also varied. They included usual care (e.g. ice pack, exercise, bandage, or analgesics), herbal
medicine, infrared radiation, tuina massage, hot pack or TENS. Recently, studies about the efficacy of topical NSAIDs for acute pain compared with oral NSAIDs were conducted actively due to the adverse events of oral NSAIDs such as gastrointestinal complications or cardiovascular toxicities. In a recent review on topical NSAIDs for musculoskeletal pain [36], topical NSAIDs demonstrated comparable efficacy and better safety compared with oral NSAIDs for acute pain including sprains and strains and the effect of topical NSAIDs was 1.6 times better than placebo at 7 days. In our review, acupuncture as an add-on or alternative treatment demonstrated no better effect than oral/topical NSAIDs but it was associated with few side effects. Acupuncture was only significantly effective for symptom improvement when added to oral/topical herbal medicine.

Thirdly, outcome measures of the included studies were not consistent. The clinical relevance of acupuncture’s benefit shown is not obvious [37]. As there are no dependable data on the minimal clinically important difference (MCID) in patient-reported global symptom improvement of ankle sprains, we may only infer that the effect of acupuncture, is small [37].
Fourthly, all trials included in this review were conducted in China. Acupuncture may be highly culture-specific and further research is necessary to investigate the reported interventions are applicable and acceptable in other countries. Receiving acupuncture everyday may not be a generalizable treatment schedule outside China.

Lastly, clinically meaningful information on severity of injury or follow-up data was sparse in the included trials. So the available evidence prevents us from determining if acupuncture exerts different effects at different injury level or how long its benefit is maintained.

**Risk of bias**

The majority of the included studies suffered from a serious risk of bias. Only three studies had a low risk of bias for adequate randomization and/or allocation concealment. It is well known that inadequate allocation concealment/random sequence generation leads to overestimation of treatment effect [13, 14]. Although the included studies uniformly reported no difference in baseline characteristics between groups, we cannot exclude possibility that selection bias may have
played a role under such circumstances. However, when we limited our main
analysis to the studies rated as having a low risk of bias for
randomization/allocation concealment, acupuncture’s benefit remained significant.
Although we could not formally test for the funnel plot asymmetry to detect small-
study effects – a tendency for the intervention effects estimated in smaller studies
to differ from those estimated in larger studies [38] – due to a small number of
studies, Chinese studies may have been more likely to publish positive outcomes
[39, 40]; but more importantly, the effect size of small studies in this review may
have been inflated due to poor methodological design and conduct [41]. As it is
well-known that small, poor-quality studies tend to spuriously inflate the
intervention’s effect, we need to be more conservative in interpretation of the
results.

**Limitations of this review**

Although we made every endeavor to search all the relevant trials in a range of
databases and related journals, comprehensive searches do not necessarily
remove publication bias or language bias. All trials were conducted in China and
published in Chinese journals in Chinese language. Egger et al. [40] reported that studies published in non-English languages or studies published in journals that are not indexed in Medline are likely to increase the degree of asymmetry in the funnel plot in a systematic review and this may have a relevance to this review.

The included trials were mostly of poor quality thus reported data are likely to be overestimated. In addition, the small sample size of the studies may have resulted in heterogeneity of the effect size. Moore et al. [15] reported in the simulation study that at least 40 participants per arm are required to get clinically relevant results in trials of pain. Our sensitivity analysis on sample size, i.e. trials ≥ 40 per group only [19, 21, 28, 31], produced no significant benefit from acupuncture.

Finally, as is usual with other Chinese acupuncture trials, most studies in our review used various subjective outcomes. As no study compared acupuncture with sham acupuncture, this makes outcome assessment blinding even more critical. Failure in outcome assessment blinding may have influenced the results.

**Implications for practice**
This systematic review suggests that there is insufficient high-quality evidence supporting the use of acupuncture to improve global symptoms of ankle sprain when it is given as an alternative treatment. Although the benefit of acupuncture as an add-on treatment for global symptom improvement in ankle sprain is significant and a sensitivity analysis of high-quality trials supports this finding, the number of studies is too small to strongly recommend it. Acupuncture was more effective than various controls in relieving pain, facilitating return to normal activity, and promoting quality of life, but these analyses were based on only a small number of studies. We have no convincing evidence supporting acupuncture compared with NSAIDs whether given as an alternative or add-on treatment. Acupuncture does not appear to be associated with adverse events but the evidence is limited. To sum up, currently we have inconclusive evidence supporting the use of acupuncture for patients with ankle sprain.

**Implications for research**

To give a more definite answer to the efficacy of acupuncture for ankle sprain, we need more carefully designed and conducted trials. Researchers should use
adequate randomization methods and make sure that group assignment is adequately concealed as these two are critical in avoiding systematic differences between baseline characteristics of the groups that are compared, i.e. selection bias. As it is virtually impossible for the therapist to be blinded to the acupuncture intervention that they provide, it may be more important to blind participants and outcome assessor. However, there was no study with sham control in this review, so performance bias is likely to play a part in our findings.

In the future, sham-controlled trial would be needed to avoid performance bias. To maintain outcome assessor blinding, validated assessment tools are required. Recent studies have tested validity, reliability and responsiveness of relevant scales [42, 43]. For example, the validity and responsiveness of ankle functional score (AFS) based on fundamental functional outcomes such as pain, swelling, weight bearing, stability and gait, was tested and the study concluded that AFS was easy-to-use and might be used alongside subjective clinical assessment to evaluate recovery after acute ankle sprain [43]. Using not only subjective patient-
reported symptom improvement but also validated outcome measures, and ensuring outcome assessment blinding should be considered for future trials.
Conclusions

Given methodological flaws of the included studies, the available evidence is insufficient to recommend acupuncture as an evidence-based treatment option for ankle sprain. Further well-designed and conducted trials are needed to draw a definitive conclusion.

Additional materials

Supplementary table 1: Characteristics of the included studies

Authors’ contributions

HSL and JMP designed this review, searched databases, and screened trials for inclusion. JMP and JYP extracted data, evaluated studies and it was checked by HSL. HSL and JMP performed analyses and discussed with HJP and SKH. All authors read and approved the final manuscript.

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**Competing Interests**

The authors declare that they have no conflicts of interest.

**Acknowledgements**

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Medicine, Kyung Hee University, Korea for helping us get additional information from original authors of the included trials.
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Treatment (no. of participants analyzed/randomized)</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acupuncture as an add-on treatment</strong></td>
<td></td>
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</tr>
<tr>
<td>Sun (2011) [19]</td>
<td>(A) MA + functional exercise (41/41) (B) Functional exercise (41/41)</td>
<td>1) PRGA* at 14 d</td>
<td>1) NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Time to cure (d)</td>
<td>2) (A) significantly better than (B)</td>
</tr>
<tr>
<td>Zheng (2010) [20]</td>
<td>(A) MA + PRICE (≤ 24 h), MA + EA (≥ 24 h) (40/40; 27/40)</td>
<td>1) PRGA* at 15 d</td>
<td>1) (A) significantly better than (B)</td>
</tr>
<tr>
<td></td>
<td>(B) PRICE (≤ 24 h), EA (≥ 24 h) (33/33; 12/33)</td>
<td>2) Time to cure</td>
<td>2) NS</td>
</tr>
<tr>
<td>Wei (2010) [32]</td>
<td>(A) WA + massage (30/30)</td>
<td>PRGA§ at 10 d</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(B) TENS + massage (30/30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tang (2010) [33]</td>
<td>(A) EA + massage + IR (30/30)</td>
<td>1) PRGA* at 10 d</td>
<td>1) (A) significantly better than (B)</td>
</tr>
<tr>
<td></td>
<td>(B) Massage + IR (30/30; 25/30)</td>
<td>2) Recurrence rate at 6 month follow-up (%)</td>
<td>2) NS</td>
</tr>
<tr>
<td>He (2010) [31]</td>
<td>(A) WA + small needle-knife therapy + drug injection + rehabilitation (87/87)</td>
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<tr>
<td></td>
<td>(B) Small needle-knife therapy + drug injection + rehabilitation (87/87)</td>
<td>1) Pain (VAS) at immediately and two yrs after treatment</td>
<td>1) (A) significantly better than (B)</td>
</tr>
<tr>
<td></td>
<td>(C) WA + rehabilitation (87/87)</td>
<td>2) QOL (SF-36) at immediately and two yrs after treatment</td>
<td>2) (A) significantly better than (B)</td>
</tr>
<tr>
<td>He (2006) [24]</td>
<td>(A) MA + PRICE (≤ 24 h), EA + WA (≥ 24 h) (46/46; 31/46)</td>
<td>1) PRGA* at 15 d</td>
<td>1) (A) significantly better than (B)</td>
</tr>
<tr>
<td></td>
<td>(B) PRICE (≤ 24 h), EA (≥ 24 h) (33/33; 12/33)</td>
<td>2) Time to cure</td>
<td>2) NS</td>
</tr>
<tr>
<td>Li (2002) [26]</td>
<td>(A) MA + oral/topical HM (23/23)</td>
<td>PRGA* at 8 d</td>
<td>(A) significantly better than (B)</td>
</tr>
<tr>
<td></td>
<td>(B) Oral/topical HM (23/23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ge (2000) [27]</td>
<td>(A) MA + oral HM (50/50)</td>
<td>PRGA§ at 10 d</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(B) Oral HM (30/30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yu (1999) [28]</td>
<td>(A) MA + topical NSAIDs (50/50)</td>
<td>PRGA†† at 7 d</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(B) Topical NSAIDs (50/50)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(C) MA (50/50)</td>
<td></td>
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</tbody>
</table>
Yu (20199) \[29\]
(A) MA + topical NSAIDs + ice pack (30/30)
(B) Topical NSAIDs + ice pack (30/30)
(C) Ice pack (30/30)
(D) MA (30/30)

PRGA\(^{††}\) at 7 d
(A) significantly better than (B), (C), or (D)

Yu (1996) \[30\]
(A) MA + topical HM + ice pack (30/30)
(B) Topical HM + ice pack (30/30)
(C) Ice pack (30/30)
(D) MA (30/30)

PRGA\(^{§}\) at 7 d
(A) significantly better than (B)

Ruan (1995) \[35\]
(A) MA + massage (116/116)
(B) MA (112/112)
(C) Massage (110/110)

PRGA\(^{‡‡}\) NS

<table>
<thead>
<tr>
<th><strong>Acupuncture alone vs. other therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ni (2010) [21]</strong></td>
</tr>
<tr>
<td>(A) MA (64/64(^†); 61/64(^‡))</td>
</tr>
<tr>
<td>(B) Ice pack (≤ 24 h), hot pack (≥ 24 h) + oral HM + IR (59/59(^†); 45/59(^‡))</td>
</tr>
</tbody>
</table>

1) PRGA\(^*\) at 3 d  
2) Time to cure  
1) (A) significantly better than (B)  
2) NS

| **Luo (2009) \[22\]**               |
| (A) EA (23/23)                     |
| (B) Topical NSAIDs (23/23)         |

PRGA\(^*\) at 4 wks  
NS

| **Zhou (2008) \[23\]**             |
| (A) WA (26/26)                     |
| (B) IR (23/23)                     |

PRGA\(^*\) at 5 d  
(A) significantly better than (B)

| **Zhao (2005) \[25\]**             |
| (A) EA (43/43)                     |
| (B) Oral/topical NSAIDs + hot pack (33/33) |

PRGA\(^*\) at 4 wks  
NS

| **Wang (2005) \[34\]**             |
| (A) EA (27/27)                     |
| (B) IR (30/30)                     |

PRGA\(^*\) at 5 d  
(A) significantly better than (B)

\*, cured/significantly improved/improved/failed; \(^†\), for outcome measure 1); \(^‡\), for outcome measure 2); \(^§\), cured/improved/failed

\(^{††}\), significantly improved/improved/failed

\(^‡‡\), cured/significantly improved/improved

There were 4 trials which reported acupuncture alone vs. other treatment and acupuncture plus other treatment vs. other treatment \[28-30, 35\]. They were put as acupuncture as an add-on treatment trials in this table.  

d indicates days; EA, electroacupuncture; h, hours; HM, herbal medicine; IR, infrared radiation; MA, manual acupuncture; no., number; NS, no significant difference between groups; NSAIDs, non-steroidal anti-inflammatory drugs; PRGA, patient-reported global assessment; PRICE, protection, rest, ice,
compression and elevation; QOL, quality of life; TENS, transcutaneous electrical nerve stimulation; VAS, visual analog scale; WA, warm acupuncture; wks, weeks; yrs, years
### TABLE 2. Summarized acupuncture interventions in the included studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Acupuncture method (Fixed/partially individualized/individualized)*</th>
<th>Treatment rationale</th>
<th>Regimen</th>
<th>Acupuncture points**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun (2011)[19]</td>
<td>MA, fixed</td>
<td>Modern acupuncture</td>
<td>14 sessions (once daily for 14 d)</td>
<td>Ex-UE205</td>
</tr>
<tr>
<td>Zheng (2010)[20]</td>
<td>MA, fixed</td>
<td>Clinical experience</td>
<td>15 sessions (once daily for 5 d X 3)</td>
<td>LI15</td>
</tr>
<tr>
<td>He (2010)[31]</td>
<td>WA, individualized</td>
<td>TCM theory</td>
<td>n.r</td>
<td>Tender points</td>
</tr>
<tr>
<td>Wei (2010)[32]</td>
<td>WA, individualized</td>
<td>TCM theory</td>
<td>10 sessions (once daily for 10 d)</td>
<td>Selected points from ST36, KI3, BL60, GB40, GB39, ST41, LR3 etc.</td>
</tr>
<tr>
<td>Ni (2010)[21]</td>
<td>MA, partially individualized</td>
<td>TCM theory</td>
<td>3 sessions (once daily for 3 d)</td>
<td>Ex-UE140 + additional points (pain sensitive points on the contralateral wrist joint)</td>
</tr>
<tr>
<td>Tang (2010)[33]</td>
<td>EA, partially individualized</td>
<td>TCM theory</td>
<td>10 sessions (once daily for 5 d X 2)</td>
<td>Ashi points (GB40, BL60, BL62, KI6) + additional points (ST41, GB39, GB34, ST36)</td>
</tr>
<tr>
<td>Luo (2009)[22]</td>
<td>WA, partially individualized</td>
<td>TCM theory</td>
<td>12 sessions</td>
<td>ST41, BL60, GB40 + ashi points</td>
</tr>
<tr>
<td>Zhou (2008)[23]</td>
<td>MA, partially individualized</td>
<td>TCM theory</td>
<td>5 sessions (once daily for 5 d)</td>
<td>Tender points</td>
</tr>
<tr>
<td>He (2006)[24]</td>
<td>MA+WA, fixed</td>
<td>TCM theory</td>
<td>15 sessions (once daily for 5 d X 3)</td>
<td>MA, WA : GB34</td>
</tr>
<tr>
<td>Zhao (2005)[25]</td>
<td>EA, fixed</td>
<td>TCM theory</td>
<td>14 sessions (once per 2 days for 2 wks X 2)</td>
<td>EA : GB39, GB40, ST41, BL60, BL62, GB43</td>
</tr>
<tr>
<td>Wang (2005)[34]</td>
<td>EA, partially individualized</td>
<td>Modern experimental</td>
<td>5 sessions (once daily for 5 d)</td>
<td>ST41, GB40, BL62, BL60, GB39, ashi points</td>
</tr>
<tr>
<td>Li (2002)[26]</td>
<td>MA, partially individualized</td>
<td>n.r.</td>
<td>8 sessions (once daily for 8 d)</td>
<td>ST36, GB39, BL60, additional points (pain sensitive points on contralateral Triple energizer meridian of wrist)</td>
</tr>
<tr>
<td>Ge (2000)[27]</td>
<td>MA, individualized</td>
<td>n.r</td>
<td>10 sessions</td>
<td>n.r</td>
</tr>
<tr>
<td>Yu (1999)[28]</td>
<td>MA, fixed</td>
<td>TCM Theory</td>
<td>14 sessions (twice daily for 7 d)</td>
<td>ST36, GB39, KI3, BL60</td>
</tr>
<tr>
<td>(1999)[29]</td>
<td>MA, fixed</td>
<td>n.r</td>
<td>14 sessions (twice daily for 7 d)</td>
<td>ST36, GB39, KI3, BL60</td>
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<tr>
<td>(1999)[30]</td>
<td>MA, fixed</td>
<td>n.r</td>
<td>7 sessions (once daily for 7 d)</td>
<td>ST36, GB39, KI3, BL60</td>
</tr>
<tr>
<td>Ruan (1995)[35]</td>
<td>MA, partially individualized</td>
<td>n.r</td>
<td>Once daily</td>
<td>Ex-LE222, Ex-LE226, BL62, GB39, GB40, BL60, KI6, SP6, K12, ST41, ST36, GB34, SP9, ashi points</td>
</tr>
</tbody>
</table>

* Acupuncture method was classified into three categories based on the levels of individualization: ‘fixed’ means all patients receive the same treatment at all sessions, ‘partially individualized’ means using a fixed set of points to be combined with a set of points to be used flexibly, and ‘individualized’ means each patient receives a unique and evolving diagnosis and treatment [10]; **, Acupuncture point LI5 refers to 5th point of large intestine meridian and extra points have different nomenclature (e.g., Ex-UE3 means 3rd extra point in upper extremity). Ashi points mean local pain points; ***, De-qi means acupuncture-evoked specific sensations such as soreness, numbness, heaviness, and distention at the site of needle placement and these sensations may spread to other parts of the body d indicates days; EA, electroacupuncture; HM, herbal medicine; IR, infrared radiation; MA, manual acupuncture; n.r., not reported; NSAIDs, non-steroidal anti-inflammatory drugs; PRICE, protection, rest, ice, compression and elevation; TCM, traditional Chinese medicine; WA, warm acupuncture; wks, weeks
### TABLE 3. Risk of bias assessment*

<table>
<thead>
<tr>
<th></th>
<th>Su</th>
<th>Zh</th>
<th>He</th>
<th>We</th>
<th>Ni</th>
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1. Was the method of randomization adequate?  
   Y U Y U U U U U U Y U U U U U U U

2. Was the treatment allocation concealed?  
   Y U U U U N N U U U U U U U U U

3. Was the patient blinded to the intervention?  
   N N N N N N N N N N N N N N N

4. Was the outcome assessor blinded to the intervention?  
   U U N U U U U N U U U U U U U U

5. Were incomplete outcome data adequately addressed?  
   N Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y

6. Are reports of the study free of suggestion of selective outcome?  
   N N Y N N N Y Y N Y Y Y Y Y Y Y
Based on the risk of bias assessment tool from the Cochrane Handbook for Systematic Reviews of Interventions [11]; ‘Y’ indicates “Yes (low risk of bias)”; ‘U’, “Unclear”; ‘N’, “No (high risk of bias)”; A study with a low risk of bias (in bold) was defined as a study receiving ‘Y’ for randomisation and/or allocation concealment.

References


42. Coster M, Karlsson MK, Nilsson JA, Carlsson A: *Validity, reliability, and responsiveness of a