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Acupuncture for the prevention of episodic migraine (Protocol)

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Acupuncture for the prevention of episodic migraine (Protocol).
Cochrane Database of Systematic Reviews 2025, Issue 2. Art. No.: CD015528.
DOI: 10.1002/14651858.CD015528.

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[Intervention Protocol]

Acupuncture for the prevention of episodic migraine

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Editorial group: Cochrane Central Editorial Service.
Publication status and date: New, published in Issue 2, 2025.

Citation: Xia R, Linde K, Freilinger T, Vickers A, Vertosick EA., Vase L, Fernández-Jané C, Ren Y, Zhao B, Low SLK, Fei Y. Acupuncture for the prevention of episodic migraine (Protocol). *Cochrane Database of Systematic Reviews* 2025, Issue 2. Art. No.: CD015528. DOI: 10.1002/14651858.CD015528.

ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To investigate whether acupuncture is more effective than 'sham' (placebo) acupuncture, no preventative treatment or routine care only, or other interventions, in reducing headache frequency in people with episodic migraine.

BACKGROUND

Description of the condition

Migraine is a highly prevalent complex and disabling neurovascular disorder characterised by recurrent headache attacks lasting from 4 to 72 hours. The estimated global prevalence of migraine is 14% (Stovner 2022). According to the diagnostic criteria of the International Headache Society, typical characteristics of the headache are unilateral location, pulsating quality, moderate to severe intensity and aggravation by routine physical activity; accompanying symptoms include nausea or vomiting, or both, photophobia and phonophobia (IHS 2018). Up to one-third of people with migraine experience transient neurological deficits (most commonly visual disturbances) before the actual headache (i.e. migraine with aura).

Migraine is subclassified into the more common episodic migraine (having a migraine for fewer than 15 days per month and at the same time no more than 15 days of headache per month) and the less common chronic migraine (more than 15 headache days per month for at least three consecutive months, with at least eight days fulfilling migraine criteria; IHS 2018). Overuse of acute medication is highly prevalent within the chronic migraine subgroup (Davies 2012). Most people with migraine can be adequately managed by treating acute headache attacks alone. However, a significant proportion of people require preventative interventions, as their attacks are either very frequent, or cannot be effectively managed by acute therapy alone. Propranolol, metoprolol, topiramate, amitriptyline, valproic acid and flunarizine are mentioned as preventative treatments for episodic migraine in Scottish Intercollegiate Guidelines Network (SIGN; SIGN 2023) guidelines, French guidelines (Ducros 2021), and the guidelines of the German Migraine and Headache Society (Diener 2022). However, oral migraine-preventative medications have a low adherence rate (Hepp 2015). Moreover, dropout rates in most clinical trials are high, suggesting that the drugs are not well tolerated by a relevant number of people with migraine (Jackson 2015). Calcitonin gene-related peptide (CGRP) monoclonal antibodies (eptinezumab, erenumab, fremanezumab, and galcanezumab) have been shown to be effective in people with episodic migraine and chronic migraine, and can be considered for people who do not respond to, or cannot tolerate, the above oral medicines (Ashina 2020; Charles 2019).

Description of the intervention

Acupuncture in the context of this review is defined as the needling of specific points of the body. Manual acupuncture is the most commonly used type of acupuncture and uses skin penetration with thin, solid, metallic needles manipulated by the hands (WHO 2007). Electro-acupuncture is additional electric stimulation following needle insertion (WHO 2007). In the field of traditional Chinese medicine, acupuncture was originally developed as a way to bring the patient back to the equilibrium postulated to exist before illness – the rebalancing of the body's life energies, yin and yang (Ernst 2010). It is one of the most widely used complementary therapies in many countries (Bodeker 2005; Cui 2017; Yang 2017). For example, according to a population-based survey in 2012 in the USA, 6.4% of respondents reported lifetime use of acupuncture, and 1.7% reported recent use (Cui 2017). A longitudinal study conducted in Australia in 2012 to 2013 showed that 9.5% and 6.2% of women in the young and middle-aged cohorts, respectively, had consulted an acupuncturist in the previous 12 months (Yang 2017). Acupuncture is often used to treat headache, especially migraine. For example, 9.9% of the acupuncture users in the US survey mentioned above stated that they had been treated for migraine or other headaches (Burke 2006).

How the intervention might work

Studies have shown that acupuncture may have short-term effects on a variety of physiological variables relevant to analgesia (Han 2011; Lin 2008; Zhao 2008). However, it is unclear to what extent the long-term effects reported by practitioners can be explained by these observations from experimental settings. It is proposed that a variable combination of local effects, spinal and supraspinal mechanisms, and cortical, psychological or 'placebo' mechanisms contribute to the clinical effects in routine care (Carlsson 2002). Like many other non-pharmacological interventions, it is difficult to create sham interventions for acupuncture that are both indistinguishable and physiologically inert due both to technical reasons and the unclear biological mechanism of acupuncture. Consequently, studies using sham acupuncture controls must be interpreted carefully, as sham treatments might not be inactive placebos, shams may not be credible, and blinding may not always be achieved. Studies that compare acupuncture with no preventative treatment, preventative drugs or other interventions must also be interpreted carefully, as they have a higher risk of bias due to lack of blinding, and cannot test for the specific effects of acupuncture.

Why it is important to do this review

Despite the widespread use of acupuncture, its effectiveness, specifically in migraine, is still being debated. Since the publication of our Cochrane review (Linde 2016), a number of new studies have been published. We also plan to search commonly used Chinese databases to obtain more available studies. In addition, Cochrane standards and methods have changed substantially. Therefore, developing this new protocol and the upcoming full review is warranted.

OBJECTIVES

To investigate whether acupuncture is more effective than 'sham' (placebo) acupuncture, no preventative treatment or routine care only, or other interventions, in reducing headache frequency in people with episodic migraine.

METHODS

Criteria for considering studies for this review

Types of studies

We will include controlled trials that investigated the preventative effect of acupuncture, in which allocation to treatment was explicitly randomised, regardless of allocation concealment and blinding, and in which participants were followed up for at least eight weeks after randomisation.

We will exclude trials that used a clearly inappropriate method of randomisation, for example, open alternation. For cross-over randomised controlled trials (RCTs), we will only include data from the first phase.

Types of participants

We will include studies in which study participants have been diagnosed with episodic migraine, defined as having a headache for fewer than 15 days per month (Description of the condition). Of note, the word 'episodic' does not have to be mentioned in the study report explicitly to be eligible for inclusion.

We will include studies that focus on episodic migraine but include participants with additional tension-type headache. We will include studies that include participants with headaches of various types (for example, some participants with migraine, some with tension-type headache) only if findings for participants with migraine were available separately, or if more than 90% of participants suffered from migraine.

We are interested in studies where the duration of the condition is longer than one year in the majority (> 80%) of participants (Linde 2016). We will consider a study meeting this inclusion criterion if:

- duration for longer than a year was an inclusion criterion of the study; or
- the mean duration minus one standard deviation was longer than one year; or
- the mean duration (standard deviation not reported) was longer than 10 years; or
- other information was reported that made it highly likely that the criterion was met (e.g. study authors presented proportions with duration ranges).

Exclusion criteria

We will exclude studies that focused exclusively on people with chronic migraine or chronic daily headache (chronic daily headache is defined as headache on fewer than 15 days a month for more than three months), as well as studies in which, at baseline, more than half of participants had more than 15 days with migrainous headache per month. We will also exclude studies in which there was no information about the duration of headache complaints.

Types of interventions

Experimental interventions

We are interested in any treatment involving needle insertion (with or without manual or electrical stimulation) at acupuncture points, pain points or trigger points, and described as acupuncture.

We will exclude studies that:

- exclusively investigated dry needling;
- investigated 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.

Control interventions

- No treatment, allowing treatment of acute migraine attacks or routine care (which typically includes treatment of acute attacks, but might also include other treatments; however, studies normally require that no new experimental or standardised treatment be initiated during the study period).
- Sham interventions (interventions mimicking 'true' acupuncture or true treatment, but deviating from at least one aspect considered important by acupuncture theory, such as skin penetration or correct point location).
- Pharmacological agents considered as preventative treatments for episodic migraine (for example, propranolol, metoprolol, topiramate, amitriptyline, valproic acid and flunarizine) given for at least eight weeks.

We will exclude studies that compared acupuncture to food supplements, herbal drugs or combinations of herbal drugs, and studies that only compared different forms of acupuncture.

Types of outcome measures

We will exclude studies that focused on the treatment and measurement of acute attacks. Reporting of the predefined primary and secondary outcomes is not an inclusion criterion.

Primary outcomes

- The primary efficacy outcome is headache frequency per month (migraine days, number of attacks, or headache days per month, in descending order of preference, calculation of standardised mean differences (SMDs)).
- The primary safety or tolerability outcomes are the number of participants who dropped out due to adverse effects, and the number and characteristics of participants who reported at least one adverse event or effect.

Secondary outcomes

- The proportion of 'responders' (participants with ≥ 50% frequency reduction documented in a headache diary). We will not consider efficacy outcomes that are not clearly defined and reported, only measures such as 'total effectiveness rate' (e.g. proportion of participants healed, much improved, improved, unchanged);
- Disability or quality of life with a validated measure (e.g. 36-Item Short Form (SF-36), Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ 2.1), migraine-specific scales will be prioritised over general scales, calculation of SMDs);
- Headache intensity (any measures available, extraction of means and standard deviations, visual analogue scales will be prioritised, calculation of SMDs);
- Frequency of analgesic use (any continuous or rank measures available, extraction of means and standard deviations, calculation of SMDs).

Timing of outcome assessment

We will consider the following time points for reporting outcomes.

- Short term: three months or less (≤ 12 weeks) after randomisation
- Medium term: three months or more to six months or less (> 12 weeks to ≤ 26 weeks) after randomisation
- Long term: more than six months (> 26 weeks) after randomisation

If studies report several short-, medium- or long-term time points, we will prioritise those closest to three months, six months, and one year.

Search methods for identification of studies

Electronic searches

We will search the following databases without language restrictions. Building on the evidence base in Linde 2016, we plan to perform searches of the same key databases from 2015 onwards as indicated below.

- The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, from 2015;
- MEDLINE (via Ovid), from 2015;
- Embase (via Ovid), from 2015;
- AMED (via Ovid), from 2015;
- PEDro, from its inception.

We will also search the Chinese biomedical databases below from inception.

- China National Knowledge Infrastructure database (CNKI; cnki.net);
- WangFang database (wanfangdata.com.cn);
- Chongqing VIP (CQVIP, cqvip.com);
- SinoMed sinomed.ac.cn/index.jsp.

The search strategies for databases will follow the model outlined for MEDLINE Ovid in Appendix 1. For the RCT filter, we will apply Cochrane's highly sensitive strategy for identifying RCTs and controlled clinical trials in MEDLINE Ovid, detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2024). Where relevant, we will employ validated RCT filters from the ISSG (Information Specialists' Sub Group) Search Filter Resource for other databases, or adaptations of these filters if direct equivalents are not available (Glanville 2024).

We will tailor searches to individual databases. The search strategies for MEDLINE and CNKI are reported in Appendix 1 and Appendix 2, respectively. The search strategies for other databases will be developed and executed by a professional information specialist and will be independently peer-reviewed.

Searching other resources

We will search the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/), ClinicalTrials.gov, and the Chinese Clinical Trial Registry (ChiCTR), for completed or ongoing trials using the search string 'acupuncture AND (headache OR migraine)'. We will also screen reference lists of all eligible studies for additional studies. We will check to ensure that none of the included studies has been retracted due to error or fraud.

Data collection and analysis

Selection of studies

Two review authors will independently screen all abstracts identified by the search and exclude those that were clearly irrelevant (for example, studies focusing on other conditions, reviews, etc.). We will obtain full texts of all remaining references and, again, screen them to exclude clearly irrelevant papers. At least two review authors will formally check all remaining articles and all studies included in Linde 2016 for eligibility according to the above-mentioned selection criteria. We will resolve any disagreements by discussion.

Data extraction and management

We will use Covidence to manage the screening and data extraction processes. At least two review authors will independently extract information on participants, methods, interventions, outcomes and results, using a specially designed form, before entry into Review Manager (RevMan; RevMan 2025). Review authors will not extract data or assess risk of bias in studies on which they were authors. In particular, we will extract:

- exact diagnoses;
- headache classifications used;
- number and type of centres;
- age;
- sex;
- duration of disease;
- number of participants randomised, treated and analysed;
- number of, and reasons for dropouts;
- duration of baseline, treatment and follow-up periods;
- details of acupuncture treatments (such as selection of points; number, frequency and duration of sessions; achievement of 'deqi' (an irradiating sensation considered to indicate effective needling); number, training and experience of acupuncturists);
- details of control interventions (sham technique, type and dosage of drugs); and
- number and characteristics (nature) of adverse events.

For details regarding methodological issues and study results, see below. Where necessary, we will seek additional information from the first or corresponding authors of the included studies.

We will refer to the Cochrane policy on problematic studies and keep alert to signs of problematic studies (essentially either erroneous or fraudulent) in this review.

Linde 2016 included a total of 22 trials, six of which were included in the individual patient database of the Acupuncture Trialists' Collaboration (ATC; Diener 2006; Jena 2008; Li 2012; Linde 2005; Streng 2006; Vickers 2004), an international collaborative network for high-quality randomised trials of acupuncture for chronic pain (Vickers 2010; Vickers 2012). We plan to use the same methods to analyse these data to ensure that we obtain the most precise estimate of treatment effect. Patient-level data for these six trials were obtained by the Acupuncture Trialists' Collaboration and thoroughly checked, including replicating all published analyses. For each trial, a linear regression model is created for each specified outcome measurement and time point. The predictor of interest is acupuncture versus control, and the model is adjusted for the outcome measurement at baseline and any variables used to stratify randomisation in that trial. As adjustment will be done on a trial level, analyses for all outcomes within the same trial will be adjusted for the same covariates, which will be clearly described in the methods and results text. Each model is then used to generate an adjusted mean outcome value for the acupuncture and control groups separately. The difference in the adjusted means between the acupuncture and control groups and the corresponding standard error for that difference will then be provided for inclusion in the review. Using the estimates generated

from patient-level data will allow for the inclusion of the maximum number of trials and outcomes in this review.

Assessment of risk of bias in included studies

We will use the Cochrane Collaboration's tool (RoB 1) for assessing risk of bias (Higgins 2011), and assess the following risk-of-bias domains.

- Sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data (up to three months after randomisation)
- Incomplete outcome data (four to 12 months after randomisation)
- Selective outcome reporting

We do not plan to include the domain, 'other potential threats to validity' in a formal manner, but will note if relevant flaws are detected.

In a first step, we will extract information relevant to making a judgment on a criterion from the original publication into an assessment table. We will enter any additional information from the study authors into the table, if it is available, along with an indication that this was unpublished information. At least two review authors will independently make a judgment on whether the risk of bias for each criterion is low, high or unclear. We will resolve any disagreements by discussion.

If studies have both blinded sham-control groups and unblinded comparison groups receiving drug treatment or no preventative treatment, in the risk of bias tables, we will report separate assessments per comparator group.

Criteria for a judgment of risk of bias for blinding are as follows.

- For blinding of participants and acupuncturists, this item should be scored 'low risk of bias' if the success of blinding was tested among the patients and acupuncturists, and it was successful. We will rate this item as being at 'high risk of bias' when blinding was not assessed, and 'unclear risk of bias' when it was not clear or not described in detail (e.g. sham acupuncture previously reported to have blinding abilities was used as the control group, but the success of blinding was not reported in the specific study).
- For blinding of outcome assessment, this item should be scored 'low risk of bias' if the success of blinding was tested among the outcome assessors, and it was successful. We will rate this item as being at 'high risk of bias' when blinding was not done, and 'unclear risk of bias' when it was not clear or not described in detail.
    - For patient-reported outcomes in which the patient is the outcome assessor (e.g. pain, disability), the blinding of outcome assessment is considered adequate if participant blinding is assessed as 'low risk of bias'.

We will rate the domain 'Incomplete outcome data (four to 12 months after randomisation)' as 'not applicable' for studies that did not follow participants for longer than three months.

We will summarise risk of bias for an outcome within a study (across domains). Overall risk of bias will be rated as:

- 'low' if all key domains are at low risk of bias;
- 'unclear' if one or more key domains are at unclear risk of bias; and
- 'high' if one or more key domains are at high risk of bias.

For cluster-randomised trials, we plan to include additional domains for recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials.

Assessment of the adequacy of the acupuncture intervention

We will also attempt to provide a crude estimate of the quality of acupuncture. At least two acupuncturists who are trained in acupuncture and have several years of practical experience will answer two questions. When assessing the adequacy of acupuncture, we will only provide the background and methods section to the acupuncturists. This can reduce the impact of knowledge of the results of studies on judgements. First, we will ask them how they would treat the participants included in the study. Answer options are 'exactly or almost exactly the same way', 'similarly', 'differently', 'completely differently' or 'could not assess' due to insufficient information (on acupuncture or on the participants). Second, we will ask them to rate their degree of confidence that acupuncture was applied appropriately on a 100 mm visual scale (with 0% = complete absence of evidence that the acupuncture was appropriate, and 100% = total certainty that the acupuncture was appropriate; Ernst 1998; Linde 2016). We will summarise the acupuncturists' assessments in a 'Characteristics of included studies' table under 'Methods' (for example, 'similarly/70%' indicates a study where the acupuncturist-reviewer would treat 'similarly' and is '70%' confident that acupuncture was applied appropriately).

Measures of treatment effect

Our primary efficacy outcome is headache frequency. As studies may report either migraine days, migraine attacks or headache days as a measure of headache frequency, we will use a system where various frequency measures can be used. As available, we will use absolute values for (in descending order of preference) migraine days, migraine attacks, or headache days. Due to the variability of outcomes, we will calculate standardised mean differences (SMD) as effect size measures. Negative values indicate better outcomes in the acupuncture group.

Our secondary efficacy outcome is the proportion of 'responders'. Response is defined as a reduction in migraine days of at least 50% compared to baseline (first preference). If the number of responders regarding migraine days is not available, we will use at least 50% reduction in number of migraine attacks (second preference), or at least 50% reduction in number of headache days (third preference). We will calculate risk ratios (RR) of having a response and 95% confidence intervals (CI) as effect size measures. Risk ratios greater than 1 indicate that there were more responders in the acupuncture group compared to the comparator group. We will base reporting of results on response in the review (in the Abstract, Plain language summary, the Results section and the Summary of findings tables) on the observed proportion in the control group (that is, the sum of participants with response divided by the sum of participants

randomised). We will base the expected proportion on the pooled risk ratio from meta-analysis.

For primary safety and tolerability outcomes, we will use the number of participants who dropped out due to adverse effects and the number and type of participants who reported at least one adverse event or effect. Further safety and tolerability outcomes are the number of participants who did not reach the primary endpoint and the number and type of participants with serious adverse events. If the number of events is typically low, we will calculate odds ratios (OR) instead of risk ratios. Odds ratios greater than 1 indicate more events (e.g. dropouts) in the acupuncture group.

When interpreting results, for dichotomous outcomes, we will present absolute risks in summary of findings tables as number of people with events per 1000 people receiving the intervention. For continuous outcomes, we will use different instruments to measure the same construct; SMDs may be used in meta-analysis for combining continuous data. We will present and interpret SMDs using generic effect size estimates. Guiding rules for interpreting SMDs are as follows: 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988).

Unit of analysis issues

The unit of analysis will preferably be the individual participant.

Cluster-randomised trials

The possibility of identifying cluster-randomised trials is small. However, if we find cluster-randomised trials, we will multiply the standard error of the effect estimate (from an analysis ignoring clustering) by the square root of the design effect (inflated variances), according to the method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2024). We will perform the meta-analysis using the inflated variances with the generic inverse variance method.

Trials with multiple arms

We will include all pair-wise comparisons of groups that meet the criteria for including studies. For example, in a three-arm trial, if participants are randomised to: (A) acupuncture, (B) sham acupuncture, (C) no treatment, then the pair-wise comparisons of acupuncture to sham acupuncture and acupuncture to no treatment will be included (Linde 2005).

Dealing with missing data

If publications reported study findings with insufficient detail or in an inconsistent manner, we will attempt to obtain further information from the study authors.

Regarding missing participant data due to dropout or loss to follow-up in the included studies, we will use the following strategies.

Efficacy outcomes

- For continuous measures, we will use, if available, the data from intention-to-treat analyses with missing values replaced; otherwise, we will use the presented data on available cases.
- For response, we will use the number of responders divided by the number of participants randomised to the respective group (counting missing information as non-response). In studies that compare acupuncture with drug treatment, we will use analyses of participants having at least started treatment as first preference, available cases as second preference, and intention-to-treat analyses as third preference.

Safety outcomes

- For all comparisons, we will use the number of participants randomised as the denominator for the following outcomes:
  - number of participants who dropped out due to adverse effects;
  - number of participants who did not reach the primary endpoint; and
  - number of participants who experienced serious adverse events;
- For the outcome, number of participants who reported adverse effects, we will use the number of participants who received at least one treatment as the denominator.

Assessment of heterogeneity

We will assess heterogeneity with the Chi^2 test (Deeks 2024), and the I^2 statistic (Higgins 2003).

We will interpret the Chi^2 test at a P value of 0.10 or less to indicate evidence of statistical heterogeneity. We will quantify heterogeneity by the I^2 statistic, which we will interpret as follows (Higgins 2024):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will order studies in forest plots according to their weight in meta-analysis. The weight depends on the standard errors of the point estimate (precision), which is dependent on sample size and variability or frequency of events. This gives readers a crude impression of whether more or less precise studies yield similar findings.

Data synthesis

We will include all eligible studies in the primary analysis regardless of the results of the risk of bias assessment.

For the purposes of summarising results, we will categorise the included studies according to control groups:

- comparisons with no acupuncture (acute treatment only or routine care);
- comparisons with sham acupuncture interventions;
- comparisons with preventative drug treatment.

If a study includes more than one acupuncture group, we will pool results of the groups so that participants in the control group will be counted more than once.

We will perform meta-analyses when the included studies have admissible homogeneity (e.g. if populations, interventions or outcomes are judged to be sufficiently similar to ensure a clinically meaningful answer). We will use a random-effects model and perform a sensitivity analysis with the fixed-effect model.

If meta-analysis is not possible, we will use alternative synthesis methods as outlined in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2024). Such as summarising effect estimates (e.g. median, interquartile range with box-and-whisker plots) or the combination of P values if there is no, or minimal, information reported beyond P values and the direction of effect.

Subgroup analysis and investigation of heterogeneity

To investigate potential sources of heterogeneity, we will perform subgroup analyses for the primary outcome, headache frequency, and for the secondary outcome, response, both after treatment and at follow-up. Considering the different mechanisms between manual acupuncture and electro-acupuncture, as well as the different theoretical systems of body acupuncture and micro-acupuncture, and the mixed biology of participants with more than one headache type, we will base predefined subgroup analyses on important potential prognostic factors:

- manual acupuncture versus electro-acupuncture;
- body acupuncture versus micro-acupuncture;
- studies including people with episodic migraine only versus studies including people with more than one headache type.

We will examine the association of the number of treatment sessions and acupuncture/electro-acupuncture with the treatment effect by performing meta-regression analysis. Meta-regression is performed directly only if at least 20 studies per comparison are available (Deeks 2024). If fewer studies are included (n is fewer than 20 but still greater than 10), we will conduct univariate regression first.

We will be cautious in the interpretation of subgroup analyses as advised in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2024). We will compare the magnitude of the effects between the subgroups by means of assessing the overlap of the CIs of the summary estimate. We will assess differences between subgroups using the Chi^2 test.

Sensitivity analysis

We will conduct sensitivity analyses in primary outcomes:

- unambiguously adequately concealed versus other;
- sham acupuncture with skin penetration versus without skin penetration;
- larger (sample size above median of the studies included in the analysis) versus smaller studies;
- fixed-effect model versus random-effects model.

We also plan to compare Chinese and non-Chinese studies to see if there were differences in the results between them, and to explore the potential reasons for any differences (such as educational background and experience of acupuncturist, acupuncture dose, and risk of bias).

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2024), using GRADEpro GDT. Two review authors (RYX, YTF) will independently rate the certainty of the evidence using the GRADE approach, which considers five factors (risk of bias, inconsistency of effect, indirectness, imprecision, and publication bias; Schünemann 2013). We will use the following GRADE Working Group grades of 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.

More details of GRADE assessment are illustrated in Appendix 3.

We will prepare three summary of findings tables comparing acupuncture versus no treatment or usual care, acupuncture versus sham acupuncture and acupuncture versus preventative drug treatment. The summary of findings tables will present the results for the following outcomes at short-term, medium-term and long-term follow-up:

- headache frequency;
- response;
- number of participants who dropped out due to adverse effects.

ACKNOWLEDGEMENTS

Thanks to all the authors of the previous version of our Cochrane review. This protocol was supported, during the presubmission phase, by the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS), which closed on 31 March 2023.

Editorial and peer-reviewer contributions

The following people conducted the editorial process for this protocol.

- Sign-off Editor (final editorial decision): Neil O'Connell, Department of Health Sciences at Brunel University London; Co-ordinating Editor of Cochrane PaPaS (closed in March 2023)
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial comments/guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service; Sara Hales-Brittain, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Denise Mitchell, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Zongshi Qin, Peking University Clinical Research Institute (clinical/content review); Hao Chen, College of Acupuncture and Chinese Tuina, Nanjing University of Chinese Medicine; Carlo Maria Giovanardi, Italian Federation of Acupuncture Societies (FISA), A.M.A.B Association of Medical Acupuncturists of Bologna; Helen Wakeford, Cochrane

(consumer review); Jennifer Hilgart and Clare Miles, Cochrane Evidence Production & Methods Directorate (methods reviews); Yuan Chi, Cochrane Campbell Global Ageing Partnership (search review); Rachel Richardson, Cochrane (methods review). One additional peer reviewer provided clinical/content review but chose not to be publicly acknowledged.

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APPENDICES

Appendix 1. MEDLINE via Ovid search strategy

1. exp Acupuncture Therapy/

2. (acupunct$ or electroacupunct$ or electro-acupunct$).mp.

3. 1 or 2

4. exp HEADACHE DISORDERS/

5. HEADACHE/

6. (headache$ or migrain$ or cephalgi$ or cephalalgi$).mp.

7. 4 or 5 or 6

8. 3 and 7

9. randomized controlled trial.pt.

10. controlled clinical trial.pt.

11. randomized.ab.

12. placebo.ab.

13. drug therapy.fs.

14. randomly.ab.

15. trial.ab.

16. groups.ab.

17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18. exp animals/ not humans.sh.

19. 17 not 18

20. 8 and 19

Appendix 2. China National Knowledge Infrastructure database (CNKI) search strategy

SU=('针灸'+'针刺'+'电针'+'手针') AND SU=('偏头痛') AND FT=('随机')

Appendix 3. GRADE assessment details

We will use the GRADE approach to assess the certainty of evidence. GRADE systematically evaluates study limitations, inconsistency, indirectness, imprecision, and publication bias. We will provide specific rationales for downgrading decisions, ensuring our approach is tailored to the context of our review. This allows for transparent and context-specific judgments in the grading process, reflecting the confidence we have in the evidence and its applicability to the research question.

Study limitations: the overall risk of bias will feed into GRADE. When assessing the study limitations of evidence on different outcomes, in addition to the overall risk of bias in each included study, we will also consider how much the study contributes to the overall effect for that outcome.

Inconsistency: inconsistency will consider not only I^2 statistics but also the magnitude and direction of effect estimates, overlap in confidence intervals, and P values from heterogeneity tests. An I^2 statistic greater than 50% without a reasonable explanation will prompt us to downgrade the evidence by one level. If the variability in results is such that it significantly impedes interpretation, a two-level downgrade may be necessary. These judgments will be made considering the potential impact of study characteristics on effect estimates and the absolute risk reduction observed across different subgroups. The final decision on downgrading for inconsistency will integrate both statistical measures and clinical judgment.

Indirectness: we will evaluate the relevance of Population, Intervention, Comparator, and Outcome, commonly named PICO. Evidence that does not fully align with our PICO but remains relevant will be downgraded by one level. If the evidence differs entirely from our PICO, we will implement a two-level downgrade.

Imprecision: one way to evaluate imprecision is to examine the size of the confidence interval (CI) and determine whether the study meets the Optimal Information Size (OIS). We will downgrade evidence certainty for imprecision if the 95% CI is wide, indicating substantial uncertainty, or if the sample size does not meet OIS. A one-level downgrade is appropriate when the CI suggests potential benefits and harms, and a two-level downgrade is applied when the evidence is based on few events with very wide CIs, reflecting significant possible benefits and serious harms.

Publication bias: a one-level downgrade may be considered if there is suspected publication bias. Publication bias can be indicated by funnel plot asymmetry or other tests. A two-level downgrade is applied in cases of strong evidence of publication bias significantly impacting results.

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DECLARATIONS OF INTEREST

RYX: none known

KL: no relevant interests; involved in two studies included in the previous version of the review (Linde 2005; Streng 2006). Both studies were funded by German Social Health Insurances (Ersatzkassen); German Social Health Insurances (Ersatzkassen) pay for any health expenditures of their members; the funders had no role in the design, data collection, analysis, or interpretation of the studies.

TF: Participation in advisory boards: TEVA Pharmaceuticals, Novartis, Lundbeck. Received speaker's honoraria: Novartis, TEVA Pharmaceuticals, Lilly. Delivers talks on migraine/treatment of migraine including use of CGRP-antibodies in the prophylactic treatment of migraine, migraine genetics at educational events, meetings, congresses. Works as Head of the Outpatient Headache Unit of the Centre of Neurology, University of Tuebingen (2013-2018). Head of research group 'Migraine and primary Headache Disorders', Hertie-Institute for Clinical Brain Research, Tuebingen (2014-2022). Works as Head of Department of Neurology, Klinikum Passau, Germany (2018-). Active member of the DMKG (Deutsche Migräne und Kopfscherzgesellschaft, German Society for Migraine and Headache); until 2018 served as "Regionalbeauftragter Baden-Wuerttemberg"; since 2022, board member ("Kooptiertes Präsidiumsmitglied"). Involved in these studies - Amici (https://clinicaltrials.gov/ct2/show/NCT02185703) (sponsor: Chordate Medical), PredCh (doi: 10.1016/S1474-4422(20)30363-X), REGAIN (doi: 10.1212/WNL.0000000000006640) and EVOLVE-2 (doi: https://10.1177/0333102418779543) (sponsor: Lilly), GM-11 (www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/gm-11-gammacore-nvns-episodic-migraine-study/) (sponsor: Gammacore), CAMG334A2301 (www.clinicaltrialsregister.eu/ctr-search/trial/2016-002211-18/NL) (sponsor: Novartis), HeMiLa (IIT; https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-003223-30/DE).

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Review authors who have been or are currently involved in a study that could be included in the review, will not make study eligibility decisions about, extract data from, carry out the risk of bias assessment for, or perform GRADE assessments of that study.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK

  Cochrane Infrastructure funding to the Cochrane Pain, Palliative and Supportive Care Review Group (PaPaS)