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Acupuncture for the prevention of episodic migraine (Review)

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[Intervention Review]

Acupuncture for the prevention of episodic migraine

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ABSTRACT

Background

Acupuncture is often used for migraine prevention but its effectiveness is still controversial. We present an update of our Cochrane review from 2009.

Objectives

To investigate whether acupuncture is a) more effective than no prophylactic treatment/routine care only; b) more effective than sham (placebo) acupuncture; and c) as effective as prophylactic treatment with drugs in reducing headache frequency in adults with episodic migraine.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL: 2016, issue 1); MEDLINE (via Ovid, 2008 to January 2016); Ovid EMBASE (2008 to January 2016); and Ovid AMED (1985 to January 2016). We checked PubMed for recent publications to April 2016. We searched the World Health Organization (WHO) Clinical Trials Registry Platform to February 2016 for ongoing and unpublished trials.

Selection criteria

We included randomized trials at least eight weeks in duration that compared an acupuncture intervention with a no-acupuncture control (no prophylactic treatment or routine care only), a sham-acupuncture intervention, or prophylactic drug in participants with episodic migraine.

Data collection and analysis

Two reviewers checked eligibility; extracted information on participants, interventions, methods and results, and assessed risk of bias and quality of the acupuncture intervention. The primary outcome was migraine frequency (preferably migraine days, attacks or headache days if migraine days not measured/reported) after treatment and at follow-up. The secondary outcome was response (at least 50%

frequency reduction). Safety outcomes were number of participants dropping out due to adverse effects and number of participants reporting at least one adverse effect. We calculated pooled effect size estimates using a fixed-effect model. We assessed the evidence using GRADE and created 'Summary of findings' tables.

Main results

Twenty-two trials including 4985 participants in total (median 71, range 30 to 1715) met our updated selection criteria. We excluded five previously included trials from this update because they included people who had had migraine for less than 12 months, and included five new trials. Five trials had a no-acupuncture control group (either treatment of attacks only or non-regulated routine care), 15 a sham-acupuncture control group, and five a comparator group receiving prophylactic drug treatment. In comparisons with no-acupuncture control groups and groups receiving prophylactic drug treatment, there was risk of performance and detection bias as blinding was not possible. Overall the quality of the evidence was moderate.

Comparison with no acupuncture

Acupuncture was associated with a moderate reduction of headache frequency over no acupuncture after treatment (four trials, 2199 participants; standardised mean difference (SMD) -0.56; 95% CI -0.65 to -0.48); findings were statistically heterogeneous (I^2 = 57%; moderate quality evidence). After treatment headache frequency at least halved in 41% of participants receiving acupuncture and 17% receiving no acupuncture (pooled risk ratio (RR) 2.40; 95% CI 2.08 to 2.76; 4 studies, 2519 participants) with a corresponding number needed to treat for an additional beneficial outcome (NNTB) of 4 (95% CI 3 to 6); there was no indication of statistical heterogeneity (I^2 = 7%; moderate quality evidence). The only trial with post-treatment follow-up found a small but significant benefit 12 months after randomisation (RR 2.16; 95% CI 1.35 to 3.45; NNT 7; 95% 4 to 25; 377 participants, low quality evidence).

Comparison with sham acupuncture

Both after treatment (12 trials, 1646 participants) and at follow-up (10 trials, 1534 participants), acupuncture was associated with a small but statistically significant frequency reduction over sham (moderate quality evidence). The SMD was -0.18 (95% CI -0.28 to -0.08; I^2 = 47%) after treatment and -0.19 (95% CI -0.30 to -0.09; I^2 = 59%) at follow-up. After treatment headache frequency at least halved in 50% of participants receiving true acupuncture and 41% receiving sham acupuncture (pooled RR 1.23, 95% CI 1.11 to 1.36; I^2 = 48%; 14 trials, 1825 participants) and at follow-up in 53% and 42%, respectively (pooled RR 1.25, 95% CI 1.13 to 1.39; I^2 = 61%; 11 trials, 1683 participants; moderate quality evidence). The corresponding NNTBs are 11 (95% CI 7.00 to 20.00) and 10 (95% CI 6.00 to 18.00), respectively. The number of participants dropping out due to adverse effects (odds ratio (OR) 2.84; 95% CI 0.43 to 18.71; 7 trials, 931 participants; low quality evidence) and the number of participants reporting adverse effects (OR 1.15; 95% CI 0.85 to 1.56; 4 trials, 1414 participants; moderate quality evidence) did not differ significantly between acupuncture and sham groups.

Comparison with prophylactic drug treatment

Acupuncture reduced migraine frequency significantly more than drug prophylaxis after treatment (SMD -0.25; 95% CI -0.39 to -0.10; 3 trials, 739 participants), but the significance was not maintained at follow-up (SMD -0.13; 95% CI -0.28 to 0.01; 3 trials, 744 participants; moderate quality evidence). After three months headache frequency at least halved in 57% of participants receiving acupuncture and 46% receiving prophylactic drugs (pooled RR 1.24; 95% CI 1.08 to 1.44) and after six months in 59% and 54%, respectively (pooled RR 1.11; 95% CI 0.97 to 1.26; moderate quality evidence). Findings were consistent among trials with I^2 being 0% in all analyses. Trial participants receiving acupuncture were less likely to drop out due to adverse effects (OR 0.27; 95% CI 0.08 to 0.86; 4 trials, 451 participants) and to report adverse effects (OR 0.25; 95% CI 0.10 to 0.62; 5 trials 931 participants) than participants receiving prophylactic drugs (moderate quality evidence).

Authors' conclusions

The available evidence suggests that adding acupuncture to symptomatic treatment of attacks reduces the frequency of headaches. Contrary to the previous findings, the updated evidence also suggests that there is an effect over sham, but this effect is small. The available trials also suggest that acupuncture may be at least similarly effective as treatment with prophylactic drugs. Acupuncture can be considered a treatment option for patients willing to undergo this treatment. As for other migraine treatments, long-term studies, more than one year in duration, are lacking.

PLAIN LANGUAGE SUMMARY

Acupuncture for preventing migraine attacks

Bottom line

The available evidence suggests that a course of acupuncture consisting of at least six treatment sessions can be a valuable option for people with migraine.

Background

Individuals with migraine have repeated attacks of severe headache, usually just on one side and often with vomiting. Acupuncture is a therapy in which thin needles are inserted into the skin at particular points. It originated in China, and is now used in many countries to treat people with migraine. We evaluated whether acupuncture reduces the number of episodes of migraine. We looked at the number of people in whom the number of migraine days per month was reduced by half or more than half.

Key results

For this update, we reviewed 22 trials with 4985 people, published up to January 2016. We omitted five trials from the original review because they included people who had had migraine for less than 12 months. We included five new trials in this update.

In four trials, acupuncture added to usual care or treatment of migraine on onset only (usually with pain-killers) resulted in 41 in 100 people having the frequency of headaches at least halved, compared to 17 of 100 people given usual care only.

In 15 trials, acupuncture was compared with 'fake' acupuncture, where needles are inserted at incorrect points or do not penetrate the skin. The frequency of headaches halved in 50 of 100 people receiving true acupuncture, compared with 41 of 100 people receiving 'fake' acupuncture. The results were dominated by three good quality large trials (with about 1200 people) showing that the effect of true acupuncture was still present after six months. There were no differences in the number of side effects of real and 'fake' acupuncture, or the numbers dropping out because of side effects.

In five trials, acupuncture was compared to a drug proven to reduce the frequency of migraine attacks, but only three trials provided useful information. At three months, headache frequency halved in 57 of 100 people receiving acupuncture, compared with 46 of 100 people taking the drug. After six months, headache frequency halved in 59 of 100 people receiving acupuncture, compared with 54 of 100 people taking the drug. People receiving acupuncture reported side effects less often than people receiving drugs, and were less likely to drop out of the trial.

Our findings about the number of days with migraine per month can be summarized as follows. If people have six days with migraine per month on average before starting treatment, this would be reduced to five days in people receiving only usual care, to four days in those receiving fake acupuncture or a prophylactic drug, and to three and a half days in those receiving true acupuncture.

Quality of the evidence

Overall the quality of the evidence was moderate.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Acupuncture compared to no treatment/usual care

Patient or population: people with episodic migraine
Setting: primary care or outpatient care
Intervention: acupuncture
Comparison: no treatment/usual care

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with no treatment/ usual care / Risk with Acupuncture				
Headache frequency (after treatment) assessed with days per month follow-up: median 3 months	Headache frequency was 0.56 SDs (-0.65 to -0.48) lower than in the groups receiving no/usual treatment	-	2199 (4 RCTs)	⊕⊕⊕◯ MODERATE [12]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference. Size of difference open to change with more trials
Headache frequency (follow-up) assessed with days per month follow-up: 12 months	Headache frequency was 0.36 SDs (-0.59 to -0.12) lower than in the groups receiving no/usual treatment	-	284 (1 RCT)	⊕⊕◯◯ LOW [23]	Only single large trial available. As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference. Size of difference open to change with more trials
Response (after treatment) assessed with proportion of participants with at least 50% headache	Study population	RR 2.40 (2.08 to 2.76)	2519 (4 RCTs)	⊕⊕⊕◯ MODERATE [2]	No blinding, variable care in control groups, variable size of effects, but moderate to large effects in all three

frequency reduction follow-up: median 3 months						larger trials
	171 per 1000	410 per 1000 (355 to 472)				
Response (follow-up) assessed with proportion of participants with at least 50% headache frequency reduction follow-up: 12 months	Study population		RR 2.16 (1.35 to 3.45)	377 (1 RCT)	⊕⊕◯◯ LOW [2,3]	Only single large trial available
	98 per 1000	212 per 1000 (133 to 339)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Interventions in control groups and study findings variable (I^2 = 57%; Chi^2 = 6.96, P value = 0.07), but effects moderate to large in all three larger trials
[2] Downgraded once: no blinding
[3] Downgraded once: only one study

BACKGROUND

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews [Issue 1, 2009] on acupuncture for migraine (Linde 2009).

Description of the condition

Migraine is a disorder with recurrent headaches manifesting in attacks lasting from four to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea, photophobia or phonophobia, or any combination of all three (IHS 2013). Epidemiological studies have consistently shown that migraine is a common disorder with a one-year prevalence of around 10% to 12% and a lifetime prevalence of between 15% and 20% (Oleson 2007). In Europe, the economic cost of migraine is estimated at EUR 27 billion per year (Andlin-Sobocki 2005). Migraine is subclassified into the more frequent episodic migraine (fewer than 15 days with migrainous headaches per month) and the less frequent chronic migraine (more than 15 days per month). Most people with migraine can be adequately managed by treatingof acute headaches alone, but a relevant minority need prophylactic interventions, as their attacks are either very frequent or are insufficiently controlled by acute therapy. Several drugs, such as propranolol, metoprolol, flunarizine, valproic acid and topiramate, have been shown to reduce attack frequency in some people (Dodick 2007; Linde M 2013a; Linde M 2013b), however, all these drugs are associated with adverse effects. Dropout rates in most clinical trials are high, suggesting that the drugs are not well accepted by patients. There is some evidence that behavioural interventions such as relaxation or biofeedback are beneficial (Holroyd 1990; Nestoriuc 2007), but additional effective, low-risk treatments are clearly desirable.

Description of the intervention

Acupuncture in the context of this review is defined as the needling of specific points of the body. It is one of the most widely used complementary therapies in many countries (Bodeker 2005). For example, according to a population-based survey in 2002 in the United States of America (USA), 4.1% of respondents reported lifetime use of acupuncture, and 1.1% reported recent use (Burke 2006). A similar survey in Germany performed in the same year found that 8.7% of adults between 18 and 69 years of age had received acupuncture treatment in the previous 12 months (Härtel 2004). Acupuncture was originally developed as part of Chinese medicine wherein the purpose of treatment was to bring the patient back to the state of equilibrium postulated to exist prior to illness (Endres 2007). Some acupuncture practitioners have dispensed with these concepts and understand acupuncture in terms of conventional neurophysiology. 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

Many studies have shown that acupuncture has short-term effects on a variety of physiological variables relevant to analgesia (Bäcker 2004; Endres 2007). However, it is unclear to what extent these observations from experimental settings are relevant to the long-term effects reported by practitioners. It is assumed 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). While there is little doubt that acupuncture interventions cause neurophysiological changes in the organism, the traditional concepts of acupuncture involving specifically located points on a system of 'channels' called meridians are controversial (Kaptchuk 2002). As for many non-pharmacological interventions, it is difficult to create sham interventions for acupuncture which are both indistinguishable and physiologically inert. This is due both to technical reasons and the unclear mechanism of action. Consequently, trials using sham acupuncture controls must be interpreted carefully, as sham treatments might not be inactive placebos, while trials comparing acupuncture with no prophylactic treatment, prophylactic drugs or other interventions must also be interpreted carefully, as they have a higher risk of bias due to lack of blinding.

Why it is important to do this review

Despite acupuncture's widespread use its effectiveness is still discussed controversially (Da Silva 2015, McGeeney 2015). Since the publication of the previous version of our Cochrane review (Linde 2009) a number of new trials have been published. Therefore, an update of the review was necessary. To sharpen the focus of our review we narrowed our selection criteria. In particular, we now focus on episodic migraine.

OBJECTIVES

To investigate whether acupuncture is a) more effective than no prophylactic treatment/routine care only; b) more effective than 'sham' (placebo) acupuncture; and c) as effective as prophylactic treatment with drugs in reducing headache frequency in patients with episodic migraine.

METHODS

Criteria for considering studies for this review

Types of studies

We included controlled trials investigating the prophylactic effect of acupuncture in which allocation to treatment was explicitly randomized, and in which participants were followed up for at least eight weeks after randomisation. We excluded trials in which a clearly inappropriate method of randomisation was used, for example, open alternation.

Types of participants

We included trials in which study participants had been diagnosed with episodic migraine (the word episodic did not have to be mentioned in the report explicitly; see exclusion criteria below to exclude trials focusing on chronic migraine). Studies focusing on migraine but including participants with additional tension-type headache were included. We included studies including 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.
The duration of the condition had to be longer than one year in the great majority (more than 80%) of participants. This criterion was considered met if:

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

We excluded trials in patients with chronic migraine, chronic daily headache or in which at baseline more than half of participants had more than 15 days with migrainous headache per month. We also excluded trials in which there was no information of the duration of headache complaints.

Changes to previous version

In this update of the review we have excluded trials focusing on chronic migraine, as the definition of chronic migraine is still debated and the separation from other diagnoses, for example headache due to medication overuse, is difficult (in the previous version of this review (Linde 2009) we were not aware of any trials on chronic migraine and they were not explicitly excluded). In the current update we have also excluded trials in which a relevant proportion of participants had been suffering from migraine for less than one year or in which duration was unclear.

Types of interventions

Experimental interventions

- Any treatment involving needle insertion (with or without manual or electrical stimulation) at acupuncture points, pain points or trigger points, described as acupuncture. The planned treatment course must have had at least six treatment sessions, and been given at least once per week. Trials with individualised strategies were included if the median or mean number of treatments was at least six sessions, and there was no reason to believe that treatments were given less frequently than once per week in the majority of participants.

- We excluded studies that:
    - exclusively investigated acupuncture at specific 'micro-systems' (e.g. scalp or ear acupuncture), although we included trials using micro-system points in addition to body acupuncture;
    - 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 other than treatment of acute migraine attacks or routine care (which typically includes treatment of acute attacks, but might also include other treatments; however, trials normally require that no new experimental or standardized treatment be initiated during the trial period).
- Sham interventions (interventions mimicking 'true' acupuncture/true treatment, but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or correct point location).
- Prophylactic pharmacological treatment (for example, β-blocking agents, calcium channel antagonists, anti-epileptic drugs) given for at least eight weeks.
- We excluded trials comparing acupuncture to food supplements, herbal drugs or combinations of herbal drugs, and trials that only compared different forms of acupuncture.

Changes to previous version

In the previous version of the review (Linde 2009) we included trials using any prophylactic treatment other than acupuncture as comparison. With a slowly increasing number of trials using a wide range of different treatments (mainly various herbal medicines) we decided to concentrate on conventional prophylactic pharmacological treatment to keep the review focused. We have defined a minimum number and frequency of acupuncture treatment sessions to ensure that treatments meet basic quality criteria.

Types of outcome measures

We included studies if they measured at least one of the following outcome measures for at least eight weeks after randomisation:

- headache frequency (attacks, days, hours, headache-free days) per defined time period;
- response (≥ 50% frequency reduction documented in a headache diary);
- disability or quality of life with a validated measure.

We excluded trials that:

- focussed on the treatment and measurement of acute attacks;
- reported only measures such as "total effectiveness rate" (e.g. proportion of participants healed, much improved, improved, unchanged);
- reported only physiological or laboratory parameters;
- had outcome measurement periods of less than eight weeks (from randomisation to final observation).

Changes to previous version

We have defined outcome measures more precisely to ensure that measurement methods meet current standards of migraine research.

Primary outcomes

The primary efficacy outcome of our systematic review was headache frequency at completion of treatment and at follow-up. The primary safety/acceptability outcomes were the number of participants dropping out due to adverse effects and the number of participants reporting at least one adverse event or effect (see Measures of treatment effect for details).

Secondary outcomes

The secondary efficacy outcome of our systematic review was the proportion of 'responders' at completion of treatment and at follow-up.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases without language restrictions (date of the last search 20 January 2016):

- Cochrane Central Register of Controlled Trials (CENTRAL; *The Cochrane Library* 2016, Issue 1), searched from 2008 to 2016;
- MEDLINE (via Ovid) 2008 to week 1 of January 2016;
- EMBASE (via Ovid) 2008 to 19 January 2016;
- AMED (via OVID) 1985 to January 2016.

The search strategies are reported in Appendix 1. In addition, the first author checked PubMed monthly for new publications, screening all hits for 'acupuncture AND (headache OR migraine)' (last search 12 April 2016). For previous versions of this review (Melchart 2001; Linde 2009) we had searched the Cochrane Complementary Medicine Field Trials Register (whose results are now included in CENTRAL without relevant delay) and the Cochrane Pain, Palliative & Supportive Care Trials Register (no longer updated).

Searching other resources

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/) and ClinicalTrials.gov (ClinicalTrials.gov) for completed or ongoing trials using the search string 'acupuncture AND (headache OR migraine)'. The last search was on February 10, 2016. We also searched the reference lists of all eligible studies for additional studies.

Data collection and analysis

Selection of studies

Two review authors screened all abstracts identified by the updated search and excluded those that were clearly irrelevant (for example, studies focusing on other conditions, reviews, etc.). We obtained full texts of all remaining references and, again, screened them to exclude clearly irrelevant papers. At least two review authors formally checked all remaining articles and all trials included in the previous version of our review (Linde 2009) for eligibility according to the above-mentioned selection criteria. We resolved any disagreements by discussion.

Data extraction and management

At least two review authors independently extracted information on participants, methods, interventions, outcomes and results using a specially designed form before entry into Review Manager (RevMan) (RevMan 2014). In particular, we extracted exact diagnoses; headache classifications used; number and type of centres; age; sex; duration of disease; number of participants randomized, 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 de-chi (an irradiating feeling considered to indicate effective needling); number, training and experience of acupuncturists); and details of control interventions (sham technique, type and dosage of drugs). For details regarding methodological issues and study results, see below. Where necessary, we sought additional information from the first or corresponding authors of the included studies.

For six trials (Diener 2006; Jena 2008; Li 2012; Linde K 2005; Streng 2006; Vickers 2004) included in the individual patient database of the Acupuncture Trialists' Collaboration (ATC), an international collaborative network for high quality randomized trials of acupuncture for chronic pain (see Vickers 2010; Vickers 2012), we obtained uniformly re-analysed summary data for numeric variables and the number of responders for calculation of effect sizes. We used these data to ensure that we obtained the most precise estimate of treatment effect. For each trial, we created an analysis of covariance (ANCOVA) model for each numeric outcome at each time point and adjusted for the baseline value of that outcome, treatment group (acupuncture or control), and any variables that were used to stratify randomisation in the original trial. Using this model, we calculated the adjusted mean outcome values for each group (acupuncture and control), and we used the standard error for the effect of treatment from the ANCOVA model to calculate the standard deviation for the difference in adjusted means. Therefore, effect sizes calculated in our analyses might to some degree deviate from those in the original publications of the six trials. Use of raw data also allowed us to calculate response rates, such as for a 50% reduction in pain, even if this was not reported in the original trial publication.

Assessment of risk of bias in included studies

For the assessment of study quality, the risk of bias approach for Cochrane reviews was used (Higgins 2011). We used the following six separate criteria:

- adequate sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data addressed (up to three months after randomisation);
- incomplete follow-up outcome data addressed (four to 12 months after randomisation);
- free of selective reporting.

We did not include the item 'other potential threats to validity' in a formal manner, but noted if relevant flaws were detected.

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

For the first five criteria (above), we followed the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For 'selective reporting', we decided to use a more liberal definition. Headache trials typically measure a multiplicity of headache outcomes at several time points using diaries, and there is a plethora of slightly different outcome measurement methods. While a single primary endpoint is sometimes predefined, the overall pattern of a variety of outcomes is necessary to get a clinically interpretable picture. If we had applied the strict guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions*, almost all trials would have been rated 'unclear' for 'selective reporting'. We considered trials as having a low risk of bias for selective reporting if they reported the results of the most relevant headache outcomes assessed (typically a frequency measure, intensity, analgesic use and response) for the most relevant time points (end of treatment and, if done, follow-up), and if the outcomes and time points reported made it unlikely that study investigators had picked them out because they were particularly favourable or unfavourable.

If trials had both blinded sham control groups and unblinded comparison groups receiving no prophylactic treatment or drug treatment, in the risk of bias tables, the 'Judgement' column always relates to the comparison with sham interventions. In the 'Description' column, we included the assessment for the other comparison group(s). As the risk of bias table does not include a 'not applicable' option, we rated the item 'incomplete follow-up outcome data addressed (four to 12 months after randomisation)? ' as 'unclear' for trials that did not follow participants longer than three months.

We also assessed the adequacy of concealment of allocation according to the criteria of the ATC (Vickers 2010) which are stricter than those in the *Cochrane Handbook for Systematic Reviews of Interventions*. In particular, in the case of envelope randomisation, investigators must have established and described detailed procedures to ensure that allocation could neither be predicted nor changed post hoc. For example, there should have been procedures to prevent investigators resealing and reusing an envelope after it had been opened (e.g. envelopes were held by an independent party). As the level of information needed for this assessment was often not available in publications, we contacted study authors for clarification. If information was not available, we did not consider adequacy of concealment to be "unambiguously adequate".

Assessment of the adequacy of the acupuncture intervention

We also attempted to provide a crude estimate of the quality of acupuncture. At least two reviewers who are trained in acupuncture and have several years of practical experience (GA, BB, YF, AW) answered two questions. First, they were asked how they would treat the participants included in the study. Answer options were '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, they were asked to rate their degree of confidence that acupuncture was applied in an appropriate manner 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). A member of the review team (AW) proposed the latter method , which was used in a systematic review of clinical trials

of acupuncture for back pain (Ernst 1998). In the Characteristics of included studies table, the acupuncturists' assessments are summarized under 'Methods' (for example, "similarly/70%" indicates a trial where the acupuncturist-reviewer would treat 'similarly' and is '70%' confident that acupuncture was applied appropriately).

Measures of treatment effect

Main analysis

Our primary efficacy outcome was headache frequency at completion of treatment and at follow-up (closest to six months after randomisation). As studies may report either attacks, migraine days or headache days as a measure of headache frequency, we used a system where various frequency measures could be used. As available, we used (in descending order of preference) absolute values from four-week periods or other periods for (again, in descending order of preference) migraine days, migraine attacks or headache days. Due to the variability of outcomes, standardized mean differences (SMD) were calculated as effect size measures. Negative values indicate better outcomes in the acupuncture group.

Our secondary efficacy outcome was the proportion of 'responders' at completion of treatment and at follow-up (closest to six months after randomisation). Response was defined as a reduction in migraine days of at least 50% compared to baseline. If the number of responders regarding migraine days was not available we used at least 50% reduction in number of migraine attacks (second preference), or at least 50% reduction in number of headache days (third preference). We calculated 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. When reporting results on response in this review (in the abstract, the plain language summary, the results section and the 'Summary of findings' tables) these are based on the observed proportion (sum of participants with response divided by the sum of participants randomized) in the control group and the expected proportion based on the pooled risk ratio from meta-analysis.

As primary safety/acceptability outcomes we used the number of participants dropping out due to adverse effects and the number of participants reporting at least one adverse event or effect. Further safety/acceptability outcomes were the number of participants not reaching the primary endpoint (we originally had planned to extract the number of participants dropping out but this proved difficult due to multiple measurement time points and reporting issues) and the number of participants with serious adverse events. As the number of events was typically low we calculated odds ratios (OR) instead of risk ratios. Odds ratios greater than 1 indicate more events (e.g. dropouts) in the acupuncture group.

Time window analysis

In the previous version of this review (Linde 2009) we analysed findings according to the four time windows described below. This had the advantage that measurement times used were similar across trials. However, it had two disadvantages. Firstly, duration of treatment periods was quite variable, so while in some trials treatment was already completed (e.g. at 8 weeks) it was still ongoing (e.g. until week 16) in others; secondly, four time windows for each outcome made the 'Summary of findings' tables very complex. Therefore, in this update we have reported the time window analyses as additional analyses only.

We used the following time windows:

- up to eight weeks/two months after randomisation;
- three to four months after randomisation;
- five to six months after randomisation; and
- more than six months after randomisation.

If more than one data point was available for a given time window, we used: for the first time window, preferably data closest to eight weeks; for the second window, data closest to the four weeks after completion of treatment (for example, if treatment lasted eight weeks, data for weeks nine to 12); for the third window, data closest to six months; and for the fourth window, data closest to 12 months.

The following outcomes were used in the time windows analysis.

- Frequency of migraine attacks (means and standard deviations) per four-week period. Mean differences were calculated as effect size measures
- Response (risk ratio of having a response).
- Number of migraine days (means and standard deviations) per four-week period (mean differences).
- Number of headache days (means and standard deviations) per four-week period (mean differences).
- Headache intensity (any measures available, extraction of means and standard deviations, calculation of SMDs).
- Frequency of analgesic use (any continuous or rank measures available, extraction of means and standard deviations, calculation of SMDs).
- Headache scores (SMDs)

All these outcomes rely on participant reports, mainly collected in headache diaries.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

If publications reported study findings with insufficient detail or in an inconsistent manner we attempted 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 used the following strategies.

- Efficacy outcomes:
    - for comparisons of acupuncture with no acupuncture and sham we used for continuous measures, if available, the data from intention-to-treat analyses with missing values replaced; otherwise, we used the presented data on available cases;
    - for response we used the number of responders divided by the number of participants randomized to the respective group (counting missing information as non-response). In studies comparing acupuncture with drug treatment, we used as first preference 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 used the number of participants randomized as denominator for the outcomes number of participants dropping out due to adverse effects, not reaching the primary endpoint and experiencing serious adverse events;
    - for the outcome number of participants reporting adverse effects we used the number of participants having received at least one treatment as denominator.

Assessment of heterogeneity

We assessed heterogeneity with the Chi² test (Deeks 2011) and the I² statistic (Higgins 2003).

Assessment of reporting biases

In forest plots studies are ordered 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/frequency of events. This gives readers a crude impression whether more and less precise trials yield similar findings.

Data synthesis

For the purposes of summarizing results, we categorized the included trials according to control groups:

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

If a trial included more than one acupuncture group, we pooled results of the groups so that participants in the control group were counted more than once.

We calculated pooled fixed-effect estimates, their 95% confidence intervals, the Chi^2 test for heterogeneity and the I^2 statistic. If the P value of the Chi² test for heterogeneity was less than 0.2 or I² greater than 40%, or both, we also reported random-effects estimates.

Change to previous version

Based on the recommendation of the statistician in our team (AV) we have used fixed-effect models for calculating pooled estimates in this updated review. This is primarily because the fixed-effect analysis constitutes a valid test of the null hypothesis. Moreover, due to very large discrepancies in sample size, a random-effects model would have resulted in participants in small studies being given greater weight that participants in large studies. . Nonetheless, if the P value of the Chi² test for heterogeneity was less than 0.2 or I² was greater than 40%, or both, we have also reported random-effect estimates.

We used the GRADE approach to assess the quality of evidence related to each of the key outcomes as appropriate (GRADEpro GDT 2015; Schünemann 2011). GRADE Working Group grades of evidence are:

- High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: 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 quality: our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect.
- Very low quality: we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

To investigate potential sources of heterogeneity and the robustness of our findings we performed subgroup analyses for the primary outcome, headache frequency, and for the secondary outcome, response, both after treatment and at follow-up for the comparison vs. sham (the number of trials being too small for the other two comparisons) for four variables. These variables were selected after reviewing the trials qualitatively but before running analyses: unambiguously adequate randomisation vs. other; larger (sample size above median of the trials included in the analysis) vs. smaller trials; number of treatment sessions up to 12 vs. 16 and more; and sham penetrating the skin vs. non-penetrating sham.

RESULTS

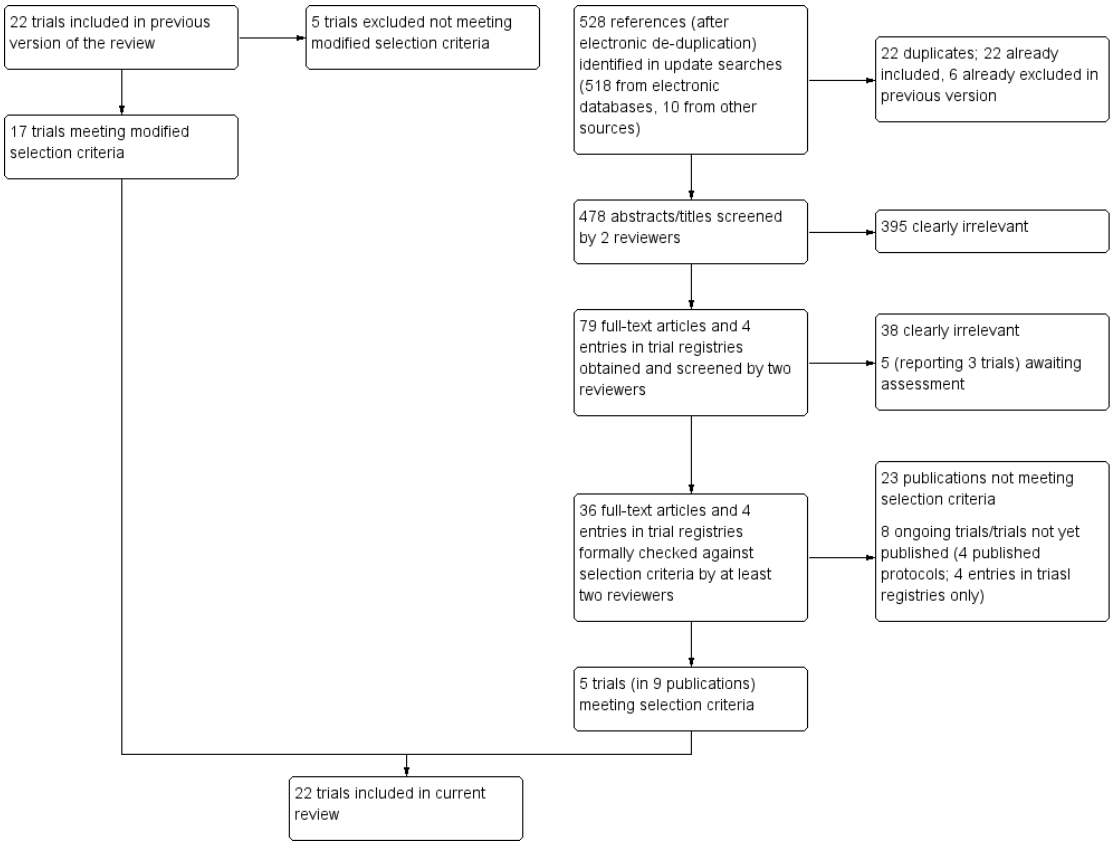
Description of studies

Results of the search

Update searches identified 528 hits (518 by database searches, six by checking references and alerts, and four from checking entries in

trials registries not identified otherwise). Thirty-six full-text publications and four entries in clinical trial registries that were deemed potentially eligible were formally checked against the eligibility criteria (see Figure 1). As we had modified selection criteria for this update, we reassessed the 22 trials included in the previous version for eligibility. Five new trials met the revised selection criteria (Facco 2013; Li 2012; Wallasch 2012; Wang 2015; Zhao 2014), while five trials included in the previous version or our review had to be excluded (Baust 1978; Doerr-Proske 1985; Dowson 1985; Henry 1985; Wylie 1997; see Characteristics of excluded studies).

Figure 1. Flow diagram



Included studies

General characteristics

Twenty-two trials including 4985 participants in total (median 71, range 30 to 1715) met our selection criteria; 18 studies were two-armed, two were three-armed and a further two were four-armed (see Characteristics of included studies). All trials used parallel-group designs; there were no cross-over studies. Fifteen trials included a sham acupuncture control group (Alecrim 2005; Alecrim 2006; Alecrim 2008; Ceccherelli 1992; Diener 2006; Facco 2008; Li 2012; Linde K 2005; Linde M 2004; Vincent 1989; Wallasch

2012; Wang 2015; Weinschütz 1993; Weinschütz 1994; Zhao 2014), five a no-acupuncture control group (Facco 2008; Jena 2008; Linde K 2005; Linde M 2000; Vickers 2004), and five a comparator group receiving prophylactic drug treatment (Allais 2002; Diener 2006; Facco 2013; Hesse 1994; Streng 2006). Sixteen trials were performed in a single centre and six were multicentre trials. Seven trials were performed in Germany, four in Italy, three in Brazil, two each in China, Sweden and the UK, and one each in Denmark and Australia. Seven trials were published between 1989 and 2002 and 15 between 2004 and 2015. We tried to contact corresponding authors of all trials at least once (either for previous versions of this review or for the current update). For one trial we could not obtain a valid contact address (Hesse 1994) and three study authors or co-authors did not provide additional information before completion of this update (Wallasch 2012; Weinschütz 1993; Weinschütz 1994). For the remaining 18 trials we obtained some additional information. Detailed additional data for effect size calculation was obtained from study authors or from the individual patient database of the ATC for 11 trials (Alecrim 2005; Alecrim 2006; Alecrim 2008; Allais 2002; Diener 2006; Jena 2008; Li 2012; Linde K 2005; Streng 2006; Vickers 2004; Vincent 1989).

Study participants

Fifteen trials included participants diagnosed as having migraine with or without aura, six exclusively participants without aura, and one recruited only women with menstrually-related migraine (Linde M 2004). In two large, pragmatic multicentre trials (Jena 2008; Vickers 2004) baseline headache frequency and the reported diagnoses make it likely that, in spite of the use of the criteria of the International Headache Society, there was some diagnostic misclassification (i.e. some participants were likely to suffer from tension-type headache and not migraine). This applied to a minor extent also to three other multicenter trials (Diener 2006; Linde K 2005; Streng 2006).

Acupuncture interventions

The acupuncture interventions tested in the included trials varied to a great extent. Five trials (Allais 2002; Ceccherelli 1992; Li 2012; Wallasch 2012; Zhao 2014) standardized acupuncture treatments (all participants were treated at the same points); seven (Alecrim 2006; Diener 2006; Facco 2013; Linde K 2005; Linde M 2000; Linde M 2004; Wang 2015) semi-standardized treatments (either all participants were treated at some basic points and additional individualized points, or there were different predefined needling schemes depending on symptom patterns); and 10 trials individualized the selection of acupuncture points (Alecrim 2005; Alecrim 2008; Facco 2008; Hesse 1994; Jena 2008; Streng 2006; Vickers 2004; Vincent 1989; Weinschütz 1993; Weinschütz 1994). The number of treatment sessions was between six and 12 in 13 trials, and 16 or more in nine trials. Most trials reporting the duration of sessions, left needles in place for between 20 and 30 minutes; one trial (Hesse 1994) investigated brief needling for a few seconds. Electro-stimulation of needles was used in one trial (Li 2012). Agreement among acupuncturists on whether they would do acupuncture similarly to that used in the study assessed and whether they had confidence in the quality of the acupuncture was low (intra-class correlation coefficients -0.08 and 0.24). For two studies (Hesse 1994; Linde M 2004) both acupuncturists rating the study had 50% or less confidence that the acupuncture had adequate quality. For a further six studies (Ceccherelli 1992; Li 2012; Linde M 2000; Wallasch 2012; Weinschütz 1993; Weinschütz 1994) at least one acupuncturist gave a rating of 50% or lower. We could not assess four trials using individualized treatments not described in detail (Alecrim 2005; Alecrim 2008; Facco 2008; Jena 2008).

Comparator interventions

Five trials included a group which either received treatment of acute attacks only (Facco 2008; Linde K 2005; Linde M 2000) or 'routine care' that was not specified by protocol (Jena 2008; Vickers 2004), while the experimental group received acupuncture in addition. In the 15 trials with a sham control, techniques varied considerably. Four trials superficially needled recognized acupuncture points considered inadequate for the treatment of migraine (Alecrim 2005; Alecrim 2006; Alecrim 2008; Zhao 2014); seven trials used needling (mostly superficial) of non-acupuncture points at variable distance from true points (Diener 2006; Li 2012; Linde K 2005; Vincent 1989; Wallasch 2012; Weinschütz 1993; Weinschütz 1994). Two trials (Facco 2008; Linde M 2004) used 'placebo' needles (telescopic needles with blunt tips not penetrating the skin). In Linde M 2004 these were placed at the same predefined points as in the true treatment group. Facco 2008 had two sham groups: in one group the placebo needles were placed at correct, individualized points after the same process of Chinese diagnosis as in the true treatment group. In the second group placebo needles were placed at standardized points without the 'Chinese ritual' (to investigate whether the different interaction and process affected outcomes). One study (Ceccherelli 1992) used a complex procedure without real needling. One study used a mix of superficial needling at non-acupuncture points and a non-penetrating technique (with a blunted cocktail stick) for points on the head (Wang 2015). Five trials compared acupuncture to prophylactic drug treatment, using metoprolol (Hesse 1994; Streng 2006), flunarizine (Allais 2002), valproic acid (Facco 2013) or individualized treatment according to guidelines (Diener 2006). In four of these trials participants were unblinded, while one blinded trial used a double-dummy approach (true acupuncture + metoprolol placebo vs. metoprolol + sham acupuncture; Hesse 1994).

Excluded studies

Results were not yet available for eight studies registered in trial registries likely to meet selection criteria. For four of these, detailed protocols have been published (Chen 2013; Lan 2013; Vas 2008; Zhang 2013); for the other four only the registry entries were available (Li 2007; Liang 2013; Wang J 2015; Xing 2015). For at least four trials recruitment has been completed (Lan 2013; Li 2007; Vas 2008; Wang J 2015) (see Characteristics of ongoing studies).

Twenty studies (described in 23 publications) did not meet selection criteria (Agro 2005; Boutouyrie 2010; Ceccherelli 2012; Deng 2006; Ferro 2012; Foroughipour 2014; Han 2011; Jia 2009; Matra 2012; Qin 2006; Vijayalakshmi 2014; Wang 2011; Wu 2011; Yang 2009; Yang 2011; Zhang 2006; Zhang 2009; Zheng 2013; Zhong 2009; Zhou 2007). A number of Chinese trials were excluded due to inadequate duration of prophylactic drug treatment (several Chinese trials gave flunarizine or other drugs for four weeks only), overall observation of less than eight weeks, inclusion of participants with recent onset of migraine, and lack of relevant outcome measures. Furthermore, five trials included in the previous version of our review were excluded (Baust 1978; Doerr-Proske 1985; Dowson 1985; Henry 1985; Wylie 1997). Reasons for exclusions are reported in the Characteristics of excluded studies.

Studies awaiting classification

We classified three trials (five publications) identified by our most recent update search as awaiting assessment (see Characteristics of studies awaiting classification). One (Giannini 2015) is an abstract of an interim analysis of a trial comparing acupuncture and individualized prophylactic drug treatment. The abstract does not provide sufficient information but based on background information available to one of us (KL) it seems likely that the trial will meet our eligibility criteria when a full publication with final data becomes available. A second trial originating from China (Li 2016) was published in February and April 2016 after all analyses for this review had been completed. The two publications focus on functional magnetic resonance imaging (fMRI) outcomes but also report headache frequency data for participants completing all fMRI measurements. It seems likely that these trials will meet inclusion criteria. A third trial of uncertain eligibility (participants with "menstrual headache") is available only in Chinese (Sun 2015). Full text translation has to be available before final assessment of eligibility.

Risk of bias in included studies

We discuss the methodological quality of trials (risk of bias) for the three comparisons separately, as problems differ according to control groups. The risk of bias assessments of single trials are displayed in Figure 2; a summary across trials is presented in Figure 3. It should be noted that three trials rated unclear for the item 'incomplete follow-up outcome data' actually did not include a follow-up (Ceccherelli 1992; Jena 2008; Zhao 2014).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Note: for trials including both a comparison with sham and a no-acupuncture control/prophylactic drugs (Diener 2006, Facco 2008, Linde K 2005) blinding was assessed for the comparisons with sham. For the comparisons with no acupuncture/prophylactic drugs the risk of bias is high (no blinding).

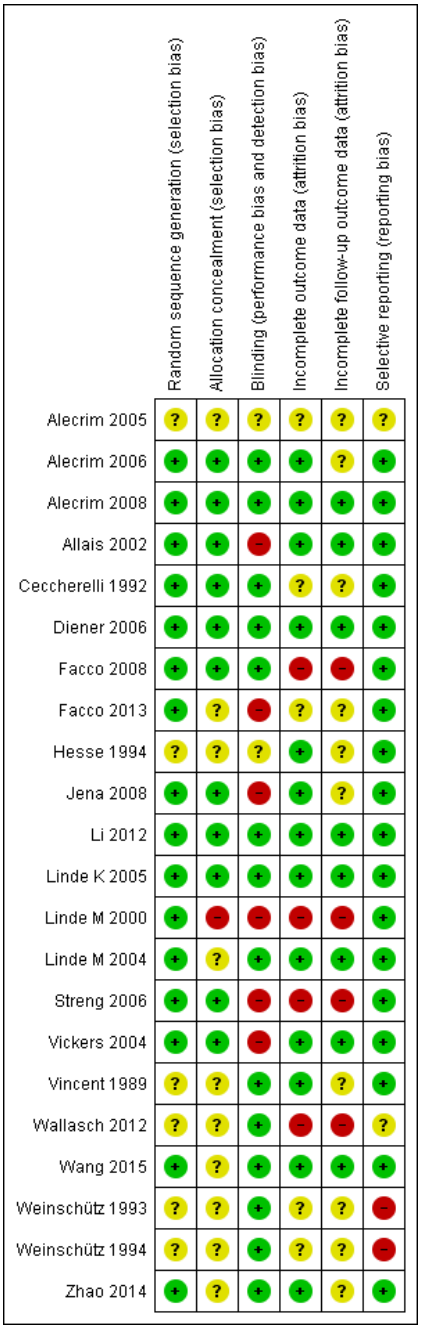
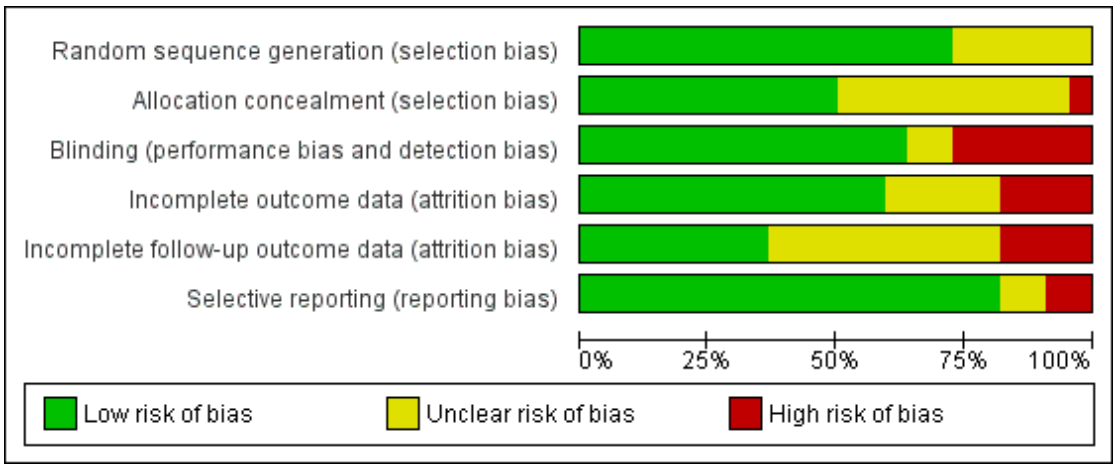


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



Comparisons with no acupuncture (acute treatment only or routine care)

Four trials (Facco 2008; Jena 2008; Linde K 2005; Vickers 2004) used adequate methods for allocation sequence generation and concealment of allocation when judged according to the Cochrane 'Risk of bias' tool (Higgins 2011). According to the definition of the ATC, three trials (Jena 2008; Linde K 2005; Vickers 2004) were "unambiguously adequately concealed". For the two other trials sequence generation was adequate but concealment was inadequate (Linde M 2000) or not fully adequate (Facco 2008). Given the comparison between acupuncture and no acupuncture, the participants (who were also assessing all relevant outcomes) were unblinded in all six trials. In consequence, bias could not be ruled out. The use of headache diaries to monitor symptoms closely over a long period of time (Linde K 2005; Linde M 2000; Vickers 2004) might be less prone to bias than the use of questionnaires with retrospective assessment of symptoms for the preceding weeks (Facco 2008; Jena 2008). Attrition in the first three months was high in Linde M 2000 and minor to moderate in the remaining trials. The analyses of Jena 2008, Linde K 2005 and Vickers 2004 took account of attrition, suggesting a low risk of bias. This also applied to the long-term follow-up in Vickers 2004. Facco 2008 presented only a per-protocol analysis. Although presentation of results was not always optimal, we considered the risk of selective reporting to be low as the most important outcome measures were always presented and consistent. Overall, due to the lack of blinding in all studies there was some risk of performance and detection bias for this comparison.

Comparisons with sham interventions

We could not formally assess the quality of Alecrim 2005, for which only an abstract and additional unpublished information provided by the authors were available. Unpublished information provided by the authors and published information from the two other trials (Alecrim 2006; Alecrim 2008) conducted by the same group suggested that the risk of bias in this trial was low. Among the 13 trials formally assessed, the risk of bias regarding sequence generation was low for 10 (Alecrim 2006; Alecrim 2008; Ceccherelli 1992; Diener 2006; Facco 2008; Li 2012; Linde K 2005; Linde M 2004; Wang 2015; Zhao 2014) and unclear in five. Publications for five trials reported adequate methods of allocation concealment (Alecrim 2006; Alecrim 2008; Diener 2006; Li 2012; Linde K 2005); for a further two trials, such information was provided by the authors (Ceccherelli 1992; Facco 2008). All the trials attempted to blind participants. Several trials that used sham interventions which were not strictly indistinguishable from 'true' acupuncture (Ceccherelli 1992; Diener 2006; Facco 2008; Linde K 2005) did not mention explicitly the use of a sham or placebo control in the informed consent procedure. This is ethically problematic, but enhances the credibility of the sham interventions. Taking into account also the results of the trials, we considered the risk of bias to be low in all trials. Reporting of dropouts was insuffi-

cient in several older trials. We considered the risk of bias to be low regarding short-term outcomes (up to three months) in nine trials (Alecrim 2006; Alecrim 2008; Diener 2006; Li 2012; Linde K 2005; Linde M 2004; Vincent 1989; Wang 2015; Zhao 2014), and low regarding long-term outcomes in six (Alecrim 2008; Diener 2006; Li 2012; Linde K 2005; Linde M 2004; Wang 2015). For two trials (Weinschütz 1993; Weinschütz 1994) outcomes were reported so inadequately that selective reporting could not be ruled out. Overall, the risk of bias was variable, but, particularly in the three largest trials, good quality. However, as acupuncturists could not be blinded in any trial performance, bias could not be ruled out completely.

Comparisons with prophylactic drug treatment

Three trials (Allais 2002; Diener 2006; Streng 2006) used adequate methods for sequence generation and concealment, one trial reported an adequate method for sequence generation but insufficient detail regarding concealment (Facco 2013), and one trial (Hesse 1994) did not describe the methods. Four trials (Allais 2002; Diener 2006; Facco 2013; Streng 2006) compared acupuncture and drug treatment in an open manner, which implies that bias on this level is possible. The use of a double-dummy technique allowed participant blinding in Hesse 1994, but this approach might be associated with other problems (see Discussion). While there is little risk of bias due to low attrition rates in Allais 2002 and Hesse 1994, and unclear risk in Facco 2013, a relevant problem occurred in the two German trials (Diener 2006; Streng 2006). The recruitment situation for these trials made it likely that participants had a preference for acupuncture. This resulted in a high proportion of participants allocated to drug treatment withdrawing informed consent immediately after randomisation (34% in Diener 2006 and 13% in Streng 2006), as well as high treatment discontinuation (18% in Diener 2006) or dropout rates due to adverse effects (16% in Streng 2006). These trials did not include participants refusing informed consent immediately after randomisation in analyses, and one (Streng 2006) also excluded early dropouts. Such analyses should normally tend to favour drug treatment. Both trials presented additional analyses restricted to participants complying with the protocol. All five trials presented the most important outcomes measured, so we considered the risk of bias of selective reporting to be low. Overall, as four of the trials were not blinded and two trials had a problem with relevant attrition in the drug group there is a considerable risk of bias (see also Discussion).

Effects of interventions

See: **Summary of findings for the main comparison** Acupuncture compared to no treatment/usual care; **Summary of findings 2** Acupuncture compared to sham interventions; **Summary of findings 3** Acupuncture compared to prophylactic drugs

Comparisons with no acupuncture (acute treatment only or routine care)

The five trials comparing acupuncture with a control group receiving either treatment of acute migraine attacks only or routine care are clinically very heterogeneous. Facco 2008 performed a four-armed trial (n = 160) in which participants in the control group all received acute treatment of attacks with rizatriptan. Jena 2008 is a very large, highly pragmatic study which included a total of 15,056 headache sufferers recruited by more than 4000 physicians in Germany. A total of 11,874 people not giving consent to randomisation received up to 15 acupuncture treatments within three months and were followed for an additional three months. This was also the case for 1613 participants randomized to immediate acupuncture, while the remaining 1569 participants remained on routine care (not further defined) for three months and then received acupuncture. The published analysis of this trial is on all randomized participants, but we received unpublished results of subgroup analyses on the 1715 participants with migraine from the study authors for the previous version of our review and we re-analysed the data from the ATC for this update. Linde M 2000 was a small pilot trial (n = 39) performed in a specialized migraine clinic in Sweden in which control participants continued with their individualized treatment of acute attacks but did not receive additional acupuncture. A similar approach was used for the waiting-list control group in the three-armed (also sham control group) Linde K 2005 (n = 302) trial. Finally, in the Vickers 2004 trial (n = 401), acupuncture in addition to routine care in the British National Health Service was compared to a strategy, 'avoid acupuncture'. In addition to the strong clinical heterogeneity, the methods and timing of outcome measurement in these trials also differed considerably.

Therefore, pooled effect size estimates have to be interpreted with caution. Nevertheless, the findings show that acupuncture treatment is associated with a moderately large short-term benefit compared to no acupuncture control groups (Figure 4; Figure 5).

Figure 4. Forest plot of comparison: 1 Acupuncture vs. no acupuncture, outcome: 1.1 Headache frequency

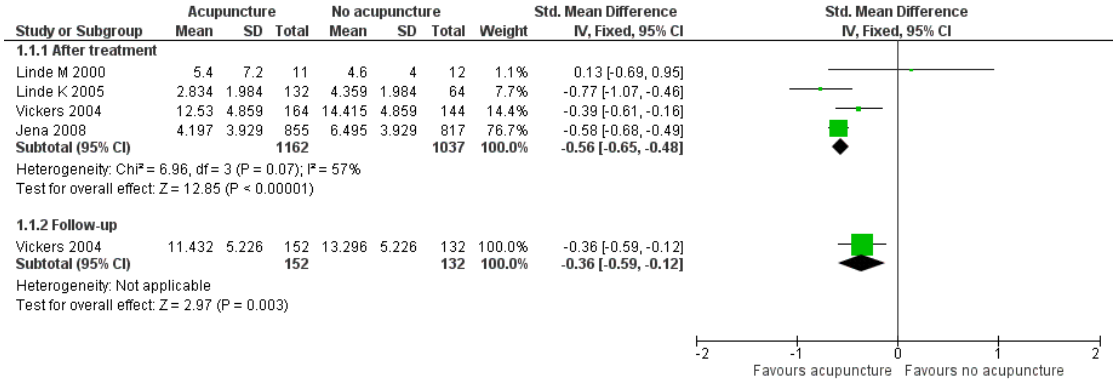
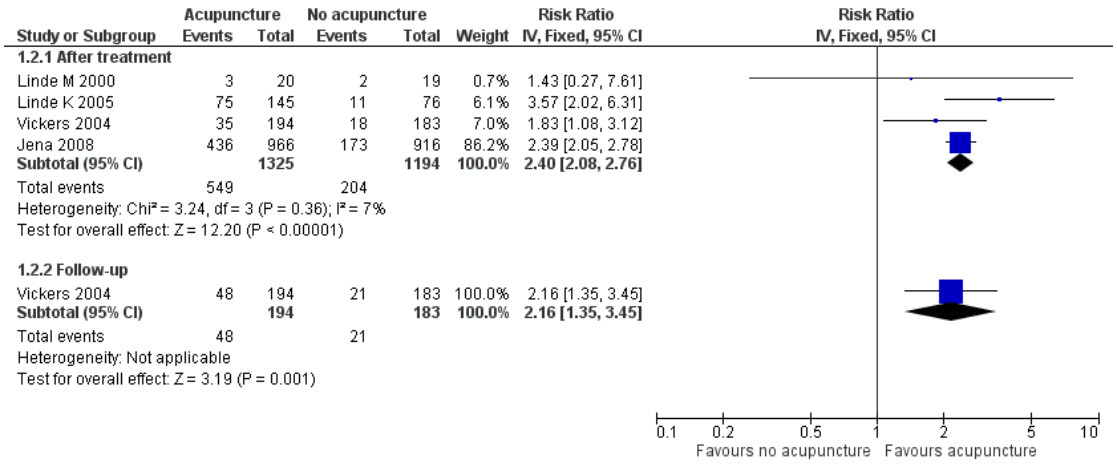


Figure 5. Forest plot of comparison: 1 Acupuncture vs. no acupuncture, outcome: 1.2 Response (at least 50% frequency reduction)



Among the four trials providing sufficient data the pooled fixed-effects standardized mean difference (SMD) was -0.56 (95% CI -0.65 to -0.48; 2199 participants); findings were statistically heterogeneous (P value = 0.07; I^2 = 57%; random-effects estimate -0.53; 95% CI -0.72 to -0.34).

After treatment, headache frequency at least halved in 41% of participants receiving acupuncture and 17% receiving no acupuncture. The fixed effects risk ratio (RR) was 2.40 (95% CI 2.08 to 2.76; 4 trials, 2519 participants); there was no indication of statistical heterogeneity (P value = 0.36; I^2 = 7%). We consider these findings after treatment as moderate quality evidence because as the large trials consistently show clinically relevant differences, in spite of the risk of bias due to lack of blinding, we found some indication of heterogeneity (headache frequency) and clinical differences between trials. The corresponding number needed to treat for an additional beneficial outcome (NNTB) was 4 (95% CI 3 to 6). There was only one trial with a follow-up beyond three months (Vickers 2004; 12 month follow-up). The SMD (frequency) was -0.36 (95% CI -0.59 to -0.12; 284 participants with data) and the RR for response was 2.16 (95% CI 1.35 to 3.45; 377 participants). The NNTB based on this trial was 7 (95% CI 4.00 to 25.00; proportion of participants with response in the sham group 11%). Although the trial was large we consider its long-term find-

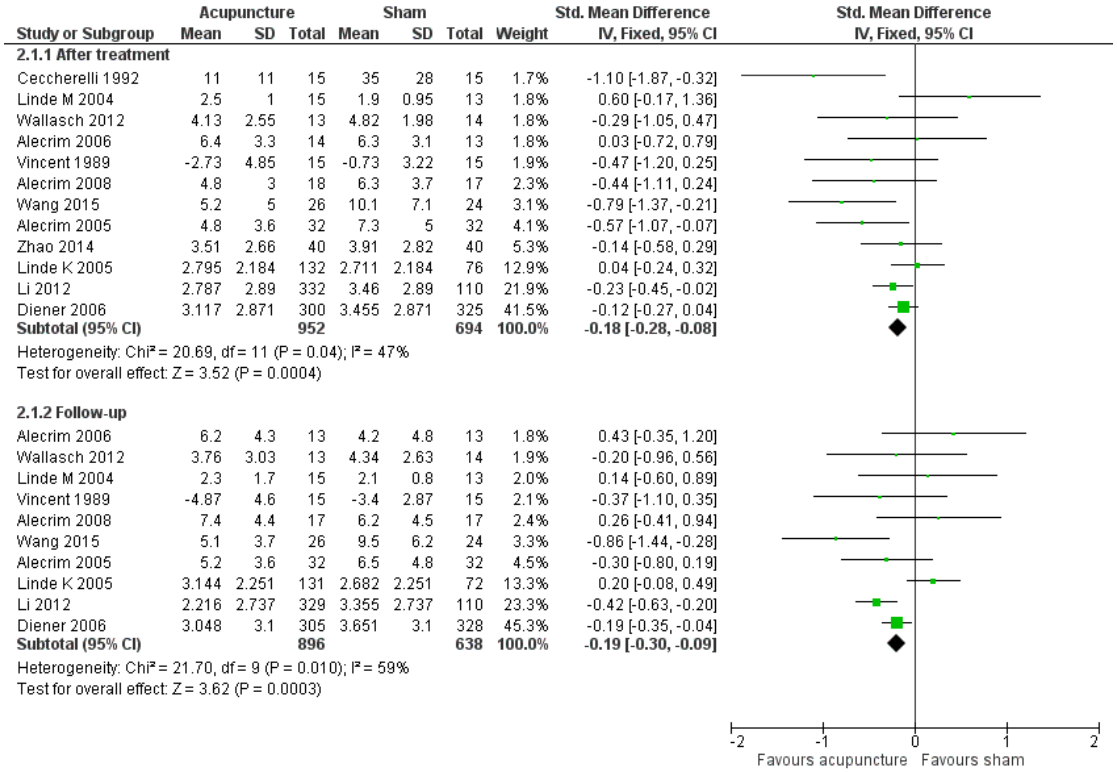
ings to be low quality evidence as, given the variable effect sizes after treatment in the available trials, future trials performed in different settings might well yield different effect sizes. Findings in the time window analyses are consistent with those of the main analysis (Analysis 1.3; Analysis 1.4). The single specific frequency outcomes, migraine attacks, migraine days and headache days were not measured or reported in any trials but findings were consistent with those in our primary outcome, headache frequency (Analysis 1.5; Analysis 1.6; Analysis 1.7). This also applies to the outcomes headache intensity, analgesic use and headache scores (Analysis 1.8; Analysis 1.9; Analysis 1.10). We did not explore reasons for heterogeneity due to the small number of trials.

The number of participants not reaching the primary endpoint was slightly lower in acupuncture than in non-acupuncture groups (OR 0.69; 95% CI 0.46 to 1.05); there was some heterogeneity (P value = 0.13; I^2 = 47%). In the two trials reporting reasons for attrition there were no dropouts due to adverse effects. Information on other safety/acceptability outcomes was reported insufficiently (see Analysis 1.11).

Comparisons with sham interventions

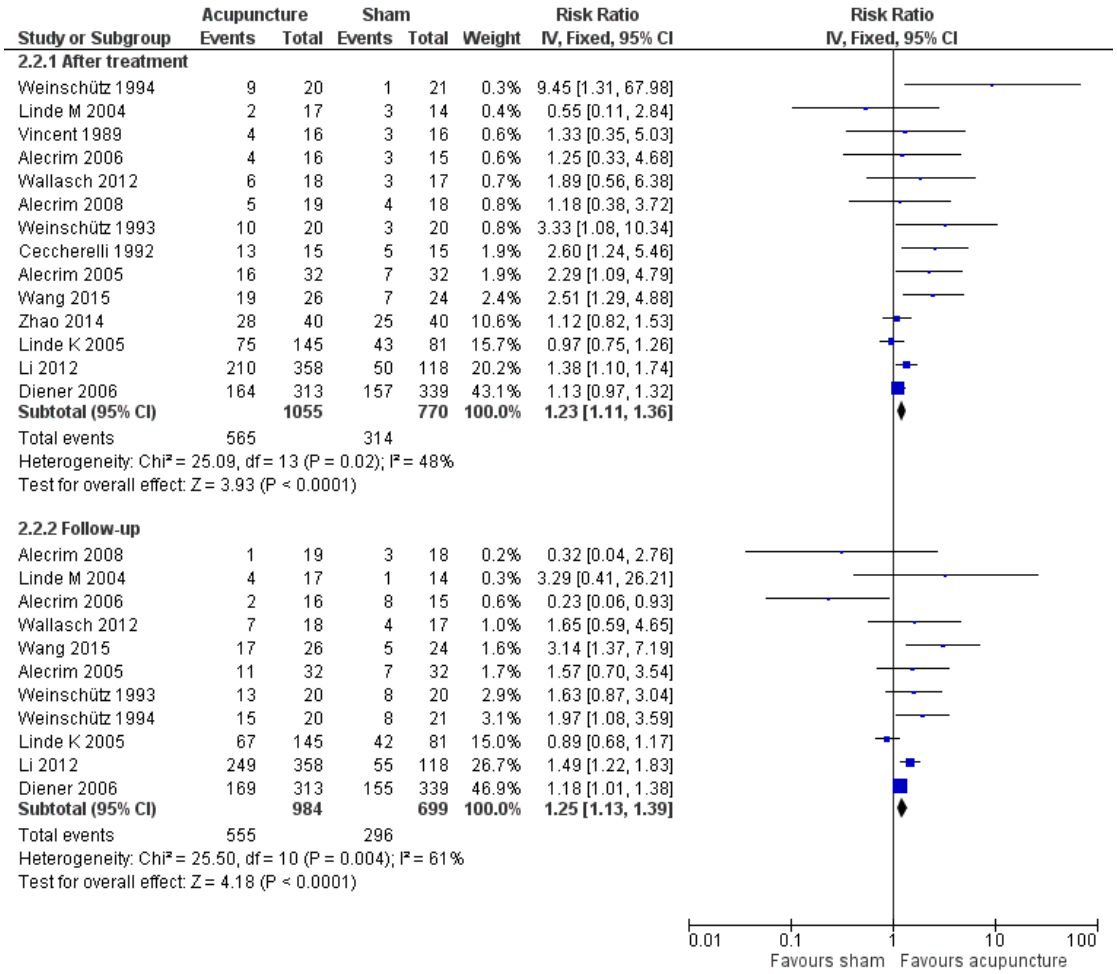
Both after treatment (12 trials providing data from 1646 participants) and at follow-up (10 trials, 1534 participants) acupuncture was associated with a small but statistically significant frequency reduction over sham in the fixed-effect analyses (Figure 6). The SMD was -0.18 (95% -0.28 to -0.08; P value from the Chi^2 test for heterogeneity = 0.04, I^2 = 47%) after treatment and -0.19 (95% -0.30 to -0.09; P value from the Chi^2 test for heterogeneity = 0.01, I^2 = 59%) at follow-up. The results of the random-effects models were similar (SMD -0.24; 95% CI -0.41 to -0.07 for post-treatment, SMD-0.16; 95% CI -0.37 to 0.04 at follow-up).

Figure 6. Forest plot of comparison: 2 Acupuncture vs. sham interventions, outcome: 2.1 Headache frequency



After treatment, headache frequency at least halved in 50% of participants receiving true acupuncture and 41% receiving sham acupuncture (pooled RR 1.23, 95% CI 1.11 to 1.36; P value = 0.02, I^2 = 48%; 14 trials, 1825 participants) and at follow-up in 53% and 42%, respectively. The pooled fixed effects RR was 1.23 (95% CI 1.11 to 1.36; P value from the Chi^2 test for heterogeneity = 0.02, I^2 = 48%; 14 trials, 1825 participants) after treatment and 1.25 (95% CI 1.13 to 1.39; P value from the Chi^2 test for heterogeneity = 0.004, I^2 = 61%; 11 trials, 1683 participants) at follow-up (Figure 7). The corresponding NNTB would be 11 (95% CI 7.00 to 20.00) after treatment and 10 (95% CI 6.00 to 18.00) at follow-up. Random-effects RRs were 1.39 (95% CI 1.14 to 1.69) and 1.33 (95% CI 1.05 to 1.70). The results were dominated by the three large, high-quality trials (Diener 2006; Li 2012; Linde K 2005; 75% and 82% weight, respectively, in the meta-analyses). We consider the findings for the outcomes headache frequency and response both after treatment and at follow-up as moderate quality evidence (indication of heterogeneity and small effect sizes leaving magnitude and statistical significance of effect open to some change with more trials). The time windows analyses yielded findings which were consistent with our main analyses (Analysis 2.3; Analysis 2.4). Specific frequency outcomes as well as intensity, analgesic use and headache scores were typically available for less than half of the trials (Analysis 2.5; Analysis 2.6; Analysis 2.7; Analysis 2.8; Analysis 2.9; Analysis 2.10).

Figure 7. Forest plot of comparison: 2 Acupuncture vs. sham interventions, outcome: 2.2 Response (at least 50% frequency reduction)



We performed subgroup analyses to investigate four potential sources of heterogeneity for both frequency and response, both after treatment and follow-up (four analyses for each potential source of heterogeneity). While there were suggestions of subgroup differences, heterogeneity tended to remain considerable in most subgroups across analyses. Effects of acupuncture over sham were significantly smaller in the three unambiguously adequately concealed trials (which were also by far the three largest trials) than in the remaining trials in three (Analysis 2.11; Analysis 2.13 Analysis 2.14) of four analyses (no significant difference in Analysis 2.12). In the analyses grouping trials into smaller and larger (number of participant up to or above the median number of participants in the trials included in the analysis) studies' differences tended to be somewhat smaller in larger trials but these findings were mainly driven by the three larger, unambiguously adequately concealed trials (Analysis 2.15; Analysis 2.16; Analysis 2.17; Analysis 2.22). Consistently, effects over sham tended to be larger in trials with 16 or more treatment sessions compared to trials with up to 12 sessions (Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21;). Effects also tended to be somewhat larger in trials using non-penetrating sham techniques, however, only three relatively small trials used such sham techniques (Analysis 2.23; Analysis 2.24; Analysis 2.25; Analysis 2.26). Re-including the five trials excluded for this update (but included in the previous version of this review) had only minimal impact on results.

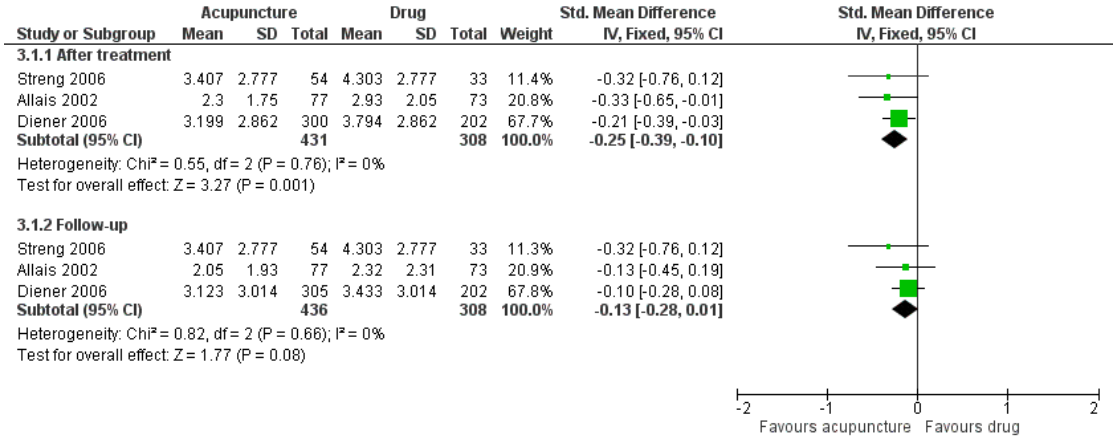
In the seven trials reporting this outcome only three of 621 participants receiving acupuncture and none of 310 in control groups dropped out due to adverse effects (OR 2.84; 95% CI 0.43 to 18.71; 7 trials, 931 participants; I^2 = 0%). We consider this low quality evidence as there is great uncertainty regarding the effect estimate due to the very small number of such dropouts. Only the four largest trials reported the number of participants reporting adverse effects. Among 847 participants receiving acupuncture 138 (16%) reported adverse effects compared to 98 (17%) receiving sham (OR 1.15; 95% CI 0.85 to 1.56; I^2 = 0%; moderate quality evidence; Analysis 2.27). There were also no significant differences in the number of participants not reaching the primary endpoint of the trial (OR 1.14; 95% CI 0.78 to 1.67; 11 trials, 1770 participants) and experiencing serious adverse events (OR 1.29; 95% CI 0.43 to 3.83; 6 trials, 1071 participants; Analysis 2.27).

Comparisons with prophylactic drug treatment

The results of Hesse 1994 regarding treatment effectiveness were not reported in a manner that allowed effect size estimation. Overall, the findings of this trial, which used a double-dummy design (true acupuncture plus metoprolol placebo versus sham acupuncture plus metoprolol), showed similar improvements in both groups, slightly favouring the sham acupuncture plus metoprolol group. The acupuncture technique used in this trial (very brief needling of individual trigger points) was rather unusual and was considered with skepticism by our acupuncturists. The pragmatic trial, Facco 2013, which compared a traditional acupuncture strategy with valproic acid, did not use a headache diary, but only a questionnaire including the Migraine Disability (MIDAS) instrument (Stewart 2001). Participants were asked to report the number of headache days over periods of three months. The publication reported very large improvements (the median number of headache days went down from 18 days before the trial, to four days during the treatment phase and during the follow-up phase in the acupuncture group, and from 17 to three and six days in the group receiving valproic acid), and very little variation (narrow interquartile ranges). The first author provided means and standard deviations, but standard deviations were very small. As we were uncertain about the reliability of the data we decided to not include it in meta-analysis.

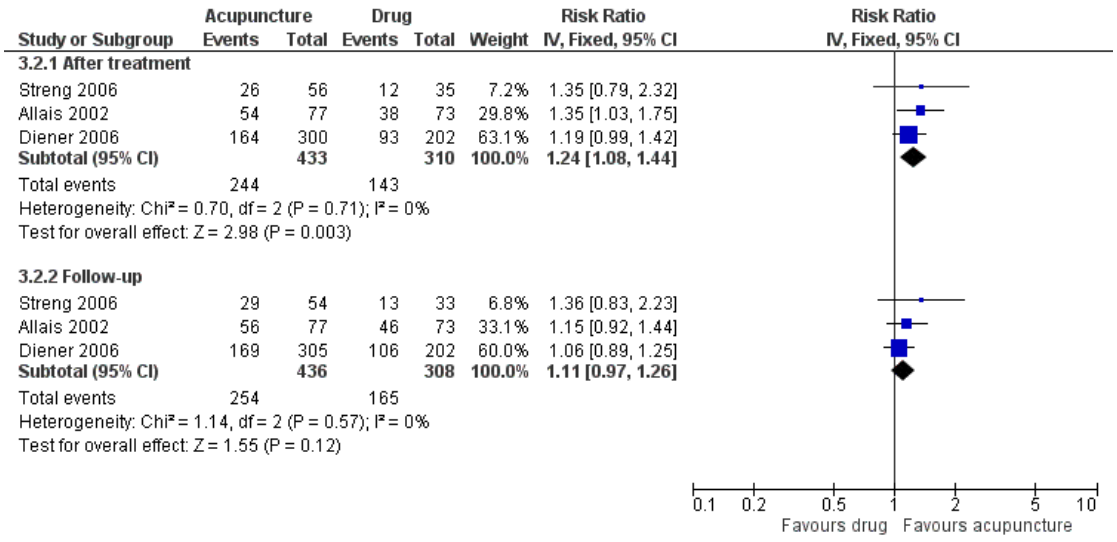
The remaining three trials could be entered into meta-analyses. Acupuncture reduced migraine frequency significantly more than drug prophylaxis after treatment (SMD -0.25; 95% CI -0.39 to -0.10; 739 participants) while differences were smaller at follow-up and were not significantly different (SMD -0.13; 95% CI -0.28 to 0.01; P value = 0.08; 744 participants; see Figure 8).

Figure 8. Forest plot of comparison: 3 Acupuncture vs. prophylactic drug treatment, outcome: 3.1 Headache frequency



Findings were similar for response (Figure 9). After a median follow-up of three months headache frequency at least halved in 57% of participants receiving acupuncture and 46% receiving prophylactic drugs, and after six months in 59% and 54%, respectively. The RR was 1.24 (95% CI 1.08 to 1.44; 743 participants) after treatment and 1.11 (95% CI 0.97 to 1.26; 744 participants) at follow-up. Findings were consistent among trials with P values from the Chi² test for heterogeneity being above 0.5 and I² being 0% in all analyses. While there was risk of bias due to lack of blinding in all three trials and relevant attrition in two trials, and future trials might not confirm the small effects of acupuncture over prophylactic drug treatment, we consider the highly consistent trial findings for both outcomes and both time points as moderate quality evidence that acupuncture is non-inferior to prophylactic drug treatment.The time window analyses are consistent with these findings as are the findings on additional outcomes (Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10).

Figure 9. Forest plot of comparison: 3 Acupuncture vs. prophylactic drug treatment, outcome: 3.2 Response (at least 50% frequency reduction)



In the four studies reporting this outcome three (1%) of 227 participants receiving acupuncture dropped out due to adverse effects compared to 16 (7%) receiving prophylactic drugs (OR 0.27; 95% CI 0.08 to 0.86; I^2 = 0%; Analysis 3.11). All five trials provided the number of participants reporting adverse effects. Probably due to different methods for documenting this outcome the absolute frequency of adverse effects in both groups varied greatly between trials. A total of 90 (17%) of 520 participants receiving acupuncture reported adverse effects compared to 140 (34%) of 411 participants receiving prophylactic drug treatment (OR 0.25; 95% CI 0.10 to 0.62; I^2 = 78%, P value from Chi^2 test for heterogeneity = 0.001). Despite some limitations (uncertainty regarding dropouts due to low event rates and heterogeneity regarding reporting of adverse effects) we consider this moderate quality evidence as study findings consistently favour acupuncture over prophylactic drug treatment. Furthermore, study findings also favoured acupuncture for the number of participants not reaching the primary endpoint (OR 0.28; 95% CI 0.10 to 0.78; 4 trials, 995 participants; I^2 = 80%; P value = 0.002). Serious adverse events were reported in seven (2%) of 313 participants receiving acupuncture compared to four (1%) of 307 participants receiving prophylactic drugs (OR 1.33; 95% CI 0.38 to 4.73; 4 trials; I^2 = 0%).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Acupuncture compared to sham acupuncture

Patient or population: people with episodic migraine
Setting: primary care or outpatient care
Intervention: acupuncture
Comparison: sham acupuncture

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with sham acupuncture / Risk with Acupuncture				
Headache frequency (after treatment) assessed with days per month follow-up: median 12 weeks	Headache frequency was 0.18 SDs (-0.28 to -0.08) lower than in the groups receiving sham treatment	-	1646 (12 RCTs)	⊕⊕⊕◯ MODERATE [1]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference
Headache frequency (follow-up) assessed with days per month follow-up: median 6 months	Assuming a mean number of 3.5 (SD 3.0) migraine days in the sham group, participants in the acupuncture group would have 0.6 days (95% CI 0.3 to 1.1 days) less (SMD = -0.19; 95% CI -0.30 to -0.09; 896 patients receiving acupuncture, 638 sham)	-	1534 (10 RCTs)	⊕⊕⊕◯ MODERATE [2]	As a rule of thumb 0.2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference
Response (after treatment) assessed with proportion of participants with at least 50% headache frequency reduction follow-up: median 12 weeks	Study population	RR 1.23 (1.11 to 1.36)	1825 (14 RCTs)	⊕⊕⊕◯ MODERATE [3]	Variable results between studies; modest effect size leaves magnitude of effect open to change with further large trials

	408 per 1000	502 per 1000 (453 to 555)				
Response (follow-up) assessed with proportion of participants with at least 50% headache frequency reduction follow-up: median 6 months	Study population		RR 1.25 (1.13 to 1.39)	1683 (11 RCTs)	⊕⊕⊕◯ MODERATE [4]	Variable results between studies; modest effect size leaves magnitude of effect open to change with further large trials
	423 per 1000	529 per 1000 (479 to 589)				
Number of participants dropping out due to adverse effects	Study population		RR 2.84 (0.43 to 18.71)	931 (7 RCTs)	⊕⊕◯◯ LOW [5]	Relevant uncertainty due to low event rates
	Only 3/621 participants receiving acupuncture and 0/310 receiving sham dropped out due to adverse effects					
Number of participants reporting adverse effects	Study population		RR 1.15 (0.85 to 1.56)	1414 (4 RCTs)	⊕⊕⊕⊕ HIGH	Only 4 large trials report this outcome adequately; variable methods to document adverse effects, yet results of trials are consistent
	173 per 1000	199 per 1000 (147 to 270)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once: pronounced heterogeneity of study results (I^2 = 47%; Chi^2 = 20.69; P value = 0.04)

[2] Downgraded once: pronounced heterogeneity of study results (I^2 = 59%; Chi^2 = 27.10; P value = 0.0003)
[3] Downgraded once: pronounced heterogeneity of study results (I^2 = 48%; Chi^2 = 25.09; P value = 0.02)
[4] Downgraded once: pronounced heterogeneity of study results (I^2 = 61%; Chi^2 = 25.50; P value = 0.004)
[5] Downgraded twice: only very few events

Acupuncture compared to prophylactic drugs

Patient or population: people with episodic migraine
Setting: primary care or outpatient care
Intervention: acupuncture
Comparison: prophylactic drug treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with prophylactic drug treatment	Risk with acupuncture				
Headache frequency assessed with days per month follow-up median 3 months	Headache frequency was 0.25 SDs (-039 to -0.10) lower than in the groups receiving prophylactic drug treatment		-	739 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	As a rule of thumb 0. 2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference. Size of difference open to change with more trials
Headache frequency assessed with days per month follow-up: median 6 months	Headache frequency was 0.13 SDs (-0.28 to 0.01) lower than in the groups receiving prophylactic drug treatment		-	744 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	As a rule of thumb 0. 2 SD represents a small difference, 0.5 a moderate, and 0.8 a large difference. Size of difference open to change with more trials
Response assessed with proportion of participants with at least 50% headache frequency reduction follow-up: median 3 months	Study population		RR 1.24 (1.08 to 1.44)	743 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	Due to the limited number of trials and risk of bias size of differences open to change with more trials

	461 per 1000	572 per 1000 (498 to 664)				
Response assessed with proportion of participants with at least 50% headache frequency reduction follow-up: median 6 months	Study population		RR 1.11 (0.97 to 1.26)	744 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	Due to the limited number of trials and risk of bias size of differences open to change with more trials
	536 per 1000	595 per 1000 (520 to 675)				
Number of participants dropping out due to adverse effects	Study population		OR 0.27 (0.08 to 0.86)	451 (4 RCTs)	⊕⊕⊕◯ MODERATE [2]	Consistent results between studies, but uncertainty about size of difference due to low frequency of events in acupuncture group
	71 per 1000	20 per 1000 (6 to 62)				
Number of participants reporting adverse effects	Study population		OR 0.25 (0.10 to 0.62)	931 (5 RCTs)	⊕⊕⊕◯ MODERATE [3]	Consistently fewer adverse effects in acupuncture groups, but strong variability of size of differences (probably due to different assessment methods)
	341 per 1000	114 per 1000 (49 to 243)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once: in two of three studies a relevant proportion of participants randomized to drug treatment dropped out early (analysis included only participants receiving at least a minimal amount of treatment); no blinding of participants

[2] Downgraded once: few events in acupuncture group; wide confidence interval

[3] Downgraded once: size of differences highly variable (I^2 = 78%; Chi^2 = 17.95, P value = 0.001), but consistently more adverse effects in drug groups

DISCUSSION

Summary of main results

Several trials using quite variable methods and interventions consistently showed that the addition of acupuncture to treatment of acute migraine attacks or to routine care was beneficial for at least three months. Compared to no treatment or routine care only (which includes treatment of acute migraine attacks and possibly other interventions) the size of the effect seemed to be moderate according to usual standards for classifying effect size measures such as standardized mean differences. The only trial that investigated long-term effects showed a sustained small to moderate response to acupuncture in addition to routine care provided by a GP (Vickers 2004). Compared to sham acupuncture, true acupuncture interventions were associated with small but statistically significant effects both after treatment and at follow-up, but findings were statistically heterogeneous. In the largest, adequately concealed trials differences were even smaller (but still statistically significant). The pooled analyses of the available trials comparing acupuncture interventions with evidence-based prophylactic drug treatment found a superiority of acupuncture at completion of treatment, though at follow-up differences were no longer statistically significant. Compared to drug prophylaxis fewer participants dropped out due adverse effects or reported adverse effects.

Possible explanations of the findings

The interpretation of the findings of our review remains challenging. While, contrary to the results of the previous version of our review, differences between true acupuncture and sham interventions became statistically significant (after the inclusion of four new sham-controlled trials), it seems still surprising that the size of the effect over sham is similar to that over prophylactic treatment with drugs that have been shown to be superior to placebo (Schürks 2008). Three factors could explain these findings (probably in combination). Firstly, sham acupuncture might have direct physiological effects on mechanisms relevant to migraine symptoms, secondly, acupuncture might be a particularly potent placebo, and thirdly, due to the lack of blinding, comparisons with routine care and prophylactic drug treatment might be biased.
We consider each of these possible explanations in turn.

Physiological effects of sham acupuncture

Many sham acupuncture procedures involve needling locations that are not traditional points with the same frequency and duration as in the true acupuncture group. In some studies needles are inserted into classical acupuncture points not indicated in migraine. Most physiological mechanisms proposed for acupuncture do not necessarily imply point specificity (Bäcker 2004). Even the non-penetrating 'placebo' needles might activate unmyelinated (C 'tactile') afferent nerves which can influence pain perception (Lund 2006). Several researchers have argued that some effects of acupuncture might not be point-specific (Han 1997; Lundeberg 2007), and that these might be particularly relevant for treating conditions other than localized nociceptive pain (Thomas 1996; Borud 2010). In individual patient data meta-analysis, acupuncture was significantly superior to all categories of control group. For trials that used penetrating needles for sham control, acupuncture had smaller effect sizes than for trials with non-penetrating sham or sham control without needles (MacPherson 2014).

Sham acupuncture as a strong placebo

According to the available evidence, the most important mechanisms for placebo effects are expectations, conditioning, anxiety reduction and social support (Crow 1999; Benedetti 2008). These elements are likely to be influenced by the treatment setting, its context and its meaning. Acupuncture - with its repeated sessions, intense provider contact, slightly painful procedure, an often 'exotic' model of symptom explanation and associated relaxation during sessions - might maximize such effects.
While the average clinical effect of placebo interventions seems to be small (Hróbjartsson 2010), there is some evidence that sham acupuncture is associated with larger effects than, for example, a placebo pill or other non-pharmacological sham interventions. This evidence comes from one of the few randomized trials directly comparing different types of placebo (Kaptchuk 2006), from indirect comparison of trials including both a sham and a no-treatment control (Linde 2010a), and from a network meta-analysis of pharmacological and non-pharmacological treatments and their placebos in migraine prophylaxis (Meissner 2013). Furthermore, a systematic review of randomized trials of acupuncture including both a sham and a no-treatment control found on average moderately large (SMD 0.45) differences (Linde 2010b). It seems highly plausible that both the physiological and strong placebo effects contribute to these considerable 'non-specific' effects of sham acupuncture. For example, a recent trial showed that the size of the effect associated with a sham acupuncture intervention can vary with the amount and characteristics of the patient-provider interaction (Kaptchuk 2008). Both the above explanations would also imply that it would be difficult to detect any small, point-specific effects in addition to potent placebo effects and non-specific needling effects.

Possible bias due to lack of blinding

While participants in the sham-controlled trials were blinded, this was (with the exception of the trial by Hesse 1994) not the case for the comparisons with treatment of acute migraine attacks only, routine care or other treatments. All clinically relevant outcome measures in clinical trials in migraine are patient-reported (IHS 2000; IHS 2012). Preferably, outcomes are documented in diaries for at least four weeks before treatment and for longer time periods during and after treatment. It cannot be ruled out that participants allocated to acupuncture reported positively biased out-

comes, while participants allocated to control reported negatively biased outcomes. However, response rates in participants allocated to drug treatment in the trials included in this review were comparable to those reported in drug trials (Van der Kuy 2002). Also, in groups receiving acute treatment only, response rates were within the range of placebo groups in drug trials (Van der Kuy 2002). In two trials comparing acupuncture and drug treatment (Diener 2006; Streng 2006), a relevant proportion of participants withdrew informed consent immediately after allocation to drug treatment. Additional participants dropped out during the study. This indicates that study participants had a preference for acupuncture. These problems could seriously bias the findings. However, participants not starting treatment were not included in the analyses, and per-protocol analyses confirmed the study findings. Still, these trials must be interpreted with caution.

A fourth possible explanation for the lack of larger effects of true acupuncture over sham comes from the perspective of acupuncture practitioners. The quality of acupuncture interventions in clinical trials is often disputed. Study protocols often limit the flexibility of treatment procedures, particularly in sham-controlled trials, and it is argued that better acupuncturists would have achieved better results. However, response rates in sham-controlled trials were on average similar to those in pragmatic trials with flexible treatments. Furthermore, while there is always the possibility that some expert acupuncturists are particularly successful, in several of the larger trials included in this review the training of treatment providers was at least comparable to that of the average acupuncturists in their country. Still, it cannot be ruled out that inadequate study interventions contribute to the lack of differences compared to sham interventions.

Overall completeness and applicability of evidence

Acupuncture is a therapy which is applied in a variable manner in different countries and settings. For example, in Germany, where the majority of the large trials included in this review were performed, acupuncture is mainly provided by general practitioners and other physicians. Their approach to acupuncture is based on the theories of traditional Chinese medicine, although the amount of training they receive in traditional Chinese medicine is limited (Weidenhammer 2007). In the UK, the providers are likely to be non-medical acupuncturists with a comparatively intense traditional training, physiotherapists or medical doctors with a more 'Western' approach (Dale 1997). The trials included in our review come from a variety of countries, and study designs range from very pragmatic (Jena 2008; Vickers 2004) to more experimental (Linde M 2004). Despite this distinct heterogeneity, within comparisons the findings seem broadly consistent.

Acupuncture is widely used in Asian countries, particularly China. We have not systematically searched Chinese databases for this version of the review, but plan to do so in the future. There is considerable skepticism toward clinical trials from China, as in the past results were almost exclusively positive (Vickers 1998). However, the quality and number of randomized trials published in Chinese have improved over recent years (Wang 2007), and it seems inadequate to neglect this evidence without examining it critically. Most of the identified, registered ongoing trials originate from China. Our update search (in non-Chinese databases) identified a number of trials from China but only two met inclusion criteria (Li 2012; Zhao 2014). When reading excluded trials we noticed several characteristics which suggest that at least some migraine studies from China are different and problematic from the point of view of Western headache research. Excluded trials often included participants with recent-onset of migraine, given acupuncture with the aim of 'curing' the condition. These trials seem hardly comparable to the many trials that included participants who had been suffering from migraine for a long time. Furthermore, most trials, including a group receiving prophylactic drugs, gave these only for four weeks, a period considered much too short by Western headache specialists (IHS 2012). Chinese trials also tend to use a higher number of treatment sessions and higher treatment frequency.

Large-scale observational studies (Jena 2008; Melchart 2006) and a systematic comparison of findings from a randomized and an observational study (Linde 2007a) suggest that the response rates observed in clinical trials are also seen in conditions similar to routine practice. However, as the overall evidence also suggests that factors other than the correct selection of acupuncture points and needling procedures play an important role in outcomes, treatment setting and participant selection could have a strong impact and might vary considerably. For example, a pooled analysis of four trials on chronic pain (including Linde K 2005) found that even four months after completion of treatment, participants who had started acupuncture with a positive attitude and expectation had significantly better outcomes than participants with lower expectations (Linde 2007b).

People with migraine typically suffer from their headaches over many years. A general shortcoming of almost all randomized trials of any prophylactic treatments is their limited duration (rarely ever more than 12 months). Therefore, based on our review nothing can be said on sustainability of effects beyond 12 months.

Quality of the evidence

The methodological quality of the included trials was variable. Methods for sequence generation, allocation concealment, handling of dropouts and withdrawals and reporting of findings were adequate in most of the recent trials. Still, designing and performing clinical trials of acupuncture is a challenge, particularly with respect to blinding and selection of control interventions. We have mentioned that bias cannot be ruled out in the unblinded studies,

and that comparisons with prophylactic drug treatment have to be interpreted with caution due to high dropout rates in two of the trials. Blinding in comparisons with drug treatment could be achieved by double-dummy designs (drug plus sham acupuncture versus acupuncture plus drug placebo) as in the trials by Hesse 1994. However, if it is the case that sham acupuncture interventions are strong placebos and not physiologically inert, this approach would also be problematic.

We considered the overall quality of the evidence for most outcomes to be moderate. Reasons for not considering the quality of evidence to be high were lack of blinding of participants (for comparisons with no acupuncture controls and prophylactic drugs), unblinded treatment providers (all comparisons), indications of heterogeneity for some outcomes or major imprecision in the case of the outcome dropouts due to adverse effects. We did not further downgrade our rating because findings consistently showed clinically relevant effects in spite of variable effect sizes (efficacy outcomes for the comparison with no acupuncture controls) or very similar findings (efficacy outcomes for the comparison with prophylactic drugs).

Potential biases in the review process

We are confident that we have identified the existing large clinical trials relevant to our question, but we cannot rule out the possibility that there are additional small trials which are unpublished or published in sources not accessible to our search.

A relevant problem for systematic reviews on prophylactic treatments of migraine is the highly variable outcome measurement and the often inadequate reporting of results. Various measures of frequency, intensity, analgesic use and other outcomes are used, and as these measures have to be observed over longer time periods, the amount of data needed to obtain a good overview of the course of symptoms is considerable. Most trials in our review reported several outcome measures at different time points without evidence that these were selected in a biased way. Nevertheless, we were confronted with a complex mosaic of data. Several authors kindly provided unpublished data. Some sort of response and frequency measure was available for almost all trials, although the timing of the measurement and details of the measure often differed. As overall results are rather consistent, it seems unlikely that our results would have changed in a relevant manner if missing data had been available.

Four members of the review team were involved in at least one of the included trials. These trials were assessed by other members of the review team. All reviewers currently have affiliations to a CAM (complementary and alternative medicine) research centre, or have had such an affiliation in the past.

Agreements and disagreements with other studies or reviews

We are not aware of any systematic reviews published after the previous version of our review (Linde 2009) focusing exclusively on randomized trials of acupuncture for the prophylaxis of episodic migraine. The analysis of the pooled individual database of the Acupuncture Trialists' Collaboration analysing high quality trials on chronic pain (Vickers 2012) included three trials also included here. The findings are consistent with those presented here. This applies also to a review of placebo- and sham-controlled trials of a variety of pharmacological and non-pharmacological prophylactic treatment focusing on the differential effectiveness of the placebo treatments (Meissner 2013).

Compared to the previous version of our review, findings are similar for the comparisons with no acupuncture and prophylactic drug treatment, while, at a first glance, our current results seem more positive for the comparison with sham. In our previous review there were no statistically significant differences between true and sham acupuncture, neither for frequency nor for response. The main reason is clearly that our current analyses have considerably more power. This is primarily due to inclusion of new trials (particularly, the large Li 2012 trial). Furthermore, the approach to group our analysis by four time windows in our previous version further decreased the number of trials per analysis. Finally, based on the advice of our statistician, in this updatewe have used fixed-effect models instead of random-effects models for the main analyses, which leads to narrower confidence intervals (yet, we also present random-effects estimates confirming our overall results). If one compares effect estimates qualitatively, findings are very similar for the time points after treatment (current version) and two/four months after treatment (previous version). Instead, the addition of the new trials made our findings more positive for six-months' follow-up.

It should also be noted that the original publication of the Li 2012 trial, which compared each of the three tested acupuncture interventions against sham separately, did not report significant differences after treatment. We pooled the data of the three acupuncture groups (ensuring that the sham group was not counted more than once as a control) which explains that the observed difference is statistically significant for this trial in our analyses.

AUTHORS' CONCLUSIONS

Implications for practice

Acupuncture seems to be effective for migraine prophylaxis. The effects over sham acupuncture found in this review were small, but there were clinically relevant effects over no acupuncture/no prophylactic treatment, and acupuncture compared well with prophylactic drugs regarding effectiveness and side effects. As the findings of our main analysis on headache frequency use standardized mean differences as an effect measure they are somewhat difficult to interpret clinically. In terms of number of migraine days, our findings approximately indicate the following: assuming a frequency

of six migraine days per month at baseline, this would be reduced to five days in the no-treatment control group, to four in the sham group and the prophylactic drug group, and to three and a half in the acupuncture group. Acupuncture can be considered as a treatment option for people with migraine needing prophylactic treatment because of frequent or inadequately controlled migraine attacks, particularly people refusing prophylactic drug treatment or experiencing adverse effects from such treatment.

Implications for research

As migraine is a chronic condition, it would be important for clinicians to know how long improvements associated with acupuncture treatment last, whether continued intermittent treatment sustains the effect, and whether a further treatment cycle again leads to improvement. These latter questions might be best investigated in cohort studies. In principle, it seems important to know which types of acupuncture work best, what is the optimal frequency and duration of sessions, and so on. Some studies have not shown important differences in the effects of different acupuncture techniques (Jena 2008; Weidenhammer 2006), but this review found an influence of number of treatment sessions, in line with other evidence on dose (number of needles, number of sessions) of treatment (MacPherson 2013); these issues could also be investigated in observational studies. For decision-makers it would be important to know who is sufficiently qualified to deliver acupuncture. Randomized trials comparing outcomes after treatment by different types of practitioner are desirable, although very large sample sizes would be needed. Such studies would also be interesting from a more scientific perspective because it is unclear to what extent the effects of acupuncture are mainly mediated by context variables and generalized (i.e. not specific to traditional points) needling effects, and what contribution correct point location makes. Although further sham-controlled trials are desirable, we think that such studies should not have the highest priority unless they also address other important questions. Further comparisons with prophylactic drug treatment and other non-pharmacological interventions are needed. To facilitate future meta-analyses, it would be helpful if some standards for reporting outcome data were established.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alecrim 2005

Methods	This trial is only available as an abstract publication. On request the first author informed us that sequence generation, allocation concealment and blinding were performed as in Alecrim 2008. Triallists performed both intention-to-treat analyses and analyses based on available data
Participants	Number of participants included/analysed: 64/64 (in intention-to-treat analysis; information from author) Condition: migraine with or without aura Demographics: not reported Setting: outpatient headache clinic of a neurology department of State University of Campinas, Brazil Time since onset of headaches: not reported
Interventions	Acupuncture points: individualized selection according to traditional Chinese medicine DeChi achieved?: yes (information from author) Number of treatment sessions: 16 Frequency of sessions: 2/week for first 4 weeks, then 1/week for 8 weeks (information from author) Information on acupuncturists: 1 acupuncturist trained in Spain and 12 years of practical experience (information from author) Control intervention: sham acupuncture (superficial needling without manipulation at non-indicated points)
Outcomes	Method for outcome measurement: diary
Notes	This trial is the third in a series performed by the study authors. The trials Alecrim 2006and Alecrim 2008 were performed before this study. The authors provided data for effect size calculations (50% response rates, migraine days, attacks, rescue medication use)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.
Allocation concealment (selection bias)	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.

Alecrim 2005 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.
Selective reporting (reporting bias)	Unclear risk	Only published abstract available, therefore the study was not assessed formally. According to study authors, methods are the same as in Alecrim 2006 and Alecrim 2008.

Alecrim 2006

Methods	Blinding: participants, research assistants, neurologist; blinding tested and successful Dropout/withdrawals: substantial bias is unlikely in the first 3 months, but it cannot be ruled out for late follow-up (< 10% attrition (3/31) in the first 3 months, 5/31 until end of month 5, 7 /31 until end of month 9; similar rates in both groups; no intention-to-treat analysis) Observation period: 4 weeks baseline, 12 weeks treatment, 24 weeks follow-up Acupuncturists' assessments: GA similarly/70% - BB differently/60%
Participants	Number of participants included/analysed: 31/28 Condition: migraine with or without aura (IHS 1988) Demographics: mean age 32.5 (acupuncture) and 39.1 (sham) years, 79% female Setting: outpatient headache clinic of a neurology department of State University of Campinas, Brazil Time since onset of headaches: mean 16.9 (acupuncture) and 20.0 (sham) years
Interventions	Acupuncture points: semi-standardized point selection (GB12/20/21 and BL10 in all participants + individualized additional points from a selection); point selection for a participant was not changed over treatment sessions Information on acupuncturists: 1 acupuncturist trained in Spain and 12 years of practical experience (information from author) De-Chi achieved?: yes Number of sessions: 16 (30 min each) Frequency of treatment sessions: 2/week for first 4 weeks, then 1/week for 8 weeks Control intervention: sham (superficial needling without manipulation at non-indicated points Ex-B1, SJ17/20, Sp7, St37, Lu5)

Alecrim 2006 (*Continued*)

Outcomes	Method for outcome measurement: diary Primary outcomes: at least 40% reduction in attack frequency, at least 50% attack reduction and total migraine days during treatment period Other outcomes: frequency of migraine attacks, duration of attacks, severity, migraine hours, rescue medication, nausea and vomiting frequency
Notes	Rigorous but small trial; selection of existing acupuncture points in the sham group problematic Authors provided additional information on methods and data for effect size calculations (50% response rates, migraine days, attacks, rescue medication use)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random digits (reference 14) were used to define the sequence"
Allocation concealment (selection bias)	Low risk	Opaque, numbered and sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded; test of blinding suggests successful blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Low attrition unlikely to cause major bias: 3 of 31 participants (2 of 16 acupuncture, 1 of 15 sham) did not complete the 12-week treatment phase
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	13 participants in both groups at 2 month follow-up after treatment (5 months after randomisation) and 12 in both groups at 6 months after treatment (9 months after randomisation); no intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Relevant outcomes described in publication and additional data provided on request

Alecrim 2008

Methods	Blinding: participants, research assistants, neurologist; blinding tested and successful Dropouts/withdrawals: bias unlikely - during the first 3 months only 1 patient in sham group without diary data, at late follow-up 1 exclusion and 1 lacking diary in the acupuncture group Observation period: 4 weeks baseline, 12 weeks treatment, 24 weeks follow-up Acupuncturists' assessments: GA can't tell - BB can't tell
Participants	Number of participants included/analysed: 37/36 Condition: migraine with or without aura (IHS 1988) Demographics: mean age 35 years, 89% female Setting: outpatient headache clinic of a neurology department of State University of Campinas, Brazil Time since onset of headaches: mean 20.6 (acupuncture) and 14.5 (sham) years
Interventions	Acupuncture points: individualized selection based on principles of traditional Chinese medicine DeChi achieved?: yes Number of treatment sessions: 16 (30 minutes each) Frequency of sessions: 2/week for first 4 weeks, then 1/week for 8 weeks (not reported in paper) Information on acupuncturists: 1 acupuncturist trained in Spain and 12 years of practical experience (information from author) Control intervention: very superficial insertion of 10-15 needles at acupuncture points considered irrelevant for headache (some on the head)
Outcomes	Method for outcome measurement: diary Primary outcome: at least 50% attack reduction (each month) Other outcomes: at least 40% attack reduction, attack frequency, number of migraine days, migraine hours, duration per attack, severity, amount and type of rescue medication, nausea and vomiting frequency
Notes	Rigorous but small trial; selection of existing acupuncture points in the sham group problematic First author provided additional information on methods and data for effect size calculations (50% response rates, migraine days, attacks, rescue medication use)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Use of random digits as in Alecrim 2006
Allocation concealment (selection bias)	Low risk	Opaque and sealed envelopes; inclusion by independent neurologist
Blinding (performance bias and detection bias) All outcomes	Low risk	participants blinded; test of blinding suggests successful blinding

Alecrim 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	36 of 37 randomized participants (1 dropout sham group) included in analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	34 of 37 participants with data at long-term follow-up (2 vs. 1 dropouts/withdrawals)
Selective reporting (reporting bias)	Low risk	Relevant outcomes described in publication and additional data provided on request

Allais 2002

Methods	Blinding: diary evaluator Dropouts/withdrawals: substantial bias unlikely (attrition only 10 of 160 participants in 6 months) Observation period: baseline 2 months; treatment 6 months, no follow-up Acupuncturists' assessments: BB different/65% - AW different/55%
Participants	Number of participants included/analysed: 160/150 Condition: migraine without aura (IHS) Demographics: mean age 38 years; all female Setting: Women's Headache Center, University of Turin, Italy Age at onset of headaches: mean 18 years
Interventions	Acupuncture points: LR3, SP6, ST36, CV12, LI4, PC6, GB20, GB14, Taiyang, GV20 Information on acupuncturists; n = 3, "experienced and qualified" DeChi achieved?: yes Number of treatment sessions: 12 Frequency of treatment sessions: 1/week for 2 months, then 1/month for 4 months Control intervention: flunarizine 10 mg (2 months daily, then 20 days per month for 4 months)
Outcomes	Method for outcome measurement: headache diary Primary outcome: attack frequency Other outcomes: intensity, use of rescue medication
Notes	Unblinded, but otherwise rigorous trial; additional information provided from author The paper presents data on attack frequency and analgesics use for 2-month intervals. For calculating mean differences in this review the means for attack frequency presented in the publication were divided by 2, as all other trials refer to 4-week periods. The same was done with the standard deviations provided by the study author. For calculation of standardized mean differences we used the 2-month means presented in the publication. We imputed frequency of response from baseline means and post-treatment (months 3-4) and follow-up (months 5-6) means and standard deviations

Allais 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central telephone procedure (information from author)
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded; diary evaluation blinded
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Only 10 (3 acupuncture, 7 flunarizine) of 160 participants did not complete the study
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	Only 10 (3 acupuncture, 7 flunarizine) of 160 participants did not complete the study
Selective reporting (reporting bias)	Low risk	Relevant outcomes presented

Ceccherelli 1992

Methods	Blinding: participants, statistician (information from author) Dropout/withdrawals: no dropouts mentioned in the publication (first author remembers that there were a limited number of participants dropping out from the study, but he did not document the exact number) Observation period: baseline unclear; treatment 10 weeks; follow-up only in participants with good response Acupuncturists' assessments: GA similarly/70% - BB differently/45%
Participants	Number of participants included/analysed: 30?/30 Condition: migraine without aura Demographics: mean age 40 years; 9 female, 6 male in acupuncture group; 15 female in sham group Setting: unclear, Italy Time since onset of headaches: 179 +/- 127 months (control group: 226 +/- 140)
Interventions	Acupuncture points: BL 2, BL10, BL 60, GB 3, GB 20, GV 11, GV 20, LR 3, CV 13 Ex HN1, ST 8 (on non-painful side) Information on acupuncturist: n = 1, trained 3 years DeChi achieved?: no information Number of treatment sessions: 10 Frequency of treatment sessions: 1/week

Ceccherelli 1992 (*Continued*)

	Control intervention: placebo acupuncture (complex procedure without real needling suggesting superficial anaesthesia to the patient)
Outcomes	Method for outcome measurement: headache diary Primary outcome: at least 50% score reduction Other outcomes: headache hours, intensity
Notes	Participants were not informed that they might get a placebo; unusual sham technique; sex differences between groups; no interpretable follow-up data (only follow-up of responders)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table (information from author)
Allocation concealment (selection bias)	Low risk	Numbered envelopes, inclusion and random allocation by different persons (information from author)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded. The sham procedures differed from true acupuncture but participants were not informed that they might get a placebo
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Unclear risk	No dropouts mentioned. The author reports on request that there were a few participants who did not complete the study
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	Follow-up only performed in treatment responders
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported

Diener 2006

Methods	Blinding: participants (comparison acupuncture vs. sham), telephone interviewers; blinding acupuncture vs. sham tested and successful Dropouts/withdrawals: no bias for comparison with sham acupuncture, major bias possible for comparison with medication (8 of 313 participants allocated to acupuncture withdrew consent before the first treatment, 11 of 339 allocated to sham acupuncture and 106 of 308 allocated to standard treatment; after start of treatment 15 of 305 in the acupuncture group did not reach the primary endpoint, 11 of 328 in the sham acupuncture group and 15 of 202 in the standard treatment group) Acupuncturists' assessment: GA similarly/85% - BB similarly/70%
Participants	Number of participants included/analysed: 960/794 Condition: migraine (IHS) Demographics: mean age 37 years, 83% female Observation period: 4 weeks baseline, 6 weeks treatment (+ optionally 2 further weeks) , 20 weeks follow-up Setting: 149 primary care physicians in Germany Time since onset of headaches: mean 16 years
Interventions	Acupuncture points: semi-standardized - depending on Chinese syndrome diagnosis predefined collections of obligatory and flexible points Information on acupuncturists: 149 physicians with at least 140 hours' acupuncture training and 2 years' professional experience DeChi achieved?: yes Number of treatment sessions: 10 (if moderate response further 5 sessions possible) Frequency of treatment sessions: 2/week Control intervention 1: sham acupuncture (superificial needling at distant non-acupuncture points) Control intervention 2: guideline-based individualized standard treatment - 1. preference beta-blockers, 2. preference flunarizine, 3. preference valproic acid
Outcomes	Method for outcome measurement: diary and interviews Primary outcome: difference in migraine days between baseline and weeks 23-26 after randomisation Other outcomes: migraine days, medication use, response (defined as at least 50% reduction of migraine days), pain intensity, impairment, pain days, quality of life, global assessments
Notes	Very large, rigorous multicenter trial. The interpretation of the comparison with standard treatment is compromised by the fact that more than a third of participants allocated to standard treatment withdrew consent. No information is given on dosage and compliance in the standard treatment group. Authors provided biometrical report Data for migraine days and response at 6, 13 and 26 used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists' Collaboration (see section Data collection and analysis)

Risk of bias

Bias	Authors' judgement	Support for judgement

Diener 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central fax procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and telephone interviewers were blinded for the comparison with sham acupuncture. Test of blinding suggests successful blinding (low risk of bias). The comparison with drug treatment was not blinded (high risk of bias)
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Very low attrition and intention-to-treat analysis for comparison with sham acupuncture (low risk of bias). For the comparison with drug treatment the risk of bias is high as a large proportion of participants allocated to drug treatment withdrew consent immediately after randomisation or discontinued treatment
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	Very low attrition and intention-to-treat analysis for comparison with sham acupuncture (low risk of bias). For the comparison with drug treatment the risk of bias is high as a large proportion of participants allocated drug treatment withdrew consent immediately after randomisation or dropped out
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported and additional data provided on request

Facco 2008

Methods	Blinding: participants (no blinding for the comparison with rizatriptan only). Participants were informed that stronger (for true acupuncture group) and milder (for mock acupuncture control groups) acupuncture treatments would be applied (information from author) Dropouts/withdrawals: 17 of 160 in the first 3 months (5, 5, 5, and 2 in the 4 groups) , further 16 in the following 3 months (3, 5, 4, 4); no intention-to-treat analysis - bias cannot be ruled out with certainty but does not seem likely Observation period: no baseline period, treatment 11 weeks, follow-up 3 months Quality scores: Acupuncturists' assessments: GA similarly/80% - BB similarly/60%

Facco 2008 (*Continued*)

Participants	Number of participants included/analysed: 160/127 Condition: migraine without aura (IHS) Demographics: mean age 36 years 54% female Setting: unclear, Italy Time since onset of headaches: > 1 year inclusion criterion
Interventions	All participants treated acute attacks with rizatriptan Acupuncture points: depending on the Chinese diagnosis (3 external and 4 internal syndromes) predefined point selection DeChi achieved?: yes Number of treatment sessions: 20 (2 courses of 10 sessions with 1 week rest between the courses) of 30 minutes each Frequency of sessions: 2/week Information on acupuncturists: n = 3, at least 560 hours training and 5 years clinical experience (information from authors) Control intervention 1: non-penetrating sham (non-penetrating needles with manipulation) at correct, individualized points with full process of Chinese diagnosis ("ritualised mock acupuncture") Control intervention 2: non-penetrating sham (non-penetrating needles with manipulation) at standardized points (ST8, GB5, GB20, GV14, LU7) without the process of Chinese diagnosis ("standard mock acupuncture") Control group 3: attack treatment with rizatriptan only
Outcomes	Method for outcome measurement: Migraine Disability questionnaire (MIDAS) at baseline and after 3 and 6 months + number of rizatriptan wafers per 3-month period
Notes	Only MIDAS score and rizatriptan intake measured, poor description of the sample, surprisingly little variability in several post-treatment and follow-up measures

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Sealed, opaque, consecutively numbered envelopes (information from author)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded for the comparison with the two sham groups (low risk of bias); no blinding for the comparison with Rizatriptan only (high risk of bias). Participants were informed that stronger and milder acupuncture treatments would be applied (information from author)

Facco 2008 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	High risk	33 of 160 dropped out; reasons were not reported; no intention-to-treat analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	High risk	33 of 160 dropped out; reasons were not reported; no intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Very limited outcome measurement; outcomes measured were adequately reported

Facco 2013

Methods	Blinding: no blinding Dropouts/withdrawals: 18 participants (9 both in acupuncture and medication group) dropped out (3 vs. 4 refusing allocated treatment; without reporting group: 9 problems with work or moving town, 1 severe traffic accident, 1 tumour) Observation period: no baseline period, about 3 months treatment, 3 months post-treatment follow-up Acupuncturists's assessment: GA similarly/85% - BB differently/55%
Participants	Number of participants included/analysed: 100/82 Condition: migraine without aura (IHS) Demographics: median age 40 (acupuncture group) and 34 years (valproate group); 66% female Setting: Institute for Traditional Medicine in Rome, Italy Time since onset of headaches: median 4 years (inclusion criterion at least 1 year)
Interventions	Acupuncture points: following Chinese syndrome classification; for exogenous syndromes: GB20, ST8, EX-HN5, plus GB8, BL12, BL60, in wind-cold syndrome, or plus TE5 and GV14 in wind-heat syndrome, or plus ST40, SP6 and CV12 in wind-dampness syndrome. For endogenous syndromes: a) hyperactivity of liver yang acupoints GB8, GB20, GB38, ST8, LR3,4, EX-HN5; b) obstruction of middle jiao due to damp-phlegm acupoints ST8, ST40, SP9,GV23, CV12, EX-HN5; c) deficiency of kidney essence acupoints GB12, GB20, BL10, BL12, BL23, KI3; stagnation of qi and blood acupoints GB8, GB20, SP6, SP10, LR3, EX-HN5, plus ashi (trigger) points on GB channel Information on acupuncturists: Licence certificated, number unclear Number of sessions: 2 courses of 10 sessions, with 1 week rest between the 2 sessions Frequency of sessions: 2/week Control intervention: valproic acid 600 mg/day for 3 months All participants used 10 mg rizatriptan (wafer) for attack treatment (second dose allowed if attack persist)
Outcomes	Migraine Disability (MIDAS) Questionnaire, pain intensity, Pain relief Score (PRF), rizatriptan intake

Facco 2013 (*Continued*)

Notes	Publication reports medians and interquartile ranges; author provided means and variability data for MIDAS data. However, we decided to not include the data on efficacy into meta-analyses because standard deviation seemed clinically implausibly small, not consistent with P values from regression analyses, and the first author could not clarify the problem

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generator in MS Excel; stratified for sex
Allocation concealment (selection bias)	Unclear risk	Centrally stored, numbered sealed envelopes, but no further details
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Unclear risk	18 of 100 participants (9 both in acupuncture and medication group) dropped out (3 vs. 4 refusing allocated treatment; without reporting group: 9 problems with work or moving town, 1 severe traffic accident, 1 tumour)
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	As above
Selective reporting (reporting bias)	Low risk	MIDAS data presented in detail; details of diary data not presented, but this was only secondary

Hesse 1994

Methods	Blinding: participants and evaluators Dropouts/withdrawals: bias unlikely (8 of 85 participants dropped out) Observation period: baseline 4 weeks; treatment 17 weeks; no follow-up Acupuncturists' assessments: GA completely differently/50% - BB different /30%
Participants	Number of participants included/analysed: 85/77 Condition: migraine with or without aura (IHS) Demographics: mean age 45 years; 84% female Setting: outpatient pain clinic in Denmark Time since onset of headaches: mean 23 years

Hesse 1994 (*Continued*)

Interventions	Acupuncture points: needling individual trigger points together with placebo tablets Information on acupuncturist: n = 1, no further information DeChi achieved?: no information Number of treatment sessions: individualized Duration of treatment sessions: needling for a few seconds only Control intervention: beta blocker metoprolol 100 mg and placebo stimulation (superficial touch with blunt end of the needle)
Outcomes	Method for outcome measurement: diary Primary outcome: probably attack frequency Other outcomes: severity, duration, global rating, consumption of analgesics
Notes	Rigorous trial; sham acupuncture procedure possibly distinguishable; non-traditional acupuncture technique (brief needling at trigger points); mean frequency and mean severity of attacks in the last 4 weeks were recalculated from raw data in Figure 1

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Blinding was obtained through a double-dummy technique and by keeping the therapist blinded to the results, whilst both investigator and statistician were blinded to the treatment" Dry needling of individual trigger point was used in the acupuncture group compared to a superficial touch with the blunt end of the needle in the medication/sham acupuncture group at a random selection of points. The success of blinding is not discussed. The way of informing participants about interventions is not reported. No details on the drug placebo reported
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	8 of 85 participants dropped out. Analysis according to intention-to-treat principle
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	Probably rigorous trial with data presented in a manner not feasible for effect size calculation. Authors could not be contacted. Trial ended 17 weeks after randomisation

Hesse 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant outcomes reported

Jena 2008

Methods	Blinding: none Dropouts/withdrawals: 1479 of 1613 included in the acupuncture group with 3 month data vs. 1456 of 1569 in the control group; sensitivity analyses with missing values replaced confirm main analysis based on available data; in addition the trial observed 11, 874 non-randomized participants receiving acupuncture Observation period: no baseline period; treatment 3 months; no follow-up (for randomized comparison) Acupuncturists' assessments: GA can't tell - AW can't tell
Participants	Number of participants included/analysed: 3182/2935 with migraine or tension-type headache (TTH) (of those included 1715 with migraine, 167 with migraine and TTH, no information on numbers of migraine participants analysed) Condition: migraine and/or TTH (IHS) Demographics: mean age 44 years, 77% female (for total group) Setting: 4686 practices in Germany Time since onset of headaches: 10.8 years (for total group)
Interventions	Acupuncture points: not documented (acupuncturists were free to treat outside the trial in routine acupuncture practice) Information on acupuncturists: at least 140 hours acupuncture training DeChi achieved?: no information Number of treatment sessions: up to a maximum of 15 (mean 10) Frequency of treatment sessions: individualized Control intervention: waiting list received "usual care" (without acupuncture)
Outcomes	Method for outcome measurement: questionnaires, no diary Primary outcome: headache days in the third month Other outcomes: pain intensity, quality of life
Notes	Large, very pragmatic study including both participants with migraine and TTH; treating physicians were completely free to choose points, number of sessions (upper limit allowed 15) etc. Unclear what usual care consisted of. Some diagnostic misclassification likely. Study authors provided raw means, standard deviations and number of observations for headache days and headache intensity for participants suffering from migraine Data for headache days and response at 3 months used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists' Collaboration (see section Data Collection and Analysis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Jena 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central telephone randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	1711 participants were allocated to acupuncture and 1693 to control, but consent forms were available for only 1613 and 1569, respectively; baseline questionnaires were available for 1572 and 1522 (all numbers refer to both participants with migraine and participants with TTH). 3-month data were available for 1479 and 1456 participants. Sensitivity analyses with replacing missing values confirmed main analyses
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	Not applicable - participants in the waiting list group received acupuncture after 3 months. While all participants were followed for six months this was no longer a randomized comparison of two treatments
Selective reporting (reporting bias)	Low risk	Limited outcome measurement. Data on relevant outcomes for migraine subgroup provided by study authors

Li 2012

Methods	Blinding: participants, outcome 'assessors', statisticians Dropout/withdrawals: 34/476 dropouts + 4 participants excluded post-randomisation, ITT analysis Observation period: 4 weeks baseline, 4 weeks treatment, follow-up weeks 5-8 and weeks 13-16 after randomisation Acupuncturists' assessment: GA completely different/20% - YF similarly/70%
Participants	Number of participants included/analysed: 480/476 Condition: migraine with or without aura (IHS second edition) Demographics: mean age 37 (SD 12) years, 83% female Setting: 9 hospital departments in China Time since onset of headaches: mean 98 months

Interventions	Acupuncture points (3 treatment groups): group 1) Shaoyang-specific acupuncture at TE5, GB34, GB40, GB20; group 2) Shaoyang nonspecific acupuncture with TE19, TE8, GB33, GB42; group 3) Yangming-specific acupuncture with ST8, LI6, ST36, ST42; in all groups, point selection for a participant was not changed over treatment sessions. Acupuncture was applied unilaterally, alternating between the left and right sides. Auxiliary points: 2 mm lateral to every acupoint or non-acupoint and punctured to a depth of 2 mm without manual stimulation. Transcutaneous electric acupoint stimulation (HANS: Han's acupoint nerve stimulator, HANS-200, made in Nanjing, China) at every acupoint or non-acupoint after needle insertion Information on acupuncturists: specialized acupuncturists who had at least 5 years' training and five years' experience; number not reported DeChi achieved?: yes Number of treatment sessions: 20 Frequency of treatment sessions: 5/week Control intervention: sham acupuncture on the points below with manipulation: i) in the medial arm on the anterior border of the insertion of the deltoid muscle at the junction of deltoid and biceps muscles; ii) the edge of tibia 1-2 cm lateral to the ST36 horizontally; iii) half between the tip of the elbow and the axilla; iv) ulnar side, half between epicondylus medialis of the humerus and ulnar side of the wrist. Auxiliary points: 2 mm lateral to every acupoint or non-acupoint and punctured to a depth of 2 mm without manual stimulation. Transcutaneous electric acupoint stimulation (HANS: Han's acupoint nerve stimulator, HANS-200, made in Nanjing, China) is used for electro-acupuncture stimulation at every acupoint or non-acupoint after needle insertion. DeChi not sought
Outcomes	Method for outcome measurement: diary, questionnaire Primary outcome: number of migraine days in weeks 5-8 Other outcomes: migraine attacks, intensity of migraine, intensity of pain, medication intake, Migraine Specific Quality of Life Questionnaire
Notes	Data for migraine days, attack frequency, intensity and response in weeks 5-8 and weeks 13-16 used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists' Collaboration (see section Data collection and analysis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomisation sequence (blocked, stratified for centres) was generated by use of the randomisation module of the synthesized management platform of the Chengdu Good Clinical Practice Centre (block length 12, unknown to centres)."
Allocation concealment (selection bias)	Low risk	"randomisation was performed by the National Clinical Trial Center of Chinese

Li 2012 (*Continued*)

		Medicine, Chengdu Good Clinical Practice Center. Central randomisation was performed by text messages sent by the investigator or by use of a website and email confirmation."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Patients, outcome assessors and statisticians were blinded as to randomisation. Patients were informed that they would receive one of four types of acupuncture treatment, three of which used traditional Chinese acupuncture theories and one which was based on modern acupuncture theory. "
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	34/476 dropouts + 4 participants excluded post-randomisation. Number and reasons for dropout similar in the four groups, ITT analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	See above
Selective reporting (reporting bias)	Low risk	Detailed reporting of findings for main outcomes; pain medication use not reported

Linde K 2005

Methods	Blinding: participants, diary evaluators Dropouts/withdrawals: major bias unlikely Observation period: baseline 4 weeks; treatment 8 weeks; follow-up 16 weeks Acupuncturists' assessments: AW similarly/80% - GA exactly as in the study/90%
Participants	Number of participants included/analysed: 302/302 Condition: Migraine (IHS) Demographics: mean age 43 years, 88% female Setting: 18 primary care practices in Germany Time since onset of headaches: mean 20 years
Interventions	Acupuncture points: in all participants recommended GB20, GB40 or 41 or 42, DU20, LIV3, SJ3 or 5, Taiyang; additional optional points recommended according to individual symptoms Information on acupuncturists: n = 30, at least 160 h of training DeChi achieved?: yes Number of treatment sessions: 12 of 30 minutes Frequency of treatment sessions: 2/week for 4 weeks, then 1/week for 4 weeks

	Control intervention: minimal acupuncture (superficial needling at non-acupuncture points) Control 2: waiting list (attack treatment only) for 12 weeks
Outcomes	Method for outcome measurement: diary and pain questionnaire Primary outcome: number of days with moderate or severe headache in weeks 9-12 Other outcomes: migraine days, attacks, headache days; days with nausea, vomiting, disability, analgesics, headache score, intensity; quality of life, pain disability, depressive symptoms
Notes	Additional information from unpublished study report used for 8-week data, migraine days and headache scores Data for number of days with moderate or severe headache, migraine days, and response in weeks 5-8, 9-12 and 21-24 used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists Collaboration (see section Data Collection and Analysis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central telephone procedure
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and diary evaluators were blinded for the comparison with sham acupuncture. Participants were informed that two different types of acupuncture were compared. Early tests of blinding indicate successful blinding, but at follow-up guesses of allocation status were different between groups (although the sham group reported slightly better outcomes). Overall we considered the risk of bias low. Comparison with no treatment waiting list not blinded (high risk of bias)
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Low attrition and intention-to-treat analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	Low attrition and intention-to-treat analysis

Linde K 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant outcomes reported and additional data available for analyses

Linde M 2000

Methods	Blinding: none Dropouts/withdrawals: substantial bias possible (16 of 39 participants dropped out/not included in analysis) Observation period: baseline 4 weeks; treatment 4-6 weeks; follow-up 12 weeks Acupuncturists' assessments: GA differently/45% - BB differently/40%
Participants	Number of participants included/analysed: 39/23 Condition: migraine without aura (IHS) Demographics: mean age 41 years, 82% female Setting: Gothenburg Migraine Clinic, Sweden Time since onset of headaches: more than 20 years on average
Interventions	Acupuncture points: GB40, GB14, DU20, LI4 and ST44 in all participants + additional points selected according to symptoms Information on acupuncturists: 1 experienced physiotherapist DeChi achieved?: yes Number of treatment sessions: 7-10 Frequency of treatment sessions: 1-2 sessions/week Control intervention: no acupuncture All participants received pharmacological acute treatment as before the study
Outcomes	Method for outcome measurement: diary Primary outcome: migraine days Other outcomes: attack frequency, medication use
Notes	Pilot study hardly interpretable due to very high dropout rate; one patient in the acupuncture group had no migraine days during the baseline period and 26 during follow-up; some additional information provided by authors (M Linde and C Dahlöf). The trial originally had a third arm (relaxation) but results were not reported and are not available

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number list
Allocation concealment (selection bias)	High risk	Inadequate method, although bias seems unlikely (random list was openly accessible to the physician including the patient; this physician was, however, not involved further - information from author)

Linde M 2000 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	High risk	16/39 participants (9 acupuncture, 7 control) dropped out early or could not be analysed. Detailed description, no intention-to-treat analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	High risk	See above
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported

Linde M 2004

Methods	Blinding: participants, statistical analysis Dropouts/withdrawals: 3 during treatment, further 5 during follow-up, major bias unlikely Observation period: baseline at least 2 months; treatment 3 months; 6 months follow-up Acupuncturists' assessments: GA completely differently/20% - BB differently/45%
Participants	Number of participants included/analysed: 31/28 Condition: menstrual-related migraine without aura (IHS) Demographics: mean age 36 years, all female Setting: Gothenburg Migraine Clinic, Sweden (information provided by study author) Time since onset of headaches: not reported
Interventions	Acupuncture points: in all participants GB8, GB20, LI4, LR3, SP6 + either GB14, Taiyang or UB10 depending on site of maximum pain Information on acupuncturists: 2 experienced physiotherapists DeChi achieved?: yes Number of treatment sessions: 9 sessions Frequency of treatment sessions: 8, 5, and 3 days before expected date of menstruation in three cycles Control intervention: non-penetrating sham needles at the same points All participants wore a cap on the head to allow fixation of plaster holders through which both true and sham needles were applied
Outcomes	Method for outcome measurement: diary Primary outcome: migraine attack frequency Other outcomes: migraine days, intensity, medication use, intensity

Notes	Rigorous but small study; use of non-penetrating sham needles at true points; additional information provided by study author. As frequency measure after treatment, only attack frequency was reported, while migraine days was reported for other time-points in addition to attack frequency. For consistency, we used migraine attack data also in the analysis of frequency in follow-up. The number of responders was only reported after treatment. Response for later time-points was imputed from means and standard deviations for attack frequency

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table (information from author)
Allocation concealment (selection bias)	Unclear risk	Method not optimal, but bias seems unlikely: inclusion of participants by a neurologist, then a research nurse randomly took a twice folded card from a collection of six cards prepared by the neurologist; the opened card was forwarded to the acupuncturist who met the prescheduled participants (information provided by study author)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and data analysis blinded. Test suggests that blinding was successful
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Low attrition rate and intention-to-treat analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	Acceptable attrition rate and intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Relevant outcome reported

Streng 2006

Methods	Blinding: diary evaluators Dropouts/withdrawals: substantial bias possible Observation period: baseline 4 weeks; treatment 12 weeks; follow-up 12 weeks Acupuncturists' assessments: BB similarly/80% - GA similarly/90%
Participants	Number of Participants included/analysed: 114/89 Condition: migraine (IHS) Demographics: mean age 40 years, 88% female Setting: 17 primary care practices in Germany Time since onset of headaches: mean 16 years
Interventions	Acupuncture points: individualized Information on acupuncturists: n = 21, at least 160 hours acupuncture training DeChi achieved?: yes Number of treatment sessions: on average 13.4 Frequency of treatment sessions: 1-2/week Control intervention: Metoprolol 100-200 mg daily for 3 months
Outcomes	Method for outcome measurement: diary and pain questionnaires Primary outcome: migraine days (in weeks 9-12) Other outcomes: migraine attacks, headache days, days with rescue medication, at least 50% attack/migraine days reduction, days with nausea, vomiting, disability; intensity, headache score; quality of life, pain disability, depressive symptoms
Notes	Additional information available from full study report; more dropout in metoprolol group Data on number of participants with side effects taken from full study report (patient questionnaire) Data migraine days, and response in weeks 5-8, 9-12 and 21-24 used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists' Collaboration (see section Data collection and analysis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program
Allocation concealment (selection bias)	Low risk	Central telephone randomisation
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded; diary evaluators blinded
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	High risk	Unequal attrition in the two groups: very low in acupuncture group while a relevant proportion of participants in the metoprolol group either withdrew consent imme-

Streng 2006 (*Continued*)

		diately after randomisation or dropped out later
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	High risk	See above
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported

Vickers 2004

Methods	Blinding: none Dropouts/withdrawals: careful handling of dropouts and withdrawals - substantial bias unlikely Observation period: 4 weeks baseline; 3 months treatment; 9 months follow-up Acupuncturists' assessments: GA can't tell - BB exactly as in the trial/90%
Participants	Number of participants included/analysed: 401/326 at 3 months and 301 at 12 months Condition: 94% migraine, 6% tension-type headache (IHS) Demographics: mean age 46 years, 84% female Setting: 12 separate sites consisting of a single acupuncture practice and 2-5 general practices in the UK Time since onset of headaches: mean 21 years
Interventions	Acupuncture points: individualized Information on acupuncturists: 12 practices, members of the Acupuncture Association of Chartered Physiotherapists with at least 250 hours acupuncture training (median 12 years acupuncture practice) DeChi achieved?: not reported Number of treatment sessions: median 9, (25th and 75th percentiles 6 and 11) in 3 months Frequency of treatment sessions: median 1/week Control intervention: usual care by general practitioner
Outcomes	Method for outcome measurement: diary and questionnaires Primary outcome measure: headache score (at 1 year) Other outcomes: headache days, severity, % improvement, medication use, at least 50% reduction of headache days, quality of life
Notes	Pragmatic trial with additional cost-effectiveness analysis Data for headache and response at 3 and 12 months used for meta-analysis in this review were obtained from individual patient data re-analysis within the Acupuncture Trialists' Collaboration (see section Data collection and analysis)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Vickers 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated minimization procedure (gender, age, chronicity, severity, diagnoses and number per group as minimized variables)
Allocation concealment (selection bias)	Low risk	Secure, password protected database
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Acceptable attrition rates and sensitivity analyses (several imputations for missing values) confirming primary analysis
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	See above
Selective reporting (reporting bias)	Low risk	Relevant outcomes reported

Vincent 1989

Methods	Blinding: participants Dropouts and withdrawals: bias unlikely for treatment and early follow-up (only 2/32 participants did not complete this phase), for late follow-up attrition is also comparably low (6/32) but bias cannot be ruled out completely Observation period: baseline 4 weeks; treatment 6 weeks; follow-up 1 year Acupuncturist's GA assessment: similarly/75% - BB similarly/70%
Participants	Number of participants included/analysed: 32/30 (6-week follow-up)/26 (1-year follow-up) Condition: classical or common migraine Demographics: mean 37 years; 84% female Setting: university outpatient department, UK Time since onset of headaches: mean 20 years
Interventions	Acupuncture points: classical points chosen individually by tenderness; 8 both local and distant points used No information on acupuncturist(s) DeChi achieved?: no information Number of treatment sessions: 6 sessions of 15 minutes each Frequency of treatment sessions: 1/week Control group intervention: superficial needling only, 2-3 cm from classical points

Vincent 1989 (*Continued*)

Outcomes	Method for outcome measurement: diary Primary outcome: total weekly pain score Outcomes: pain-free days, intensity, medication use
Notes	Significant effect on intensity, but no relevant effect on number of pain-free days; credibility of blinding tested; rigorous trial; author provided individual patient data which allowed calculation of responders and number of headache days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes (information from author)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants blinded. Test suggests successful blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	Very low attrition rate (3/32 participants) in early phase of the trial
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	25/32 participants completed the follow-up 4 months after treatment and 26/32 participants after 12 months; no intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Most important outcomes presented and individual patient data for headache days provided

Wallasch 2012

Methods	Blinding: participants (personnel doing transcranial Doppler measurement - data not used for meta-analysis) Droput/withdrawals: It seems that 5/18 acupuncture and 3/17 sham participants were excluded from analysis due to missing Doppler data Observation period: 6 weeks baseline, 8 weeks treatment, 12 weeks follow-up Acupuncturists' assessment: BB differently/50% - AW similarly/85%
Participants	Number of participants included/analysed: 35/27 Condition: migraine with or without aura (IHS second edition) Demographics: mean age 38 years, 31/35 participants female Setting: not reported

Wallasch 2012 (*Continued*)

	Time since onset of headaches: mean 18 years
Interventions	Acupuncture points: chosen by expert consensus. 6-10 needles used (however, the given points required a total of 22 needles; therefore a selection was used. But the text states: "the same combination of acupuncture points and mode of stimulation was used in all participants and sessions". Available points were LI4, ST36, TE5, GB41, SI3, BL62, GV20, GB20, Taiyang, TE23, LR3, KI3 Information on acupuncturists: licensed, with long experience in traditional Chinese medicine and history of practising acupuncture methodology in China. Number not stated DeChi achieved?: yes, implied once each session Number of treatment sessions: 8 of 30 minutes Frequency of treatment sessions: once weekly Control intervention: sham (superificial needling 1-2 cm from true points)
Outcomes	Method for outcome measurement: headache diary, transcranial Doppler Primary outcome: unclear Other outcomes: frequency, duration and intensity of migraine/headache, function Doppler measurements
Notes	Study author contacted but no additional information received. The number of responders was imputed from baseline means and post-treatment and follow-up means and standard deviations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allocated" "Groups were paralleled according to age, sex, duration of migraine disorder, and headache frequency." Unclear how this could be implemented unless all participants were included simultaneously
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded for the treatment. None of the participants had received acupuncture treatment prior to the study
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	High risk	It seems that 5/18 acupuncture and 3/17 sham participants were excluded/counted as dropouts as Doppler measurements were missing

Wallasch 2012 (*Continued*)

Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	High risk	See above
Selective reporting (reporting bias)	Unclear risk	Frequency data well reported, pain intensity not reported. Medication not mentioned

Wang 2015

Methods	Blinding: participants Droput/withdrawals: one participant per group until completion of treatment, one more participant at early follow-up; the study also included a long-term follow-up about 17 months after randomisation with high loss to follow-up (> 50%) Observation period: 4 weeks baseline, 20 weeks treatment, early follow-up further 3 months; long-term follow-up 1 year after completion of treatment Acupuncturists' assessment: BB similarly/85% - AW differently/90%
Participants	Number of participants included/analysed: 50/50 Condition: frequent migraine (at least 5 migraine days per month; 23/50 participants on prophylactic drug treatment Demographics: mean age 43 years, 37/50 female Setting: outpatient unit at hospital in Melbourne, Australia; recruitment through media releases/advertisements Time since onset of headaches: mean 20 years
Interventions	Acupuncture points: semi-standardized, 9-12 needles: (GB20, Taiyang, GB8, LI4 in all participants + supplementary points selected from GV20, LR2, LR3, KI3, GB39, SP6 according to syndrome diagnosis) Information on acupuncturists: one registered acupuncturist, 5-year degree and 3 years' clinical experience DeChi achieved?: Yes, with stimulation every 10 minutes Number of treatment sessions: 16, over 20 weeks (25 minutes each) Frequency of treatment sessions: 2/week for 4 weeks, 1/week for 4 weeks, 1/2 weeks for 4 weeks, 1/month for 2 months Control intervention: sham acupuncture: (combination of non-penetrating blunted cocktail stick tapped on sham locations on scalp, face and neck + superficial needle insertion to sham locations, 1-2 cm away from real points, on four extremities according to syndrome differentiation; no manipulation; duration not specified)
Outcomes	Method for outcome measurement: diary, questionnaires Primary outcomes: intensity, frequency and duration of migraine and percentage of participants with more than 50% reduction in the number of migraine days Other outcomes: usage of relief medication, severity and quality of migraine, quality of life, pressure pain threshold
Notes	

Wang 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, block size 8
Allocation concealment (selection bias)	Unclear risk	Independent researcher generated the sequence, prepared opaque, sealed envelopes. These were stored in a locked cabinet in blocks of 8. The next eligible participant took an envelope from the block. This could imply that at the end of blocks the next treatment in line might have been predictable to the person including a participant
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded. Restricted communication between patient and acupuncturist. Credibility of procedure was assessed with a questionnaire after one week - suggests successful blinding
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	1/26 dropout in acupuncture groups vs. 1/24 in sham group until completion of treatment (week 20)
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Low risk	1 more dropout in the acupuncture group until month 8
Selective reporting (reporting bias)	Low risk	Detailed reporting of results

Weinschütz 1993

Methods	Blinding: participants Dropouts/withdrawals: unclear Observation period: baseline 6 weeks; treatment 8 weeks; follow-up 12 months Acupuncturists' assessments: GA exactly the same way/95% - BB differently/45%
Participants	Number of participants included/analysed: 40?/40? Condition: migraine with or without aura (IHS) Demographics: mean age 41 years; 90% female Setting: pain outpatient department of a university hospital, Germany Time since onset of headaches: mean 18 years

Weinschütz 1993 (*Continued*)

Interventions	Acupuncture points: up to 10 points chosen according to pain localization and modalities Information on acupuncturist: n = 1, experienced and qualified DeChi achieved?: yes Number of treatment sessions: 8 sessions of 15 minutes each Frequency of treatment sessions: 1/week Control intervention: sham acupuncture (superficial needling 1-2 cm distant from true points)
Outcomes	Method for outcome measurement: diary Primary outcomes: attack frequency and migraine hours (data mainly presented as responder rate evaluated by time-series analysis)
Notes	Possibly rigorous, but insufficiently reported (in spite of multiple publication); no information on whether there were dropouts/withdrawals Additional information could not be obtained despite of several requests

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded, sham acupuncture with superficial needling of the same number of needles 1 to 2 cm from true points without DeChi
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Unclear risk	No statements on whether any attrition or exclusions from analyses occurred
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	See above
Selective reporting (reporting bias)	High risk	Only responder data derived from single-case statistics reported

Weinschütz 1994

Methods	Blinding: participants Dropouts/withdrawals: unclear Observation period: baseline 6 weeks; treatment 8 weeks; follow-up 12 months Acupuncturists' assessments: GA exactly the same way/95% - BB differently/45%
Participants	Number of participants included/analysed: 41?/41? Condition: migraine with or without aura (IHS) Demographics: mean age 38 years; 90% female Setting: pain outpatient department of a university hospital, Germany Time since onset of headaches: mean 18 years
Interventions	Acupuncture points: up to 10 points chosen according to pain localization and modalities Information on acupuncturist: n = 1, experienced and qualified DeChi achieved?: yes Number of treatment sessions: 8 sessions of 15 minutes each Frequency of treatment sessions: 1/week Control intervention: sham acupuncture (superficial needling 1-2 cm distant from true points)
Outcomes	Method for outcome measurement: diary Primary outcomes: attack frequency and migraine hours (data mainly presented as responder rate evaluated by time-series analysis)
Notes	Possibly rigorous, but insufficiently reported (in spite of multiple publication); no information on whether there were dropouts/withdrawals; replication of Weinschütz 1993 (with additional needling of foot points)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants were blinded, sham acupuncture with superficial needling of the same number of needles 1-2 cm from true points without DeChi
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Unclear risk	No statements on whether any attrition or exclusions from analyses occurred
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	See above

Weinschütz 1994 (*Continued*)

Selective reporting (reporting bias)	High risk	Only responder data derived from single-case statistics reported

Zhao 2014

Methods	Blinding: participants, study personnel except acupuncturists Dropout/withdrawals: 2/40 vs. 5/40 dropped out Observation period: 4 weeks baseline, 8 weeks treatment, no post-treatment follow-up Acupuncturists' assessment: YF similarly/75% - AW differently/60%
Participants	Number of participants included/analysed: 80/80 Condition: migraine without aura (IHS) Demographics: mean age 33 years, 57/80 female Setting: teaching hospital in Chengdu, China Time since onset of headaches: mean 11 years
Interventions	Acupuncture points: 'Chinese style' based on literature and consensus. TE5, GB20, GB34, GB40 Information on acupuncturists: two specialised acupuncturists with at least 5 years' training and 3 years' experience; trained to achieve consistent approach in this study DeChi achieved?: yes Number of treatment sessions: 32 (30 minutes each) Frequency of treatment sessions: 4 times per week Control intervention: sham - points considered as 'inactive': TE22, PC7, GB37, SP3
Outcomes	Method for outcome measurement: diary, questionnaires, neuroimaging Primary outcome: pain intensity Other outcomes: migraine days and attack, HIT-6 questionnaire
Notes	Focus on resting-state brain activity. The number of responders was imputed from baseline means and post-treatment and follow-up means and standard deviations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomisation numbers of 80 patients were generated through computerized block-randomisation with the SAS procedure PROC PLAN in the SAS package (SAS Version 9.0, SAS Institute, Inc., Cary, NC) by an independent statistician. In this study, the block size was set to 4, and the number of blocks was 20."
Allocation concealment (selection bias)	Unclear risk	"Opaque, sealed envelopes with consecutive numbers were used for allocation concealment. Investigators who selected the

		eligible participants after baseline screening opened the envelopes according to the patients' screening sequence numbers, and placed the patients into either the active group or the inactive group." Unclear whether people, including participants, aware of the block size?
Blinding (performance bias and detection bias) All outcomes	Low risk	"Due to the procedure of the acupuncture technique, two acupuncturists in this study were not blinded. Investigators in charge of patient screening and randomized distribution were not involved in treatment and data analyses. They knew the group assignment, but they did not know the corresponding treatment schedule." "To guarantee that the patients were blinded during the treatment period, several approaches were performed for migraine patients in both groups: they were informed that they would receive one of two types of acupuncture treatment, which depended on different traditional Chinese acupuncture theories; acupuncture treatment was achieved in a large independent single room with screen dividers for patient blinding and privacy; and two groups of patients received bilateral and equivalent number of acupoint stimulations each time."
Incomplete outcome data (attrition bias) All outcomes up to 3 month after randomisation	Low risk	2/40 vs. 5/40 participants dropped out; reasons reported and similar; ITT analysis using a last value carried forward approach for replacing missing data
Incomplete follow-up outcome data (attrition bias) All outcomes later than 3 months after randomisation	Unclear risk	Not applicable (no follow-up)
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported

Acupuncturists' assessment = At least two reviewers who are trained in acupuncture and have several years of practical experience (GA, BB, YF, AW) answered two questions. First, they were asked how they would treat the participants included in the study. Answer options were '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, they were asked to rate their degree of confidence that

acupuncture was applied in an appropriate manner 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).
DeChi = irradiating sensation said to indicate effective needling
IHS = International Headache Society
ITT = intention to treat
TTH = tension-type headache

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agro 2005	Participants/control/outcomes: duration of complaints unclear, part of control group received dihydroergotamine as prophylactic treatment, only headache index reported. Only short report with limited detail
Baust 1978	Outcomes: post-randomisation observation period is unclear (individualized 10 typical intervals between attacks before trial); the only outcome data reported is some sort of response derived from a headache index (additional information not available). Trial was included in 2009 version of the review
Boutouyrie 2010	Intervention: only 3 treatments with monthly intervals (trial focusses on physiological measurements)
Ceccherelli 2012	Control: compares somatic and ear acupuncture only
Deng 2006	Methods/participants/control/outcomes: allocation possibly by alternation, participants enter study with acute attack, only 14 days of treatment with flunarizine, no fitting outcome measure
Doerr-Proske 1985	Participants: contradictory information on headache frequency in baseline/before trial (19 participants had attacks on 4 or more days per week = > 50%), but baseline data suggest mean slightly below 15 days in all 3 groups); suspicion that the trial included a majority of participants with analgesic abuse (28/30 used - mostly daily - analgesics). In addition (no formal selection criteria): no usable data, group 3 received a psychological intervention (but group 2 was a 8-week wait-list which would meet criteria); very low acupuncture scores by both acupuncturists voting. Trial was included in 2009 version of the review
Dowson 1985	Participants: no information on duration of migraine. Trial was included in 2009 version of the review
Ferro 2012	Participants: chronic migraine (mean of headache days/month 20.6 to 24.2). 3-arm trial (acupuncture, feverfew, both)
Foroughipour 2014	Methods: randomisation probably inadequate (dropouts in groups were replaced)
Han 2011	Comparator/outcomes: nimodipine only given for 30 days, not fitting outcome measure. Some participants with disease duration < 1 year duration, but probably < 20%
Henry 1985	Outcomes: only headache index and global assessments as outcomes. Trial was included in 2009 version of the review
Jia 2009	Participants/control/outcomes: includes an unclear number of participants with disease duration < 1 year, compares 2 types of acupuncture, only improvement rates based on a score reported

(*Continued*)

Matra 2012	Participants: chronic migraine. Only abstract available
Qin 2006	Trial focusing on acute attack treatment with 1 month follow-up, drug treatment not prophylactic and short-term (ergotamine and caffeine for one month), only 4 week outcome measurement
Vijayalakshmi 2014	Observation after randomisation only 30 days (study compares acupuncture and flunarizine)
Wang 2011	Control: only 4-week treatment with flunarizine as control
Wu 2011	Control: only 4-week treatment with flunarizine as control
Wylie 1997	Control/comparator group: received massage and relaxation. Trial was included in 2009 version of the review
Yang 2009	Participants: chronic migraine
Yang 2011	Participants: chronic migraine
Zhang 2006	Methods/control: randomisation not mentioned, acupuncture + herbs vs. acupuncture alone
Zhang 2009	Control: flunarizine for only 4 weeks
Zheng 2013	Control: flunarizine for only 4 weeks
Zhong 2009	Control: flunarizine for only 4 weeks
Zhou 2007	Participants/comparator/outcome: trial focusing on acute attack treatment, drug treatment not prophylactic (ergotamine + caffeine, probably not longer than 4 weeks), no outcomes ≥ 8 weeks

Characteristics of studies awaiting assessment *[ordered by study ID]*

Giannini 2015

Methods	Randomized trial (no blinding)
Participants	Suffering from episodic migraine, n = 85 (preliminary)
Interventions	12 sessions acupuncture vs. individualized prophylactic drug treatment
Outcomes	Migraine frequency, response at 4 months
Notes	Abstract with preliminary data on an ongoing trial

Li 2016

Methods	Randomized trial
Participants	Suffering from migraine without aura, n = 100 (20 per group)
Interventions	3 different acupuncture groups, 1 sham acupuncture and 1 waiting list group
Outcomes	Focus on physiological outcomes (functional magnetic resonance imaging) but clinical outcomes (frequency, intensity) also measured
Notes	

Sun 2015

Methods	Possibly randomized
Participants	85 women with menstrual headache
Interventions	Body acupuncture combined with combined with auricular acupuncture
Outcomes	Physiological measures, total effectiveness rate
Notes	Translation of full text needs to be done before eligibility assessment possible

Characteristics of ongoing studies *[ordered by study ID]*

Chen 2013

Trial name or title	
Methods	Multicenter randomized trial
Participants	249 (planned) participants with migraine without aura
Interventions	Group 1: individualized acupuncture; group 2: non-acupoint control group; waiting-list control group
Outcomes	Primary: "change in frequency of migraine attacks during the 16th week after randomisation"
Starting date	
Contact information	
Notes	see also apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01687660 (accessed July 13 2015); last refreshed in trials register February 19 2015 recruiting participants at that date

Lan 2013

Trial name or title	
Methods	RCT
Participants	100 participants with migraine
Interventions	3 verum and 2 sham acupuncture groups
Outcomes	Focus on functional MRI, but also headache diary for 8 weeks
Starting date	
Contact information	
Notes	see also apps.who.int/trialsearch/Trial2.aspx?TrialID=NCT01152632 (accessed July 13 2015); last refreshed in trials register February 19 2015 - recruitment completed at that date

Li 2007

Trial name or title	
Methods	RCT
Participants	600 participants with migraine
Interventions	4 groups: Zheng acupuncture, head acupuncture, simulation acupuncture, no acupuncture
Outcomes	Frequency of headache
Starting date	January 1 2008
Contact information	
Notes	apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-TRC-07000024 (accessed July 13 2015; last refreshed April 20 2015, status completed)

Liang 2013

Trial name or title	
Methods	RCT
Participants	60 participants with migraine
Interventions	1 acupuncture and 2 sham groups
Outcomes	Headache diary

Liang 2013 (*Continued*)

Starting date	June 18 2012
Contact information	
Notes	Registered September 27 2013. See apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-TRC-13003635 (accessed July 13 2015)

Vas 2008

Trial name or title	
Methods	RCT
Participants	270 participants with migraine with or without aura
Interventions	3 groups: active acupuncture, minimal acupuncture or conventional treatment
Outcomes	Migraine days
Starting date	
Contact information	
Notes	The clinical phase is completed and all data entered (database locked). However, statistician currently not available. See also apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN98703707 (accessed July 13 2015)

Wang J 2015

Trial name or title	
Methods	RCT
Participants	90 participants with migraine with or without aura
Interventions	2 acupuncture and 1 sham group
Outcomes	Migraine days
Starting date	March 1 2010
Contact information	
Notes	apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR-TRC-10000807 (accessed July 13 2015; status recruitment completed June 8 2015)

Xing 2015

Trial name or title	
Methods	RCT
Participants	80 women with menstrual migraine
Interventions	3 acupuncture groups, 1 sham group
Outcomes	Migraine attacks and migraine days
Starting date	First enrolment July 24 2015
Contact information	
Notes	chictr.org.cn/showproj.aspx?proj=11273 (accessed July 13 2015; not yet recruiting)

Zhang 2013

Trial name or title	
Methods	RCT
Participants	184 participants with menstrual-related migraine
Interventions	1 acupuncture and 1 sham group
Outcomes	Migraine days
Starting date	December 30 2011
Contact information	
Notes	Recruitment completed; manuscript submitted (summer 2015); see also apps.who.int/trialsearch/Trial2.aspx?TrialID=ISRCTN57133712

DATA AND ANALYSES

Comparison 1. Acupuncture vs. no acupuncture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache frequency	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 After treatment	4	2199	Std. Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.65, -0.48]
1.2 Follow-up	1	284	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.59, -0.12]
2 Response (at least 50% frequency reduction)	4		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 After treatment	4	2519	Risk Ratio (IV, Fixed, 95% CI)	2.40 [2.08, 2.76]
2.2 Follow-up	1	377	Risk Ratio (IV, Fixed, 95% CI)	2.16 [1.35, 3.45]
3 Headache frequency (various measures)	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Up to 8 weeks/2 months after randomization	1	197	Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.83, -0.23]
3.2 3 to 4 months after randomization	4	2199	Std. Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.65, -0.48]
3.3 5 to 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 > 6 months after randomization	1	284	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.59, -0.12]
4 Response	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 8 weeks/2 months after randomization	1	221	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.32, 3.07]
4.2 3 to 4 months after randomization	4	2519	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [2.10, 2.78]
4.3 5 to 6 months after randomization	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.4 > 6 months after randomization	1	377	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [1.35, 3.45]
5 Migraine attacks	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Up to 8 weeks/2 months after randomization	1	197	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.07, -0.33]
5.2 3 to 4 months after randomization	2	219	Mean Difference (IV, Fixed, 95% CI)	-0.79 [-1.12, -0.47]
5.3 5 to 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Migraine days	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Up to 8 weeks/2 months after randomization	1	198	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-2.31, -0.69]
6.2 3 to 4 months after randomization	2	220	Mean Difference (IV, Fixed, 95% CI)	-1.75 [-2.43, -1.07]
6.3 5 to 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

6.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Headache days	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Up to 8 weeks/2 months after randomization	1	198	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.13, 0.33]
7.2 3 to 4 months after randomization	3	2177	Mean Difference (IV, Fixed, 95% CI)	-2.17 [-2.50, -1.83]
7.3 5 to 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 > 6 months after randomization	1	284	Mean Difference (IV, Fixed, 95% CI)	-1.86 [-3.08, -0.65]
8 Headache intensity	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Up to 8 weeks/2 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 3 to 4 months after randomization	2	1652	Std. Mean Difference (IV, Fixed, 95% CI)	-0.75 [-0.85, -0.65]
8.3 5 to 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.4 > 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Analgesic use	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Up to 8 weeks/2 months after randomization	1	198	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-0.59, 0.01]
9.2 3 to 4 months after randomization	4	581	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-1.22, 0.18]
9.3 5 to 6 months after randomization	1	50	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.82, 0.33]
9.4 > 6 months after randomization	1	301	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.24, 0.21]
10 Headache scores	3		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Up to 8 weeks/2 months after randomization	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 3 to 4 months after randomization	3		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 5 to 6 months after randomization	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.4 > 6 months after randomization	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Safety/acceptability	4		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
11.1 Number of participants dropping out due to adverse effects	2	260	Odds Ratio (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Number of participants not reaching primary endpoint	4	741	Odds Ratio (IV, Fixed, 95% CI)	0.69 [0.46, 1.05]
11.3 Number of participants with serious adverse events	1	221	Odds Ratio (IV, Fixed, 95% CI)	1.05 [0.19, 5.86]

Comparison 2. Acupuncture vs. sham interventions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache frequency	12		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 After treatment	12	1646	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
1.2 Follow-up	10	1534	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.09]
2 Response (at least 50% frequency reduction)	14		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 After treatment	14	1825	Risk Ratio (IV, Fixed, 95% CI)	1.23 [1.11, 1.36]
2.2 Follow-up	11	1683	Risk Ratio (IV, Fixed, 95% CI)	1.25 [1.13, 1.39]
3 Headache frequency (various measures)	12		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Up to 8 weeks/2 months after randomization	9	1538	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.27, -0.06]
3.2 3 to 4 months after randomization	9	1486	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.31, -0.10]
3.3 5 to 6 months after randomization	7	1031	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.25, -0.01]
3.4 > 6 months after randomization	5	200	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.40, 0.16]
4 Response	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 8 weeks/2 months after randomization	10	1682	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.08, 1.32]
4.2 3 to 4 months after randomization	9	1579	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.12, 1.39]
4.3 5 to 6 months after randomization	9	1170	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.05, 1.35]
4.4 > 6 months after randomization	5	213	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.94, 2.31]
5 Migraine attacks	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Up to 8 weeks/2 months after randomization	6	849	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.57, -0.13]
5.2 3 to 4 months after randomization	6	802	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.53, -0.10]
5.3 5 to 6 months after randomization	4	321	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.16, 0.43]
5.4 > 6 months after randomization	4	150	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.10, 0.71]
5.5 New Subgroup	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Migraine days	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Up to 8 weeks/2 months after randomization	8	1508	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.65, -0.10]
6.2 3 to 4 months after randomization	7	1426	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.74, -0.15]
6.3 5 to 6 months after randomization	7	1031	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.62, 0.11]
6.4 > 6 months after randomization	5	190	Mean Difference (IV, Fixed, 95% CI)	-0.42 [-1.56, 0.73]

7 Headache days	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Up to 8 weeks/2 months after randomization	2	240	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-1.05, 0.83]
7.2 3 to 4 months after randomization	2	238	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.89, 0.92]
7.3 5 to 6 months after randomization	2	233	Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.65, 1.08]
7.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Headache intensity	6		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Up to 8 weeks/2 months after randomization	2	521	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.44, -0.05]
8.2 3 to 4 months after randomization	4	1285	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.17, 0.06]
8.3 5 to 6 months after randomization	4	886	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.26, 0.01]
8.4 > 6 months after randomization	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.96, -0.05]
9 Analgesic use	7		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Up to 8 weeks/2 months after randomization	5	368	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.29, 0.14]
9.2 3 to 4 months after randomization	7	455	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.42, -0.03]
9.3 5 to 6 months after randomization	6	409	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.42, 0.02]
9.4 > 6 months after randomization	5	171	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.30, 0.35]
10 Headache scores	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Up to 8 weeks/2 months after randomization	2	240	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.22, 0.34]
10.2 3 to 4 months after randomization	2	238	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.24, 0.33]
10.3 5 to 6 months after randomization	2	228	Std. Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.10, 0.47]
10.4 > 6 months after randomization	1	26	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Frequency after treatment - subgroup analysis 1: Adequacy of concealment	12	1646	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
11.1 Unclear adequacy	9	371	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.57, -0.16]
11.2 Unambigously adequate concealment	3	1275	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.24, -0.01]
12 Frequency follow-up - subgroup analysis 1: Adequacy of concealment	10	1534	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.09]
12.1 Unclear adequacy	7	259	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.45, 0.05]
12.2 Unambigously adequate concealment	3	1275	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.31, -0.08]
13 Response after treatment - subgroup analysis 1: Adequacy of concealment	14		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only

13.1 Unclear adequacy	11	471	Risk Ratio (IV, Fixed, 95% CI)	1.54 [1.23, 1.92]
13.2 Unambigously adequate concealment	3	1354	Risk Ratio (IV, Fixed, 95% CI)	1.16 [1.03, 1.30]
14 Response at follow-up - subgroup analysis 1: Adequacy of concealment	11		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
14.1 Unclear adequacy	8	329	Risk Ratio (IV, Fixed, 95% CI)	1.67 [1.22, 2.28]
14.2 Unambigously adequate concealment	3	1354	Risk Ratio (IV, Fixed, 95% CI)	1.21 [1.08, 1.35]
15 Frequency after treatment - subgroup analysis 2: Sample size	12	1646	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
15.1 Up to median	6	177	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.59, 0.02]
15.2 Above median	6	1469	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.28, -0.06]
16 Frequency follow-up - subgroup analysis 2: Sample size	10	1534	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.09]
16.1 Up to median	5	145	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.28, 0.38]
16.2 Above median	5	1389	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.33, -0.11]
17 Response after treatment - subgroup analysis 2: Sample size	14		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
17.1 Up to median	8	277	Risk Ratio (IV, Fixed, 95% CI)	1.95 [1.29, 2.96]
17.2 Above median	7	1589	Risk Ratio (IV, Fixed, 95% CI)	1.20 [1.08, 1.33]
18 Response at follow-up - subgroup analysis 3: Number of treatment sessions	11		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
18.1 Up to 12	6	1025	Risk Ratio (IV, Fixed, 95% CI)	1.16 [1.02, 1.32]
18.2 16 and more	5	658	Risk Ratio (IV, Fixed, 95% CI)	1.48 [1.23, 1.80]
19 Frequency after treatment - subgroup analysis 3: Number of treatment sessions	12	1646	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
19.1 Up to 12	6	948	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.24, 0.02]
19.2 16 and more	6	698	Std. Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.46, -0.14]
20 Frequency follow-up - subgroup analysis 3: Number of treatment sessions	10	1534	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.09]
20.1 Up to 12	5	921	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.24, 0.02]
20.2 16 and more	5	613	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.53, -0.18]
21 Response after treatment - subgroup analysis 3: Number of treatment setssions	14		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
21.1 Up to 12	8	1087	Risk Ratio (IV, Fixed, 95% CI)	1.15 [1.01, 1.30]
21.2 16 and more	6	738	Risk Ratio (IV, Fixed, 95% CI)	1.38 [1.17, 1.64]
22 Response at follow-up - subgroup analysis 2: Sample size	11		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
22.1 Up to median	6	215	Risk Ratio (IV, Fixed, 95% CI)	1.48 [1.02, 2.15]
22.2 Above median	5	1468	Risk Ratio (IV, Fixed, 95% CI)	1.23 [1.11, 1.38]

23 Frequency after treatment - subgroup analysis 4: Type of sham	12	1646	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.28, -0.08]
23.1 Penetrating	9	1538	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.26, -0.06]
23.2 (At least partly) non-penetrating	3	108	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-0.89, -0.10]
24 Frequency follow-up - subgroup analysis 4: Type of sham	10	1534	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.09]
24.1 Penetrating	8	1456	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.29, -0.07]
24.2 (At least partly) non-penetrating	2	78	Std. Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.94, -0.02]
25 Response after treatment - subgroup analysis 4: Type of sham	14		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
25.1 Penetrating	12	1744	Risk Ratio (IV, Fixed, 95% CI)	1.21 [1.09, 1.34]
25.2 (At least partly) non-penetrating	2	81	Risk Ratio (IV, Fixed, 95% CI)	2.02 [1.09, 3.75]
26 Response at follow-up - subgroup analysis 4: Type of sham	11		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
26.1 Penetrating	9	1602	Risk Ratio (IV, Fixed, 95% CI)	1.23 [1.11, 1.37]
26.2 (At least partly) non-penetrating	2	81	Risk Ratio (IV, Fixed, 95% CI)	3.16 [1.46, 6.82]
27 Safety/acceptability	13		Odds Ratio (IV, Fixed, 95% CI)	Subtotals only
27.1 Number of participants dropping out due to adverse effects	7	931	Odds Ratio (IV, Fixed, 95% CI)	2.84 [0.43, 18.71]
27.2 Number of participants reporting adverse effects	4	1414	Odds Ratio (IV, Fixed, 95% CI)	1.15 [0.85, 1.56]
27.3 Number of participants not reaching primary endpoint	11	1770	Odds Ratio (IV, Fixed, 95% CI)	1.14 [0.78, 1.67]
27.4 Number of participants with serious adverse events	6	1071	Odds Ratio (IV, Fixed, 95% CI)	1.29 [0.43, 3.83]

Comparison 3. Acupuncture vs. prophylactic drug treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache frequency	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 After treatment	3	739	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.39, -0.10]
1.2 Follow-up	3	744	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.28, 0.01]
2 Response (at least 50% frequency reduction)	3		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 After treatment	3	743	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.08, 1.44]
2.2 Follow-up	3	744	Risk Ratio (IV, Fixed, 95% CI)	1.11 [0.97, 1.26]
3 Headache frequency (various measures)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only

3.1 Up to 8 weeks/2 months after randomization	3	746	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.32, -0.03]
3.2 3 to 4 months after randomization	3	741	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.37, -0.08]
3.3 5 to 6 months after randomization	3	744	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.28, 0.01]
3.4 > 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Response	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Up to 8 weeks/2 months after randomization	3	746	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.01, 1.35]
4.2 3 to 4 months after randomization	3	741	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.06, 1.40]
4.3 5 to 6 months after randomization	3	744	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.97, 1.26]
4.4 > 6 months after randomization	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Migraine attacks	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Up to 8 weeks/2 months after randomization	2	241	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.91, -0.08]
5.2 3 to 4 months after randomization	3	316	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.59, -0.04]
5.3 5 to 6 months after randomization	2	237	Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.61, -0.01]
5.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Migraine days	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Up to 8 weeks/2 months after randomization	2	596	Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.83, 0.06]
6.2 3 to 4 months after randomization	2	591	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-1.03, -0.10]
6.3 5 to 6 months after randomization	2	594	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-0.90, 0.08]
6.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Headache days	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Up to 8 weeks/2 months after randomization	1	91	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.26, 1.46]
7.2 3 to 4 months after randomization	1	89	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.52, 1.32]
7.3 5 to 6 months after randomization	1	87	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-1.99, 0.79]
7.4 > 6 months after randomization	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Headache intensity	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Up to 8 weeks/2 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 3 to 4 months after randomization	3	639	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.44, -0.10]
8.3 5 to 6 months after randomization	2	565	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.49, -0.14]

8.4 > 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Analgesic use	2		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Up to 8 weeks/2 months after randomization	2	241	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.49, 0.02]
9.2 3 to 4 months after randomization	2	239	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.33, 0.18]
9.3 5 to 6 months after randomization	2	237	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.35, 0.17]
9.4 > 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Headache scores	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 Up to 8 weeks/2 months after randomization	1	91	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.50, 0.34]
10.2 3 to 4 months after randomization	1	89	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.59, 0.27]
10.3 5 to 6 months after randomization	1	87	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.67, 0.20]
10.4 > 6 months after randomization	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Safety/acceptability	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Number of participants dropping out due to adverse effects	4	451	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.08, 0.86]
11.2 Number of participants reporting adverse effects	5	931	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.10, 0.62]
11.3 Number of participants not reaching primary endpoint	4	995	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.78]
11.4 Number of participants with serious adverse events	3	721	Odds Ratio (M-H, Random, 95% CI)	1.33 [0.38, 4.73]

WHAT'S NEW

Last assessed as up-to-date: 20 January 2016.

Date	Event	Description
19 April 2018	Review declared as stable	See Published notes

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 1, 2001

Date	Event	Description
10 August 2016	Amended	Minor amendment to Acknowledgements section.
12 April 2016	New citation required and conclusions have changed	I. Compared to the previous version the selection criteria were slightly modified, new analyses have been added, new trials have been added and previously included trials excluded, and conclusions for the comparison with sham acupuncture were changed II. The main search was updated on 20 January 2016 (further update searches in PubMed on 12 April 2016 and in the WHO Clinical Trials Platform 10 February 2016) III. Five previously included trials excluded (Baust 1978; Doerr-Proske 1985; Dowson 1985; Henry 1985; Wylie 1997), five new trials included (Facco 2013; Li 2012; Wallasch 2012; Wang 2015; Zhao 2014). IV. The 22 trials reviewed include 4985 participants; the 22 trials in the previous version included 4419 participants V. We changed the primary outcome from response to headache frequency; added new primary analysis time points (after treatment and follow-up instead of four fixed time windows); and added safety/acceptability outcomes VI. After the inclusion of the four new sham-controlled trials differences between true and sham acupuncture are now statistically significant but they are small. Previous readers should re-read the update
12 April 2016	New search has been performed	This review has been updated to include the results of a new search; selection criteria have been slightly narrowed; new analyses have been added; new trials have been added and previously included trials excluded, and conclusions for the comparison with sham acupuncture were changed
10 August 2009	Amended	Contact details updated.
29 January 2009	Amended	Contact details updated.
7 November 2008	New citation required and conclusions have changed	1) A previously published Cochrane review on 'Acupuncture for idiopathic headache' has been split into two reviews: the present review on 'Acupuncture for migraine prophylaxis', and a separate review on

(*Continued*)

		'Acupuncture for tension-type headache' 2) Twelve new trials of acupuncture for migraine prophylaxis are included in the present review (Alecrim 2005; Alecrim 2006; Alecrim 2008; Allais 2002; Diener 2006; Facco 2008; Jena 2008; Linde K 2005; Linde M 2000; Linde M 2005; Streng 2006; Vickers 2004) 3) Conclusions have changed as follows: In the previous version of this review, the evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. Now the authors conclude that acupuncture should be considered as a treatment option for migraine patients needing prophylactic treatment, although the available results suggest that the selection of specific acupuncture points may not be as important as has been thought by providers 4) The list of review authors has been slightly amended vis-à-vis the earlier review (D Melchart and B Berman no longer authors; E Manheimer added as new author)
10 April 2008	Amended	Converted to new review format.
9 January 2008	New search has been performed	All searches updated.

CONTRIBUTIONS OF AUTHORS

KL, GA, BB, YF, MM, AV and AW participated in the revision process of the protocol for this update, the extraction and assessment of the primary studies. EV re-analysed individual patient data included in the database of the Acupuncture Trialists' Collaboration for this update. All authors reviewed drafts and approved the final version of this manuscript. KL co-ordinated the review process and wrote the draft of the review.

DECLARATIONS OF INTEREST

This review includes trials in which some of the reviewers were involved, as follows: Allais 2002 - Gianni Allais; Jena 2008 - Benno Brinkhaus; Linde K 2005 - Benno Brinkhaus and Klaus Linde; Streng 2006 - Klaus Linde; and Vickers 2004 - Andrew Vickers. These trials were reviewed by at least two other members of the review team.

Gianni Allais, Benno Brinkhaus, Yutong Fei, and Michael Mehring use acupuncture in their clinical work. Adrian White has used acupuncture in the past but has retired from clinical practice.

Within the last three years (June 2013 to May 2016): Gianni Allais received fees for teaching acupuncture in private schools; Klaus Linde once received a fee from the German Medical Acupuncture Society for speaking about research at a conference; Benno Brinkhaus has received fees for presenting research findings at meetings of acupuncture societies in various countries; Adrian White is employed by the British Medical Acupuncture Society as a journal editor and has received fees for lecturing on acupuncture on several occasions.

Emily Vertosick's and Andrew Vickers' contribution to this review was supported by the NIH grant R01AT006794 (see Sources of support).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this 2016 update we made the following changes.

The title was changed to 'Acupuncture for the prevention of episodic migraine' (formerly 'Acupuncture for migraine prophylaxis').

Additional subgroup analyses were performed post-hoc for the secondary outcome response to check the robustness of differences found in the predefined subgroup analyses using the primary outcome, headache frequency.

Changes to types of participants:

- in this update of the review we have excluded trials focusing on chronic migraine, as the definition of chronic migraine is still debated and the separation from other diagnoses, for example headache due to medication overuse, is difficult (in the previous version of this review (Linde 2009) we were not aware of any trials on chronic migraine and they were not explicitly excluded);

- we have excluded trials in which a relevant proportion of participants had been suffering from migraine for less than one year or in which duration was unclear.

Changes to types of interventions: in the previous version we included trials using any prophylactic treatment other than acupuncture as comparison. With a slowly increasing number of trials using a wide range of different treatments (mainly various herbal medicines) we decided to concentrate on conventional prophylactic pharmacological treatment to keep the review focused. We have defined a minimum number and frequency of acupuncture treatment sessions to ensure that treatments meet basic quality criteria.

In this update we have defined outcome measures more precisely to ensure that measurement methods meet current standards of migraine research, and we have expanded the list of outcomes. Based on the recommendation of the statistician in our team (AV), we have used fixed-effect models for calculating pooled estimates.

We have added 'Summary of findings' tables, including a judgement on the quality of evidence following the GRADE approach (GRADEpro GDT 2015; Schünemann 2011).

NOTES

A restricted search in April 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions

INDEX TERMS

Medical Subject Headings (MeSH)

*Acupuncture Therapy [adverse effects]; Migraine Disorders [drug therapy; *prevention & control]; Migraine with Aura [prevention & control]; Migraine without Aura [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Male