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Review Article

Acupuncture as an alternative or in addition to conventional treatment for chronic non-specific low back pain: Systematic review and meta-analysis

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ABSTRACT

Background: Conventional therapies (CTs), pharmacological (PH) and non–pharmacological (NPH), do not always achieve benefits in the treatment of chronic low back pain (CLBP). We assessed efficacy and safety of acupuncture for CLBP as alternative or addition to CT.

Methods: We included randomised controlled trials (RCTs) comparing acupuncture alone or in combination with CT to CT. We searched Medline, Cochrane Library, Embase up to May 2022. We assessed risk of bias with the original Cochrane tool and GRADE certainty of evidence. Results were pooled through meta-analysis.

Results: Ten RCTs (2122 participants) were included comparing acupuncture versus CT and 6 (374 participants) comparing acupuncture plus CT to CT alone. Comparing acupuncture with NPH or PH, no differences were found for pain and disability. Comparing with combined PH and NPH, pain and disability were reduced (SMD=-0.50, 95%CI-0.62 to -0.37; SMD=-0.71, 95%CI-1.17 to -0.24). Comparing acupuncture plus NPH with NPH alone, pain and disability were reduced (SMD=-0.70, 95%CI-0.94 to -0.46; SMD=-0.95, 95%CI-1.36 to -0.54). Comparing acupuncture plus PH with PH alone, pain and disability were reduced (MD=-0.21,8 95%CI-433.28 to -10.42; MD=-3.1, 95%CI-4.87 to -1.83). Comparing acupuncture plus combined treatment versus combined treatment alone, no differences were found in pain, while disability was reduced (MD=-3.40 95%CI-5.17 to -1.63). No studies assessed adverse event. Certainty of evidence ranged from moderate to very low.

Conclusion: We are uncertain whether acupuncture is more effective and safer than CT. In the comparisons without estimates' imprecision, acupuncture showed promising results. Acupuncture could be an option based on patients' preferences.

1. Introduction

Low back pain (LBP) is defined as pain, discomfort, muscle tension or stiffness localized below the costal margin and above the inferior gluteal folds. If it persists for more than three months and is not attributable to a recognizable specific pathology, it is defined as chronic non-specific low back pain (CLBP)[1] and it accounts for the majority of cases.[2,3] Chronic LBP is a major cause of disability in Western countries which results in a high socioeconomic burden, with an estimated USD 1.93 to 81.24 billion per person, adjusted in 2015, spent in developed countries.[4] A systematic review[5] estimates that the prevalence of CLBP

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ranges from 5.9 to 18.1% and another Italian epidemiological study[6] reports a prevalence equal to 31.5%.

People affected with CLBP often require long-term treatment. Conventional therapies aim to resolve pain, improve quality of life and reduce disability, but they don't always achieve the expected results.[4,7] Non-pharmacological treatment options include exercise, acupuncture, spinal manipulation therapy (SMT), physiotherapy, cognitive-behavioral therapy, yoga, mindfulness, interdisciplinary rehabilitation and massage. Pharmacological options include paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, oral opioids, anticonvulsants, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs) and oral muscle relaxants.

None of these treatment options, however, can fully achieve the expected results. Paracetamol has proved to be ineffective and harmful;[8,9] the use of NSAIDs is associated with the risks of gastrointestinal, liver and cardiorenal toxicity.[10] Routine use of opioids is associated with the risks of overdose and addiction, and poorer long-term results have been observed.[11,12] Anti-seizure medications have been shown to be ineffective.[13] Muscle relaxants should be further investigated for short-term use.[8] Acupuncture can be a viable option in alternative or in addition to conventional therapy. Over the past few decades, the mechanisms of action of acupuncture have been widely investigated and neurobiological models have been developed to explain how this technique achieves its effects in many clinical applications including treatment of CLBP.

Several studies indicate that prolonged skin stimulation with needles inhibits transmission of pain by activating the gate-control system[14] and acting on the human limbic and basal forebrain areas which are thought to be involved in pain processing.[15] Acupuncture appears to activate the release of opioids in the central nervous tissue thus resulting in a long-lasting activation of the ascending sensory tracks and making it possible to relieve several pain conditions.[16] Advances in research have proved that acupuncture can modulate the release of adenosine, a neurotransmitter acting as a potent endogenous anti-inflammatory agent: adenosine is a signaling molecule in immunity and inflammation[17] that can regulate transmission of pain to the spinal cord and periphery.[18]

Two systematic reviews were recently published on acupuncture for the treatment of chronic low back pain. One is a Cochrane review[4] that compared acupuncture with sham acupuncture, no treatment, usual care and other treatments. In this review, usual care is considered as an unique entity without distinguishing between pharmacological and non-pharmacological components. Another systematic review[19] reported on 15 meta-analyses on different treatments. In this review, acupuncture was compared to placebo only.

In the light of the above, the objective of this systematic review was to assess the efficacy and safety of acupuncture for the treatment of chronic non-specific low back pain as an alternative or in addition to conventional therapy (pharmacological and or non-pharmacological treatment).

2. Methods

We reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary materials).[20]

2.1. Inclusion criteria

2.1.1. Participants

Adults (≥18 years) with chronic non-specific low back pain. Chronic non-specific low back pain was defined as pain occurring for more than three months, and not attributable to a recognizable specific pathology (e.g., infection, tumor, osteoporosis, lumbar spine fracture, structural deformity, inflammatory disorder, radicular syndrome, or cauda equina syndrome).[1]

2.1.2. Intervention

Any treatment involving needle insertion (with or without manual or electrical stimulation) at acupuncture points, pain points or trigger points, described as acupuncture given alone on in addition to any pharmacological and or non-pharmacological treatments.

2.1.3. Comparison

Any pharmacological and or non-pharmacological treatments alone.

2.1.4. Outcomes

Primary outcomes:

- Pain intensity as measured by validated scales at the end of treatment.
- Disability as measured by validated scales at the end of treatment.
- Secondary outcomes.
- Quality of life as measured by validated scales (e.g., SF-36; SF-12).[21,22]
- Functional state ad measured by validated scales.
- Use of analgesics (for the comparisons with non-pharmacological treatment).
- Number of subjects with at least one adverse event (AE).
- Dropout from treatment.

2.1.5. Study design: *randomized-controlled trials (RCTs)*

We excluded studies that evaluated acupuncture at specific "microsystems" (e.g., scalp or ear acupuncture) and studies that evaluated other methods of stimulating acupuncture points without needle insertion, for example, acupressure, laser stimulation, or transcutaneous electrical stimulation, injected fluids at acupuncture or trigger points. We also excluded studies that compared acupuncture with "usual care", when the component of usual care (i.e., pharmacological, non-pharmacological or combined treatments were nor described.

2.2. Search strategy

Cochrane Database of Systematic Reviews (CENTRAL), Embase, MEDLINE, and ClinicalTrial.gov were searched for eligible studies. Literature search was performed using free text and Thesaurus terms from inception up to 24 May 2022 without language restriction. The detailed search strategy is reported in the Supplementary Material. We identified other potentially eligible studies by searching the reference lists of included studies, systematic reviews and meta-analyses.

2.3. Selection of studies and data extraction

Two authors (MGL, CMG) independently screened articles retrieved via the search strategy from the titles and abstracts. Potentially relevant studies were acquired in full text and assessed for final inclusion independently by two authors (MGL, CMG). Any disagreement was discussed with the other authors. Two review authors independently extracted data from the studies (MGL, CMG). We extracted the following information: number and characteristics of participants: mean age,% female, duration of disease in years, details of acupuncture treatments: number of sessions, number of acupoints, achievement of de-chi (an irradiating feeling considered to indicate effective needling), duration of treatment in weeks; details of control intervention, length of follow-up after the end of treatment, types of outcomes assessed, country where the study was conducted.

2.4. Assessing the risk of bias

Two authors (MGL, CMG) independently assessed risk of bias according to the criteria set out in the Cochrane Handbook for Systematic Reviews of Interventions.[23] The following criteria were considered: sequence generation and allocation concealment (selection bias), blinding

of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Disagreement between reviewers was resolved by discussion.

2.5. Data synthesis

We analyzed dichotomous outcomes by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed with a 95% confidence interval (CI). We analyzed continuous outcomes by calculating the mean difference (MD) with 95% CI when the studies used the same instrument for assessing the outcome. We used the standardized mean difference (SMD) when the studies used different instruments. We interpreted SMD values with the classification proposed by Cohen[24] where an effect size of 0.2 means a small effect, 0.5 means a medium effect, 0.8 means a large effect. As we supposed a certain degree of heterogeneity among studies, due to treatment schedules, way in assessing response criteria, risk of bias and other factors which may have affected direction and magnitude of treatment effect, we pooled data used the random effect model for each outcome. Seeking statistical heterogeneity among studies, the Cochrane Q-test was performed, with a significant threshold of alpha = 0.1 and inconsistency among studies was quantified by the I-squared statistic;[23] an I square >70% was judged a significant heterogeneity.

Results are depicted in all figures as conventional meta-analysis forest plots. RevMan 5.4 was used for producing forest plot figures.[25] We planned to use visual inspection of funnel plots (plots of the effect estimate from each study against the sample size or effect standard error) to indicate possible publication bias if there were at least 10 studies included in the meta-analysis.

Subgroup Analysis:

Although the STRICTA (Standards for Reporting Interventions in Controlled Trials of Acupuncture) recommendations describe the components of acupuncture procedures[26] better outcomes appear to be associated with a greater number of needles and treatment sessions[27] and on the other hand, an insufficient dose of acupuncture may be an obstacle to good patient care.[28] We established standard criteria to define the adequate dose of acupuncture, as already expressed by other authors,[29,30] considering the following three parameters:

- number of points needled during each treatment,
- de-qi response,
- number of treatment sessions.

The “de qi” response, that is the sensation from needling experienced by the patient, may be reported as numbness (A-beta fiber activation) or as aching, dull, heavy, and warm sensation (A-delta or C fiber activation).[31] The concept of dose-intensity has thus been introduced and used to group the studies according to the intensity of acupuncture based on the following criteria:

- number of sessions (≥8 vs. <8),
- number of acupoints treated (≥10 vs. <10),
- achievement of de-qi (yes vs. no/not reported).

Acupuncture was judged as at low intensity if only one criterion was met; on medium intensity if two criteria were met; high intensity if all the three criteria were met. We planned to conduct subgroup analyses for intensity of acupuncture. However, due to the small number of included studies in each analysis, subgroup analysis was not possible.

2.6. Grading of evidence

We assessed the overall certainty of the evidence for the primary outcomes using the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) according to the GRADE approach.[32] Based on the above domains, the GRADE system uses the following criteria to grade the evidence: High: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. The existing evidence was summarized in a “Summary of Findings” table that provides key information about the magnitudes of relative and absolute effects of the interventions, the amount of available evidence and the certainty of available evidence.[33]

3. Results

3.1. Search results

The bibliographic search retrieved 596 records after duplicates were removed. Thirty-six studies were judged as potentially relevant. Twenty-two articles were excluded because they did not meet the inclusion criteria, references of excluded studies and reasons for exclusion are described in the Supplementary material. Fourteen randomized trials were finally included.[34-47] We grouped the included studies in two main groups: 1) acupuncture alone: studies comparing acupuncture to conventional therapy (pharmacotherapy, non-pharmacologic treatments, combination of pharmacologic and non-pharmacologic treatments); 2) acupuncture as add-on to conventional treatment: studies comparing acupuncture in addition to conventional therapy to conventional therapy alone. Ten studies assessed the efficacy and safety of acupuncture alone and six assessed the efficacy of acupuncture as add-on to conventional therapy (Fig. 1).

3.2. Characteristics of the included studies

Two studies[38,47] provided data for both the comparisons. The trials included a total 2440 participants; mean age ranged from 33 to 81 years, two studies did not report this information; mean percentage of female (ranged from 23% to 90%), three studies did not report this information; mean percentage of participants with chronic pain for at least one year ranged from 61% to 75% in five studies; four studies reported a mean duration of back pain of 8.1 (SD 8),[37] 6.9 (SD NR),[47] 9.6,[43] 9.9[44] years respectively and one of 22 months,[40] four studies did not report this information.[36,38,39,46] Mean duration of treatments ranged from 3 to 12 weeks Three studies were conducted in US, three in Germany and one each in Japan, Taiwan, India, Hong Kong, Lebanon, China, Iran and UK.

The scales used in the studies to measures the outcomes were: pain intensity: Visual analogue scale (VAS) 0–10 or 0–100,[48] Von Korff Chronic Pain Grade Scale (CPGS);[49] disability: Roland Morris Disability Questionnaire,[50] Hannover Functional Ability Questionnaire,[51] Oswestry disability index,[52] Pain disability index;[53] functional state: Aberdeen Low back pain;[54] quality of life: SF −36 total,[21] SF-12 physical health, SF-12 mental health.[22]

Types of comparisons: Among the studies included in group “acupuncture alone”, four studies compared acupuncture with non-pharmacologic treatment: massage,[34] TENS,[36,38] pulse radiofrequency;[39] three studies compared acupuncture with pharmacologic treatment (baclofen[47] ibuprofen[41] drugs not described[39]).

Among the studies included in group “acupuncture as add-on to conventional therapy”, four assessed the addition of acupuncture to non-pharmacologic treatment compared non-pharmacologic treatment alone: exercise,[45] TENS,[38] active physiotherapy,[43] physiotherapy, back school, mud packs, infrared heat therapy;[44] one assessed the addition of acupuncture to combined pharmacologic and non-pharmacologic treatment (NSAIDs, muscle relaxants, paracetamol and back exercises) compared to combined treatment alone;[46] one study compared the addition

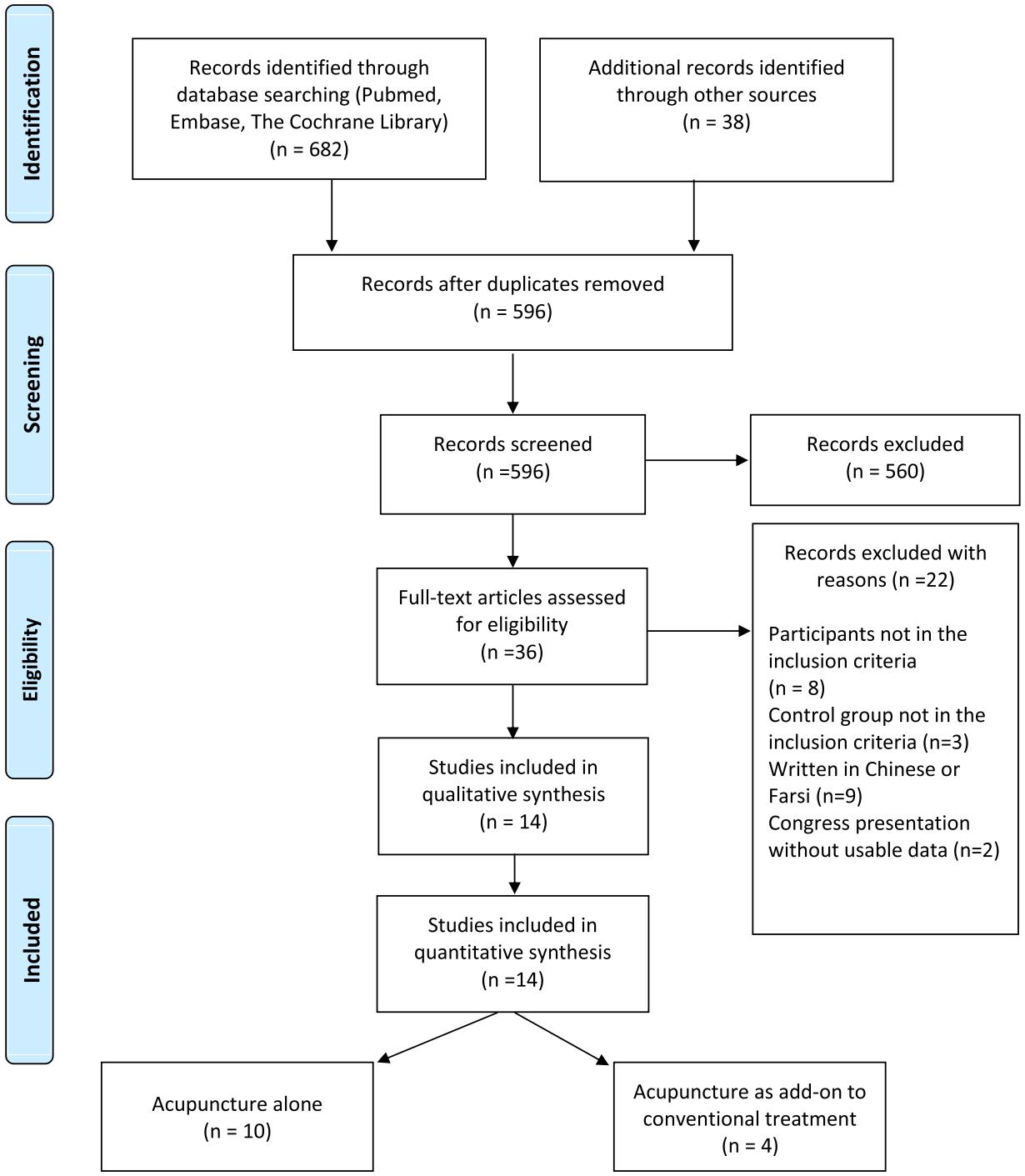

Fig. 1. PRISMA Flow diagram.

of acupuncture to pharmacologic treatments compared to pharmacologic treatment alone[47] (Table 1).

3.3. Risk of bias of included studies

Six studies were judged at low risk of selection bias because both the methods for random sequence generation and allocation concealment were appropriate;[35-37,44,46,47] six studies[34,38,40-42,45] followed ad adequate method for random sequence generation but did not provide information about concealment of allocation. The remaining two studies[43,39] were judged at unclear risk for selection bias because they did not provide any information about randomization procedure and allocation concealment. All the studies were judged at high risk of both performance and detection bias because they were open label. Three studies were judged at high of attrition bias[38,43,46] because of the high number of subjects who dropped out from studies. The study protocol was available only for three studies[35,37,47] and the outcomes reported in the final publication coincided with the outcomes listed in the protocol; for all the remaining studies the protocol was not available, and they were judged at unclear risk of selective outcome reporting (Fig. 2. Risk of bias summary: Review authors' judgments of bias items for each included study).

Table 1
Characteristics of RCTs of acupuncture compared to several controls in patients with chronic low back pain (CLBP).

First author (year) Country	Sample size (% of female) Mean age (years)/mean disease duration (years) Medication (in the past week)	Intervention (regimene) Follow-up Dose intensity	Comparison	Outcomes	Funding Note
Cherkin (2001)[35] US	172 (58%) NS-CLBP 44.9/NR 63%	(A) AT (10 sessions, 10 weeks, de-qi, $n = 94$) 52 weeks medium	(B) Massage ($n = 78$)	Disability Drop-out	Yes
Cherkin (2009)[36] US	476 (63%) NS-CLBP 47/NR 63%	(A) AT (8–10 sessions, 8 weeks, de-qi, $n = 315$) 52 weeks medium	(B) Usual care (medications, primary care, and physical therapy, $n = 161$)	Disability Drop-out	Yes
Grant (1999)[37] UK	60 (90%) NS-CLBP 73.5/NR 35 (Mean tablet of medication)	(A) AT (8 sessions, 4 weeks, NR de-qi, $n = 32$) 12 weeks low	(B) TENS ($n = 28$)	Pain Drop-out	Yes
Haake (2007)[38] Germany	775 (57.4%) NS- CLBP 50.4/8.1 NR	(A) AT (10–15 sessions, 5–7weeks, NR de-qi, $n = 387$) 24 weeks low	(B) Usual care (drugs, physical therapy, and exercise, $n = 388$)	Pain Disability Drop out	Yes
Lin (2010)[40] Taiwan	100 (NR) NS-CLBP NR/NR NR	(A) EA (12 sessions, 4 weeks, de-qi, $n = 39$) NA medium	(B) Pulse radiofrequency ($n = 29$) (C) Medications ($n = 35$)	Pain Disability Drop-out	NR
Shankar (2011)[41] India	60 (63%) NS-CLBP 35.5/1.83 NR	(A) EA (10sessions, 3 weeks, NR de-qi, $n = 30$) electroacupuncture NA medium	(B) Valdecoxib (20 mg BD for 10 days) plus supervised physiotherapy (3 weeks)	Pain Drop-out	NR
Yun (2012)[43] China	187 (23%) NS-CLBP 34/NR 40%	(A) AT (18sessions, 7 weeks, de-qi, $n = 124$) 48 weeks medium	(B) Massage, physical therapy and medications (NSAID) ($n = 63$)	Pain Disability Drop out	NR
Yun (2012)[42] Lebanon	236 (30%) NS-CLBP 33/NR 41%	(A) AT (12 sessions, 4 weeks, de-qi, $n = 162$), plus massage and physical therapy 24 weeks high	(B) Massage, physical therapy and ibuprofen ($n = 74$)	Pain Disability Drop-out	NR
Zaringhalam (2010)[48] Iran	60 (NR) NS-CLBP 54.5/6.9 NR	(A) AT (10 sessions, 5 weeks, de-qi, $n = 20$) (B) AT plus (C) ($n = 20$) 10 weeks medium	(B) Baclofen (30 mg/day, $n = 20$)	Pain Disability Drop-out	NR
Itoh (2009)[39] Japan	24 (NR) NS-CLBP range :61–81/NR NR	(A) AT (5 sessions, 5 weeks, de-qi, $n = 8$) (B) AT, plus (C) ($n = 8$) 10 weeks low	(B) TENS ($n = 8$)	Pain Disability Drop-out	NR
Leibing (2002)[44] Germany	86 (57%) NS-CLBP 47.7/9.6 54%	(A) AT (20sessions, 12 weeks, $n = 40$), plus (B) 52 weeks high	(B) Active physiotherapy ($n = 46$)	Pain Disability Drop-out	Yes
Molsberger (2002)[45] Germany	186 (47.8%) NS-CLBP 50/9.9 17%	(A) AT (12sessions, 4 weeks, de-qi, $n = 65$), plus (B) 12 weeks medium	(B) Physiotherapy, back school, mud packs, infrared heat therapy n. 60	Pain Drop-out	Yes
Yeung (2003)[46] Hong Kong	52 (82%) NS-CLBP 53/NR 1.9%	EA (12 sessions, 4 weeks, de-qi, $n = 26$), plus (B) 12 weeks medium	(B) Exercise ($n = 26$)	Pain Drop-out	Yes
Meng (2003)[47] USA	55 (NR) NS-CLBP 71/NR 71%	AT (10 sessions, 5 weeks, de-qi, $n = 31$), plus (B) 9 weeks high	(B) NSAIDs, muscle relaxants, paracetamol and back exercises ($n = 24$)	Pain Disability Drop-out	Yes

AT: acupuncture treatment; EA: electro acupuncture; NA: not applicable; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; NS-CLBP: non-specific chronic low back pain; TENS: transcutaneous electrical nerve stimulation.

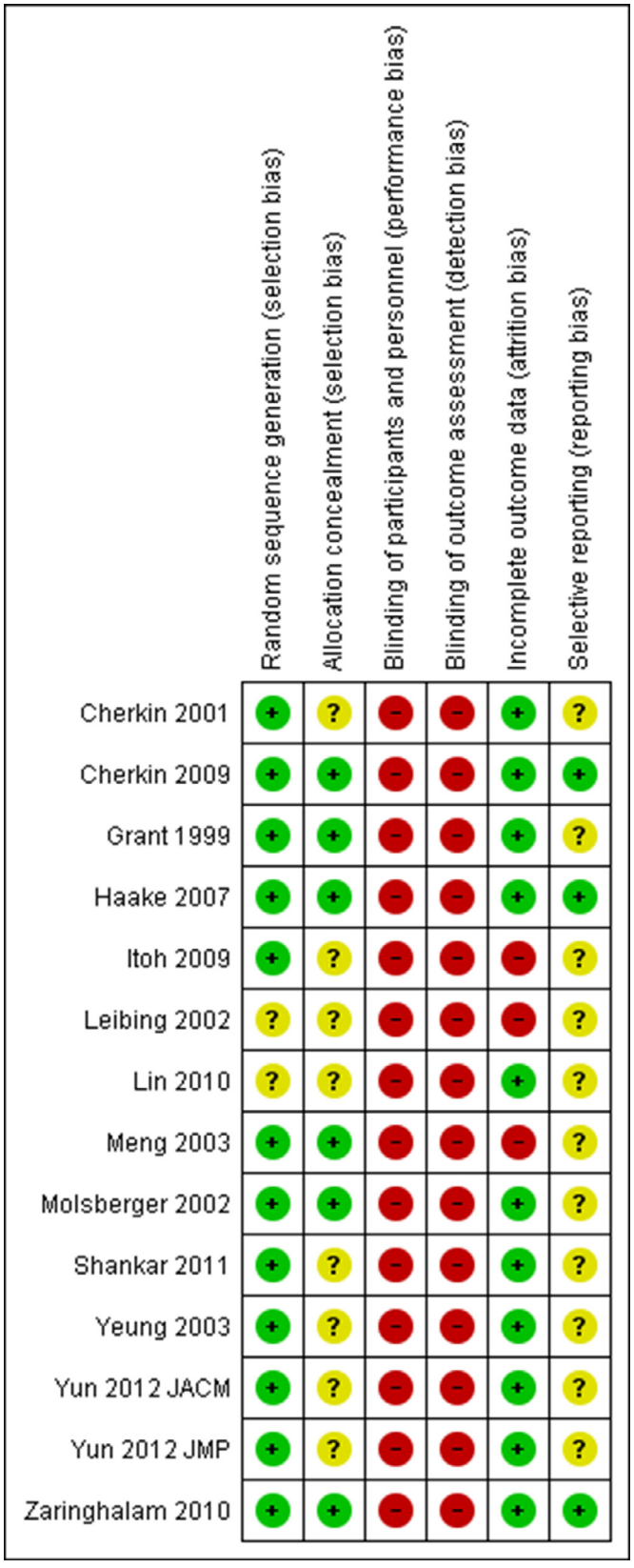

Fig. 2. Risk of bias summary: Review authors' judgments of bias items for each included study.

3.4. Effects of interventions

3.4.1. Acupuncture alone

3.4.1.1. Acupuncture versus non-pharmacologic treatment. We didn't find any significant difference in pain measured by visual analogue scale (VAS) (MD 0.10, 95%CI −15.05 to 15.25; 3 studies, 141 participants, low certainty of evidence), disability (SMD 0.19 95%CI −0.06 to 0.44; 3 studies, 256 participants, low certainty of evidence), drop out from treatment (RR 1.56, 95%CI 0.43 to 5.61; 4 studies, 316 participants, low certainty of evidence). None of the studies reported the number of subjects with at least one adverse event (Table 2; Figure 3 in the Supplementary material).

We didn't find any significant difference for quality of life (MD −4.20, 95%CI −10.11 to 1.71; 1 study, 68 participants), subjects using analgesics (RR 1.08, 95%CI 0.79 to 1.46; 1 study, 172 participants), while the mean use of drugs in the last week of treatment decreased with acupuncture (MD −13.00, 95%CI −25.63 to −0.37; 1 study, 60 participants).

3.4.1.2. Acupuncture versus pharmacologic treatment. We didn't find any significant difference in pain measured by visual analogue scale (VAS) (MD −2.17, 95%CI −12.69 to 8.35; 3 studies, 347 participants, low certainty of evidence), disability (SMD −0.44 95%CI −1.22 to 0.34; 3 studies, 347 participants, very low certainty of evidence); there were only 1 participant who dropped out from treatment in each arm in one study[47] in both arms (RR 1.00 [95%CI 0.07 to 14.90] 3 studies, 347 participants, very low certainty of evidence). None of the studies reported the number of subjects with at least one adverse event (Table 2; Figure 4 in the Supplementary material).

We didn't find any significant difference for quality of life (MD 0.20, 95%CI −5.82 to 6.22; 1 study, 71 participants).

3.4.1.3. Acupuncture versus combined pharmacological and non-pharmacological treatment. Pain was reduced with acupuncture (SMD −0.50, 95%CI −0.62 to −0.37; 3 studies, 1022 participants, moderate certainty of evidence); disability was reduced with acupuncture (SMD −0.71, 95%CI −1.17 to −0.24; 3 studies, 1438 participants, low certainty of evidence); we didn't find difference in dropout rate (RR 0.64, 95%CI 0.41 to 1.02; 4 studies, 1498 participants, low certainty of evidence). None of the studies reported the number of subjects with at least one adverse event (Table 2; Figure 5 in the Supplementary material).

3.4.2. Acupuncture as add-on to conventional treatment

3.4.2.1. Acupuncture in addition to non-pharmacological treatment versus non-pharmacological treatment alone. Pain was reduced with acupuncture (SMD −0.70, 95%CI −0.94 to −0.46; 4 studies, 279 participants, very low certainty of evidence); disability was reduced with acupuncture (SMD −0.95, 95%CI −1.36 to −0.54; 2 studies, 1028 participants, very low certainty of evidence); we didn't find difference in dropout rate (RR 1.24, 95%CI 0.54 to 2.81; 4 studies, 279 participants, very low certainty of evidence). None of the studies reported the number of subjects with at least one adverse event (Table 2; Figure 6 in the Supplementary material).

We didn't find any significant difference in subjects using analgesics (RR 3.00, 95%CI 0.67 to 13.51; 1 study 52 participants), while we found an improvement in functional state measured by Aberdeen LBP scale (MD −10.80, 95%CI −17.22 to −4.38; 1 study, 52 participants).

3.4.2.2. Acupuncture in addition to pharmacological treatment versus pharmacological treatment alone. Pain was reduced with acupuncture (MD: −21.80, 95%CI −33.18 to −10.42, 1 study, 40 participants low certainty of evidence); disability (Roland Disability Questionnaire) was reduced with acupuncture (MD −3.10, 95%CI −4.87 to −1.83; 1 study, 40 participants, low certainty of evidence. One patient dropped out from treatment in each arm (RR: 1.00, 95%CI 0.07 to 14.90, 1 study, 40 partici-

Table 2
Summary of results.

Outcome	Result	No. of studies (participants)	Certainty of Evidence	Favors
Acupuncture alone vs. non-pharmacological treatment				
Pain	MD 0.10 (95% CI −15.05 to 15.25)	3 (141)	LOW	=
Disability	MD 0.19 (95% CI −0.06 to 0.44)	3 (256)	LOW	=
Drop out	RR 1.56 (95% CI 0.43 to 5.61)	4 (316)	LOW	=
Quality of Life	MD −4.20 (95% CI −10.11 to 7.17)	1 (68)	VERY LOW	=
Analgesics use	RR 1.08 (95% CI 0.79 to 1.46)	1 (172)	VERY LOW	=
Use of drug (last week of treatment)	MD −13.00 (95% CI −25.63 to 0.37)	1 (60)	VERY LOW	=
Acupuncture alone vs. pharmacological treatment				
Pain	MD −2.17(95%CI −12.69 to 8.35)	3 (347)	LOW	=
Disability	MD −0.44 (95% CI −1.22 to 0.34)	3 (347)	VERY LOW	=
Drop out	RR 1.00 (95%CI 0.07 to 14.90)	3 (347)	VERY LOW	=
Quality of Life	MD 0.20 (95% CI −5.82 to 6.22)	1 (71)	VERY LOW	=
Acupuncture alone vs. combined pharmacological & non-pharmacological treatment				
Pain	SMD −0.50 (95% CI −0.62 to −0.37)	3 (1022)	MODERATE	+
Disability	SMD −0.71 (95% CI −1.17 to −0.24)	3 (1438)	LOW	+
Drop out	RR 0.64 (95% CI 0.41 to 1.02)	4 (1498)	LOW	=
Acupuncture + non-pharmacological treatment vs. non-pharmacological treatment				
Pain	SMD −0.70 (95% CI −0.94 to −0.46)	4 (279)	VERY LOW	+
Disability	SMD −0.95 (95% CI −1.36 to −0.54)	2 (1028)	VERY LOW	+
Drop out	RR 1.24 (95% CI 0.54 to 2.81)	4 (279)	VERY LOW	=
Analgesics use	RR 3.00 (95% CI 0.67 to 13.51)	1 (52)	VERY LOW	=
Functional status	MD −10.80 (95% CI −17.22 to −4.38)	1 (52)	VERY LOW	+
Acupuncture + pharmacological & non-pharmacological treatment vs. pharmacological & non-pharmacological treatment				
Pain	MD −0.60 (95% CI −1.22 to 0.02)	1 (55)	VERY LOW	=
Disability	MD −3.40 (95% CI −5.17 to −1.63)	1 (55)	VERY LOW	+
Drop out	RR 5.42 (95% CI 0.71 to 41.11)	1 (55)	VERY LOW	=
Analgesics use	RR 0.88 (95% CI 0.73 to 1.04)	1 (52)	VERY LOW	=
Acupuncture + pharmacological treatment vs. pharmacological treatment				
Pain	MD −21.80 (95%CI −33.18 to −10.42)	1 (40)	LOW	+
Disability	MD −3.10 (95%CI −4.87 to −1.83)	1 (40)	LOW	+
Drop out	RR 1.00 (95%CI 0.07 to 14.90)	1 (40)	VERY LOW	=

= No statistically different; + Favors acupuncture alone or in combination with other treatments.

pants, very low certainty of evidence) (Table 2; Figure 7 in the Supplementary material).

3.4.2.3. Acupuncture in addition to combined pharmacological and non-pharmacological treatment versus combined pharmacological and non-pharmacological treatment alone. We didn't find any significant difference in pain measured by visual analogue scale (VAS) (MD −0.60, 95%CI −1.22 to 0.02; 1 study, 55 participants, very low certainty of evidence), while disability was reduced with acupuncture (MD −3.40 95%CI −5.17 to −1.63; 1 study, 55 participants, very low certainty of evidence); we didn't find difference in dropout rate (RR 5.42, 95%CI 0.71 to 41.11; 1 study, 55 participants, very low certainty of evidence). None of the studies reported the number of subjects with at least one adverse event (Table 2; Figure 8 in the Supplementary material).

We didn't find any significant difference in subjects using analgesics (RR 0.88, 95%CI 0.73 to 1.04; 1 study 55 participants).

Certainty of evidence ranged from moderate to very low (Table 2 in the Supplementary material).

4. Discussion

We found no difference in pain or disability with low or very low certainty evidence when acupuncture was compared to non-pharmacologic or pharmacological treatment. When compared to combined pharmacological and non-pharmacological treatment, we found moderate certainty evidence that acupuncture reduced pain and low-quality evidence that it reduced disability. When acupuncture was prescribed as add-on to non-pharmacological treatment, we found that acupuncture was efficacious in reducing pain and disability, but the certainty of evidence was very low. Finally, when acupuncture was prescribed as add-on to combined pharmacological and non-pharmacological treatment, we found no difference in reducing pain, but an improvement in disability, with very low certainty evidence.

When we defined our inclusion criteria, we decided to not use the term "usual care" for the definition of the comparison interventions, as under the broad and vague term "usual care" authors could consider any kind of treatment which is very often not described in the studies. This lack of description could limit the applicability of the results in clinical practice as clinicians could not understand with what acupuncture was actually compared. Therefore, we grouped the studies for the type of comparison intervention, namely pharmacological treatment, non-pharmacological treatment, and combined pharmacological and non-pharmacological treatment. Furthermore, we distinguished the studies that assessed the efficacy of acupuncture given as an alternative to conventional treatment for the studies that used acupuncture as an additional treatment.

For this reason, we excluded trials that simply defined the comparison intervention as "usual care" and, although the total number of finally included studies was not small, we were able to pool a small number of studies in each comparison as the retrieved studies used a large variety of comparison interventions. This could explain, at least partially, the lack of significant results, as the sample size were small and results largely imprecise.

After applying the concept of dose of acupuncture,[29] we tried to standardize treatment by considering the three most important parameters involved to provide effective treatment: number of points needled during each session, de qi response, and number of treatment sessions. By setting these parameters, we were able to introduce the concept of dose-intensity with the aim to reduce heterogeneity among studies. However, while this subgroup analysis yielded informative results in other setting,[30] we were unable to find significant differences among studies, probably because of due to the small number of studies that we able to include in each comparison.

Studies using sham and placebo acupuncture as control groups were not included in our review, since they are not suitable comparators.[55]

According to the widely recognized principle that no skin stimulation is inert, "sham acupuncture" cannot be inert since any skin stimulation brings about central and peripheral responses[56] and the same applies to whatever form of placebo acupuncture involving skin stimulation. A light touch of the skin stimulates mechanoreceptors coupled to slow conducting unmyelinated (C) afferents; activity in these afferents has been suggested to induce a "limbic touch" response resulting in emotional and hormonal reactions. Control procedures which are meant to be inert are likely to activate these afferents.[57] In conclusion, comparison of verum acupuncture vs sham or placebo acupuncture may unnecessarily confuse rather than clarify the interpretation of the effects: that is why they were both excluded from our study. More positive and reliable outcomes from the administration of acupuncture can be expected if acupuncture is compared only with usual care.[58]

The most relevant flaws of the included studies were the high risk of performance and detection bias due to lack of blinding in all the studies, though it should be noted that both performance and detection bias are unavoidable for the types of intervention compared; the risk of bias is further increased by the subjective nature of the outcomes assessed. Overall, the certainty of evidence was judged as low or very low according to the GRADE approach for most primary outcomes due to risk of bias and imprecision in the estimate, as few and heterogeneous studies with different comparison interventions and small sample size were included in each comparison.

However, in the comparisons where the sample size was adequate, the clinically meaningful role played by acupuncture emerged more clearly and outcomes revealed a tendency to confirm the effectiveness of acupuncture.

Our results are not directly comparable with the results of a recent Cochrane review[4] as the inclusion criteria and the comparisons were different; nevertheless, the overall conclusions reached by Mu 2020 were consistent with our findings.

Our review relies on a comprehensive bibliographic search on several databases without time restriction and in the rigor of the methodology that followed the highest standards as recommended by Cochrane.[23]

However, our review has some limitations. The lack of information about adverse effects experienced by participants in the primary studies prevented us from comparing safety data, particularly relevant for the comparison with pharmacologic treatments. However, the adverse effects of drugs usually prescribed for CLBP are well known, especially in the long term[59-61]; and information about safety of acupuncture could be drawn from indirect evidence.[62]

We limited our inclusion criteria to studies published in western languages due to our inability to translate studies published in Chinese or other eastern languages. Given the widespread use of acupuncture in Eastern countries and particularly in China, we probably missed some studies that made our comparison of interest. Furthermore, we were unable to visually inspect funnel plot for the presence of possible publication bias because if fewer than 10 studies are included in meta-analyses, the funnel plot is considered uninformative.[24]

On the basis of the results of this systematic review, we are uncertain whether acupuncture as either an alternative or add-on treatment to conventional therapy is more effective and safer than conventional therapy. However, in the comparison with large sample size without imprecision of the estimates, the clinically meaningful role played by acupuncture emerged more clearly and outcomes revealed a tendency to confirm its effectiveness. Acupuncture could be a viable option based on patients' underlying disorders, costs, availability, and preferences. Further randomized trials should be conducted with large sample sizes and a detailed description of the comparison intervention.

Author contributions

CMG, MGB and MGL conceptualized and designed the study. MGL and CMG screened studies from title and abstract, extracted data from included studies, assesses risk of bias, undertook data analysis, evaluated the certainty of evidence, and drafted the initial manuscript. MGL performed search strategies, screened studies from title and abstract, extracted data from included studies and drafted supplementary material. CMG, AP, MGB, and EM wrote the introduction and the discussion. All review authors contributed to writing and revising the final manuscript.

Conflicts of interest

CMG is an editorial board member of the journal. However, his membership had no bearing on the review process or decision. The authors declare no other conflicts of interest.

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Ethical statement

Not applicable.

Data availability

The data that support the findings of this study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2023.100972.

Supplement 1. Search strategy
Supplement 2. Excluded studies and reasons for exclusion
Supplement 3. Summary of findings results.
Supplement 4. Supplementary figures
Supplement 5. PRISMA 2020 Checklist

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