

Linde K, Allais G, et al. Acupuncture for migraine prophylaxis. Cochrane Database of Systematic Reviews 2009; Issue 1, Art # CD001218.

Design: Meta-analysis of randomized clinical trials

PICOS:

- **Patient population:** study participants diagnosed with migraine; trials which included tension headaches were included if the results for migraine were reported separately, or if more than 90% of participants had migraine
- **Interventions:** Acupuncture involving needle insertion at acupuncture points, or otherwise described as acupuncture; laser stimulation or TENS were excluded from definition of acupuncture
- **Comparison interventions:** routine care only; sham acupuncture mimicking true acupuncture but differing in at least one important aspect (point location, skin penetration); other migraine treatments such as medication, relaxation, physical therapy; studies comparing different forms of acupuncture were excluded
- **Outcomes:** at least one clinical measure of headache, such as headache frequency, intensity, analgesic use, or “response” to treatment
 - o “Response” was defined as a 50% reduction in at least one measure of headache frequency, headache score, or global assessment of improvement; effect sizes were rate ratios of acupuncture responders to control responders
 - o Headache frequency, intensity, and analgesic use were measured with means and standard deviations, with effect sizes measured as weighted mean differences between acupuncture and control
 - o The 3 to 4 month time window was the primary measure; it was the time window most often available for comparison of outcomes
- **Study types:** Studies which were explicitly randomized and in which the duration of follow-up was at least 8 weeks

Study search and selection:

- Databases were searched through 2008
- Databases included MEDLINE, EMBASE, the Cochran Central Register of Controlled Trials, Cochrane Complementary Medicine registry, and bibliographies of review articles and included studies
- Quality assessment was based on estimating the Cochrane risk of bias criteria: adequate random sequence generation, allocation concealment, blinding, completeness of outcome data at 3 months, completeness of outcome data at 12 months, and freedom from selected reporting
- While single therapeutic endpoints are sometimes predefined, the authors considered that the overall pattern of responses was necessary to get an interpretable outcome: typically a headache frequency measure at the most relevant time points
- Two experienced acupuncturists were asked to rate their degree of confidence that the acupuncture was applied in an appropriate manner, such that a rating

of 70% meant that the acupuncturist was 70% confident that acupuncture was applied appropriately

Results:

- 22 trials were included in the review, with a total of 4419 migraine patients; some trials made more than one type of comparison (e.g., acupuncture vs. sham acupuncture and acupuncture vs. drug treatment)
- 6 trials comparing acupuncture with no acupuncture (routine care or acute treatment only) were clinically heterogeneous and the weighted analysis was dominated by one very large trial (weight of 85.8% in a random-effects model); this very large trial estimated a response rate for acupuncture which was 2.30 times as great as for no acupuncture; the pooled response rate was 2.33 in favor of acupuncture measured 3 to 4 months after randomization
 - o The pooled response rate at 3-4 months was 40% for acupuncture and 17% for no acupuncture
- 14 trials compared acupuncture with sham acupuncture; the response rate 3 to 4 months after randomization did not favor either acupuncture or sham acupuncture (response ratio was 1.13, 95% confidence interval 0.95 to 1.35) with low heterogeneity
 - o In addition to the response rate at 3-4 months, several other comparisons at different time points also showed no difference between acupuncture and sham acupuncture
- 4 trials of acupuncture vs prophylactic drug treatment showed reduced headache frequency at 3-4 months with acupuncture compared to prophylactic medication (beta-blocker, calcium channel blocker, or valproate)
- 2 trials comparing acupuncture with relaxation or relaxation plus massage did not report outcome measures which could be used to estimate treatment effects

Authors' conclusions:

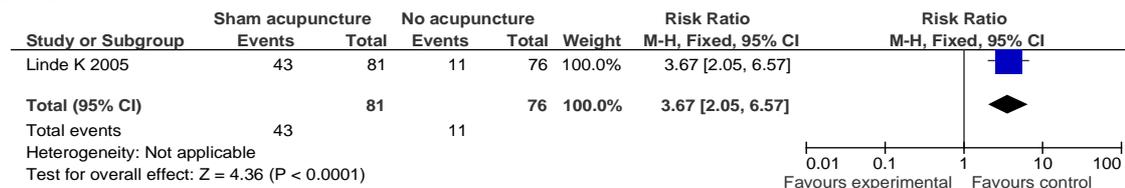
- The evidence base for acupuncture has been increasing in recent years due to the publication of several trials of adequate quality
- The results are challenging and not easy to interpret
 - o The equivalence of acupuncture and sham acupuncture may be due to a large placebo response, to direct physiologic responses to needle placement outside acupuncture points, or to biased reporting of acupuncture response in headache diaries
 - o Placebo responses occur when there are expectations of benefit, conditioning, and social support
 - o Placebo responses may be greater for complex interventions such as acupuncture than for less complex interventions such as taking a pill
 - o Physiological mechanisms proposed for acupuncture do not all imply point specificity
 - o While patients randomized to acupuncture may report their headache response in a biased way, the headache response to prophylactic

medications in the included studies are comparable to those reported in other drug trials

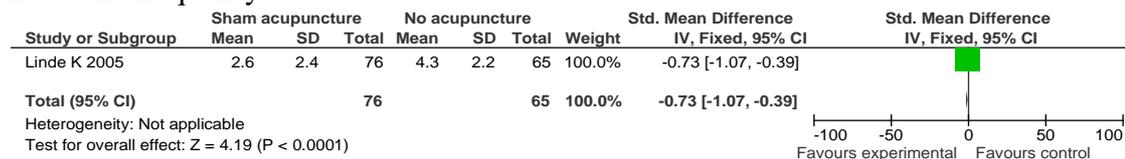
- Bias cannot be ruled out in the unblinded studies
- Safety was not a predefined objective of this review, but there were fewer dropouts for adverse effects in the acupuncture groups than in the prophylactic drug groups
- Acupuncture can be considered an option for prophylaxis of migraine in patients who have adverse effects from other treatments or whose response to other treatments is not adequate

Comments:

- The most robust result, due to the largest number of included studies, is the therapeutic equivalence of acupuncture and sham acupuncture
- There is no direct comparison between sham acupuncture and no acupuncture, but one trial (Linde 2005) had a true acupuncture, a sham acupuncture, and a no acupuncture (wait list) group, permitting the data from this trial to be entered into a separate comparison using the RevMan software from Cochrane
- The comparison of the response rate between sham acupuncture and the wait list shows a treatment effect for sham acupuncture of 3.67 in favor of sham acupuncture



and a standard mean difference of 0.73 in favor of acupuncture for headache frequency



- This may show an expectation effect of acupuncture, since the Linde 2005 study recruited patients through reports in local newspapers in Germany, and the waiting list patients received acupuncture after the 12 weeks of the trial; however, the difference between sham acupuncture and the waiting list is substantial
- The comparison of acupuncture with drug treatment is more modest than the comparison with no acupuncture; the effect of acupuncture is close to that of the beta-blocker, calcium channel blocker, and valproate effect
- The response rate for the sham acupuncture group is 53% and for the waiting list group is 14%; the sham acupuncture group has a higher response rate than for any placebo response in a review of placebo responses in drug trials (van der Kuy 2002), in which the highest placebo group response rate (defined similarly as a 50% reduction in attack frequency) was 34.4%, and the average placebo response rate was 23.5%

- This would support the authors' conjecture that a complex intervention (sham acupuncture) elicits a greater placebo response than a simple placebo (an inert pill)
- It is possible to define the therapeutic response as the sum of the specific and non-specific responses to any intervention; although the non-specific responses to placebo dominate any specific response, the therapeutic response to acupuncture compares favorably with other migraine prophylaxis interventions
- The most current study of acupuncture for migraine prophylaxis (Li 2012) compares three forms of acupuncture to a sham acupuncture intervention, and reports no significant difference between true and sham acupuncture for the primary outcome; this would further add to the strong body of evidence that true and sham acupuncture do not differ in effectiveness for migraine prophylaxis

Assessment: Adequate for strong evidence that true and sham acupuncture have similar effects for migraine prophylaxis, adequate for good evidence that acupuncture is similar to drug treatment for migraine prophylaxis, and adequate for some evidence that sham acupuncture is superior to no acupuncture for migraine prophylaxis

Additional References

Li Y, Zheng H, et al. Acupuncture for migraine prophylaxis: a randomized controlled trial. *CMAJ* 2012;184(4):401-410

Linde K, Streng A, et al. Acupuncture for Patients with Migraine. A Randomized Controlled Trial. *JAMA* 2005;293:2118-2125.

Van der Kuy P, Lohman JJ. A quantification of the placebo response in migraine prophylaxis. *Cephalalgia* 2002;122:265-270.