

The persistence of the effects of acupuncture after a course of treatment: A meta-analysis of patients with chronic pain

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We used the pain intensity score as the dependent variable with baseline score, time and treatment group and an interaction term for group and time as predictors. Since the length of acupuncture treatment varied between trials, time was defined as the number of days since the end of treatment for this model.

To test whether the effects of treatment changed differently over time between the acupuncture and control groups, the analysis was repeated separately for each trial. The coefficients for the interaction term between treatment group and time since end of treatment were saved out along with the standard error of the estimate and entered into a meta-analysis.

As a sensitivity analysis, this model was also used to perform a one-stage meta-analysis for no acupuncture controlled and sham controlled trials separately. Data from all trials were included and the model was also adjusted for trial.

To give a visual representation of how the effects of acupuncture change over time, the results are presented graphically in two ways: as standardized pain scores over time since randomization, and as standardized pain scores over time since the end of treatment. A longitudinal model for the effect of time on pain change score (including cubic splines with knots at the tertiles) was used to predict and graph pain change over time for the acupuncture and control groups separately.

RESULTS

In most trials, patients received 8 – 15 treatments over 10 – 12 weeks. Only one trial had a longer treatment duration, 26 weeks[3]. A subset of studies recorded the number and frequency of sessions actually received by patients on the trial. In the acupuncture arm of trials with a no acupuncture control group, the mean number of treatments was 8 over 8 weeks (N=551). For sham trials, the number and duration of treatment was similar for both the acupuncture and sham arms: a mean of 10 treatments over 6 weeks (N=662).

Acupuncture compared to no acupuncture controls

In our analysis of acupuncture versus no acupuncture controls, a total of 8 trials and 2,985 patients were included. The results of the meta-analysis for these 8 trials with no acupuncture controls are shown in Figure 1. Note that in this figure the weights are determined using inverse variance weighting, so for example if a trial had a small confidence interval (very low variance), it had a higher weight than other trials of the same or even larger sizes that had higher variances. Effect size is reported as a post-treatment change in SD per 3 months for the acupuncture trials compared to the no acupuncture controlled trials. The fixed-effects estimate for the between-group comparison of acupuncture versus no acupuncture controls showed a non-significant decrease in the effect size of acupuncture of (0.011 SD per 3 months, 95% C.I. -0.014 to 0.037, $p = 0.4$) after the end of treatment. As the difference between acupuncture and control has previously been found to be close to 0.5 SD[35], the effect size of 0.011 SD per 3 months is equivalent to about a 9% diminution of treatment effects in the acupuncture versus no acupuncture group at 12 months. There was significant heterogeneity between trials ($p=0.006$).

Insert Figure 1 here

Figure 2 and Supplementary File Figure 1 both show a trend of an increase in the effect of both acupuncture and no acupuncture groups over time, while the difference in the pain change scores

between the two groups remains relatively consistent from randomization up to one year after the end of treatment. The effect sizes for the individual arms in these trials that report data beyond six months are presented in Table 3. The increase in overall effects in both arms might be attributable to the smaller effect sizes in the trial at 49 weeks[10] and the larger effect sizes of the trial with the longest follow-up at 92 weeks[30](Table 3).

Insert Figure 2 here

Insert Table 3 here

We conducted a sensitivity analysis in which data were entered into a one-stage meta-analysis. In the one-stage approach, the longitudinal model described above was applied to a data set including all trials with a no acupuncture control group. The model incorporated the non-independence between observations on a single patient and between observations on different patients in the same trial. Results for no acupuncture controlled trials were almost identical to the two-stage meta-analysis, with an overall reduction of 0.011 SD per 3 months, (95% CI -0.034, 0.013).

Acupuncture compared to sham acupuncture controls

We included a total of 16 trials and 4,534 patients in our analysis for acupuncture versus sham-controlled trials. The results of the meta-analysis for these 16 sham acupuncture controlled trials are shown in Figure 3. Among these trials, we found a significant reduction in pain change scores over time between the sham and acupuncture groups (effect size = -0.025 SD per 3 months, 95% C.I. -0.050 to 0.000, $p=0.05$) after the end of treatment. Because the difference between acupuncture and sham controls has previously been found to be close to 0.2 SD[35] this reduction would mean about a 50% diminution of effect size for acupuncture compared to sham patients at 12 months. Significant heterogeneity was also seen in sham-controlled trials ($p < 0.0001$).

Insert Figure 3 here

For all three neck pain trials[16][34][38] included in this analysis, the effects of acupuncture decreased over time compared to sham (see Figure 3), with two of these trials [34][38] showing a statistically significant decrease. In a sensitivity analysis that excluded neck pain trials, we found that there was a smaller non-significant reduction in how differences in pain between groups changed over time (effect size = -0.014, 95% CI -0.039, 0.011, $p = 0.3$) after treatment. Moreover there was no longer significant heterogeneity between sham acupuncture-controlled trials ($p = 0.2$). When excluding these three neck pain trials from the analysis, the diminution of effect in acupuncture patients compared to sham is about 28% at one year, suggesting that most of the effects of acupuncture might persist over time for the non-neck related chronic pain conditions. The Vas trial of acupuncture for shoulder pain[33] had a relatively large weight because outcome was measured three times after the end of treatment, allowing more precise estimates of the time course of treatment. However, excluding this trial had very little effect on the analyses (-0.024SD per 3 months, 95% CI -0.053, 0.005).

For sham-controlled trials, the one-stage meta-analytic approach found a slightly larger reduction in effect size compared to two-stage meta-analysis (-0.036 SD per 3 months, 95% CI -0.060, -0.012). However, the principal findings were not importantly affected: there was a large reduction in effect for neck pain trials (-0.581 SD per 3 months, -0.736, -0.427) but reductions in effect size for trials on non-neck pain indications were non-significant (-0.021 SD per 3 months, 95% CI -0.046, 0.003).

The pain change scores in each group over time after the end of treatment are shown in Figure 4 after randomization are shown in Supplementary File Figure 2. In the latter, the benefits of both acupuncture

and sham acupuncture groups appear to be largely sustained over time, with the difference in the pain change scores between the two groups remaining relatively consistent up to one year after randomization. Figure 4 shows a trend of a decrease in the effect of both the acupuncture delivered within a sham controlled trial and the sham acupuncture over time. Among these sham-controlled trials, one trial reported larger effect sizes at six months after the end of treatment[34], and three trials reported data nearer to 12 months after the end of treatment[4][10][40] (Table 3). The fact that the effect sizes in these three trials at one year after treatment are smaller overall than the trial with the large effect sizes reporting data at six months is likely to explain in part the observed decrease in treatment effect in sham controlled trials over time.

Insert Figure 4 here

Post hoc analyses

In light of our findings, we conducted a number of unplanned analyses. To determine whether the estimates of decrease in acupuncture effect relative to sham acupuncture or no acupuncture control are different, we compared the mean difference between acupuncture and each control group. We found no evidence of heterogeneity in how the effects of acupuncture dissipate between sham and no acupuncture-controlled trials when including all trials in the analysis ($p=0.5$) or when excluding neck pain trials from the analysis ($p=0.9$).

One reason why we may have failed to find significant reductions in acupuncture effects over time is that the analysis included trials irrespective of whether they reported differences between acupuncture and control. Obviously, a trial that showed no difference between groups cannot show a reduction in acupuncture effects over time. Hence we repeated our analyses excluding trials that concluded no significant effect of acupuncture compared to sham or no acupuncture control. Five no acupuncture controlled trials with 2,059 patients found a significant effect of acupuncture compared to no acupuncture control. Among these trials, there was a non-significant increase in the effects of acupuncture relative to no acupuncture control (0.013 SD per 3 months, 95% CI -0.018, 0.44, $p=0.4$). There were 7 sham controlled trials with 1,450 patients that found a significant effect of acupuncture compared to sham acupuncture. There was a significant decrease in the effects of acupuncture relative to sham for every 3 months of follow up of 0.049 SD (95% CI -0.086, -0.013, $p=0.008$) and significant heterogeneity between trials ($p<0.0001$). Excluding neck pain trials from this sensitivity analysis left 5 trials with 1,203 patients. There was no longer significant heterogeneity ($p=0.060$) and the decrease in the effect of acupuncture compared to sham was smaller and no longer significant when excluding both neck pain trials and trials that found no effect of acupuncture relative to sham: a decrease of 0.028 SD for every 3 months follow up (95% CI -0.065, 0.009, $p = 0.13$).

When including all trials that found an effect of acupuncture, there was significant heterogeneity, with the effects of acupuncture decreasing much more rapidly in the sham acupuncture trials than in the no acupuncture controlled trials ($p=0.011$). However, when excluding the neck pain trials from this analysis, we found a non-significant reduction in the effects of acupuncture over time between the sham controlled and no acupuncture controlled trials that found a significant effect of acupuncture ($p=0.097$).

To explore these results further, we repeated our analyses separately for neck pain and compared our findings to other pain patient subgroups combined. The estimate of a reduction in neck pain treatment benefit of 0.587 (95% CI 0.406, 0.767) standard deviations per three months is very much higher than the estimate of 0.014 (95% CI -0.039, 0.011) for comparison conditions ($p < 0.0001$). On closer inspection of data from each trial, improvements from baseline in the acupuncture group were stable in

one trial at 8 weeks post-randomization[38] but decreased by 40 – 50% in two trials with 10 – 25 weeks additional follow-up[16][34].

DISCUSSION

Principal findings

The effects of acupuncture compared to no acupuncture for chronic pain do not appear to decrease importantly over a projected 12 month period. We did not see a statistically significant association with time. The central estimate suggests that about 90% of the benefit of acupuncture relative to controls would be sustained at 12 months, or when using the upper bound of the confidence interval, about 70% of the benefit of acupuncture relative to controls would be sustained at 12 months.

The results for acupuncture versus sham were similar after exclusion of studies on neck pain. We did see clear evidence that the effects of acupuncture versus sham on neck pain do diminish over time. When excluding neck pain trials from the analysis to reduce heterogeneity, the diminution of effect in acupuncture patients compared to sham was about 30% at one year, suggesting that much of the effects of acupuncture persist over time for the non-neck related chronic pain conditions. This might be explained in part by the shorter courses of treatment provided in the neck pain trials[16,34,38], which were in the range of 3 to 4 weeks, in contrast to the more commonly provided courses lasting 6 to 8 weeks or longer for the other conditions (see Table 2).

Strengths and limitations

The key strength of this study is that we have used a meta-analysis drawing on an individual patient data from high quality randomized controlled trials of acupuncture for chronic pain, which found that acupuncture was superior to both sham and no acupuncture controls for each pain condition.[35] Using this large dataset of nearly 18,000 patients, we have been able to explore sub-groups with a precision not possible when using only summary trial data, as would be the case when using conventional meta-analytic methods. A key limitation was that not all trials in the dataset provided data at more than one post-treatment follow-up. We only have data from eight of the twenty trials that followed patients for 40 weeks or more. One trial provided follow-up at two years after randomization.[22] We do believe it is reasonable to draw conclusions about the time course of acupuncture effects over a one-year period. First, the data that we do have from trials with longer term follow-up does indeed suggest persistence of effects, incidentally a characteristic that may not be unique to acupuncture. Second, we did not see any difference on how treatment benefit changed over time comparing trials with longer versus shorter follow-up, which is why we used data from all trials to estimate the effects of time on treatment. It would be incorrect to conclude that “no important diminution of effect at 12 months” means “effects persist well beyond 12 months”.

Relationship to the wider literature

Our conclusions as to the time course over which acupuncture appears to provide benefits differ to some extent from data reported in a number of prior systematic reviews of acupuncture for chronic pain based on summary.[1][2][7][11][13][12][23][21][28][29][31] The critical difference between the current paper and prior reviews is that the latter reviews did not directly evaluate the time course of acupuncture effects. When a prior review reports that results were significant at an early time point, but not at a later time point, this cannot be taken as evidence that results changed over time. There are several reasons why significance may change even if underlying effects do not. The most obvious is if the

number of patients changes over time due to drop out. For instance, a trial with 150 patients per group and a 0.25 standard deviation difference between groups at post-treatment would be statistically significant ($p=0.031$). If results were identical at a six-month follow-up, but 25% of patients dropped out, the p value would be 0.063. Alternatively, if there was no drop out and no changes in mean pain scores, but longer follow-up was associated with a 25% increase in standard deviation, perhaps associated with greater variability of pain over time, the p value would again be non-significant ($p=0.084$). In both cases, the effects of treatment persist, and an analysis directly testing trends over time would confirm this finding; taking the approach of the conventional reviews and indirectly assessing change over time by separate inference at different timepoints would lead to incorrect conclusions regarding the time course of underlying effects. We are the first systematic review to directly analyze change over time using appropriate methods for longitudinal data.

Differences between our results and the previously published systematic reviews can be illustrated by taking as an example the review by Furlan et al[12] who found that, “acupuncture did not significantly differ from placebo in improving pain intensity scores” for low back and neck pain. In our meta-analysis, we used different inclusion criteria to select trials for review, which included the multiple pain conditions of headache/migraine, osteoarthritis and low back and neck pain, whereas Furlan only included low back and neck pain. Our more strict inclusion criteria required evidence of unambiguous allocation concealment, leading to our inclusion of only higher quality trials, which are less likely to be susceptible to bias. The critical difference however between the analysis we present here and the analyses of Furlan et al. is that they did not directly address the time course of acupuncture effects. Their analyses were limited to those trials that measured similar outcomes during approximately the same time periods. We obtained patient data from all eligible trials and performed an individual patient data meta-analysis within which we were able to standardize and compare multiple types of outcome. Since we had individual patient data, we were able to incorporate outcomes measured at all time points from all trials into one analysis, rather than drawing conclusions from multiple separate analyses and we therefore conducted an analysis that directly addressed the question at hand.

Implications for research and practice

The major clinical implication of our findings is that we can reassure chronic pain patients considering acupuncture that any treatment benefit does persist after the end of treatment. This is naturally also a consideration for other clinicians who may refer patients for acupuncture. A concern for such clinicians and their patients is that they may go through the time, trouble and expense of a course of acupuncture treatment, but then regress to having the same amount of pain shortly after treatment ends. This cannot be assumed, given the evidence that the effects of acupuncture for chronic pain persist for at least a year. A possible exception is neck pain, as we saw some evidence that differences between acupuncture and sham decrease over time for this condition.

Our findings also have implications on cost-effectiveness studies that use utility measures. Such studies calculate benefit, in terms of increase in quality adjusted life years (QALYs) associated with an intervention, and divide by the increase in cost associated with that intervention. Increase in QALYs depends on a “time horizon” for treatment effectiveness. In many cost-effectiveness studies on acupuncture, this time horizon is given as the length of follow-up, effectively assuming that the benefits of acupuncture disappear completely the moment that a patient completes their final questionnaire or follow-up assessment. Changing the time horizon dramatically impacts cost-effectiveness. In the case of a trial with the final follow-up at three months, but using a time horizon of 12 months (a minimum based on our data) rather than a time horizon of 3 months, would reduce the cost per QALY by 75%.

In terms of future prospective research, it is clear that further studies should continue to measure outcomes beyond the end of acupuncture treatment, at least at 12 months follow-up and, ideally, beyond. In one Acupuncture Trialists' Collaboration study[37], the average duration of chronic pain in the study cohort was over 20 years. It surely behoves the research community to adequately fund studies to assess long-term outcomes in patients with chronic pain. Given the discrepant results for chronic neck pain, future studies could focus specifically on the time course of acupuncture for this type of pain. Moreover there is a case for exploring the biological plausibility of physiological changes in sub-studies embedded within clinical trials in order to provide a mechanistic explanation of the longer term benefits associated with acupuncture. It is also plausible that the sustained effects of acupuncture may be explained by, as yet unspecified and unmeasured, treatment mediating factors.

CONCLUSION

With the possible exception of neck pain, the effects of acupuncture compared to no acupuncture for chronic pain do not appear to decrease importantly over 12 months. Patients can generally be reassured that treatment effects are likely to persist. Cost-effectiveness studies should take our findings into account when considering the time horizon of acupuncture treatment. Further research should measure long-term outcome of acupuncture for patients with chronic pain.

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Table 1. Trials with a no acupuncture control

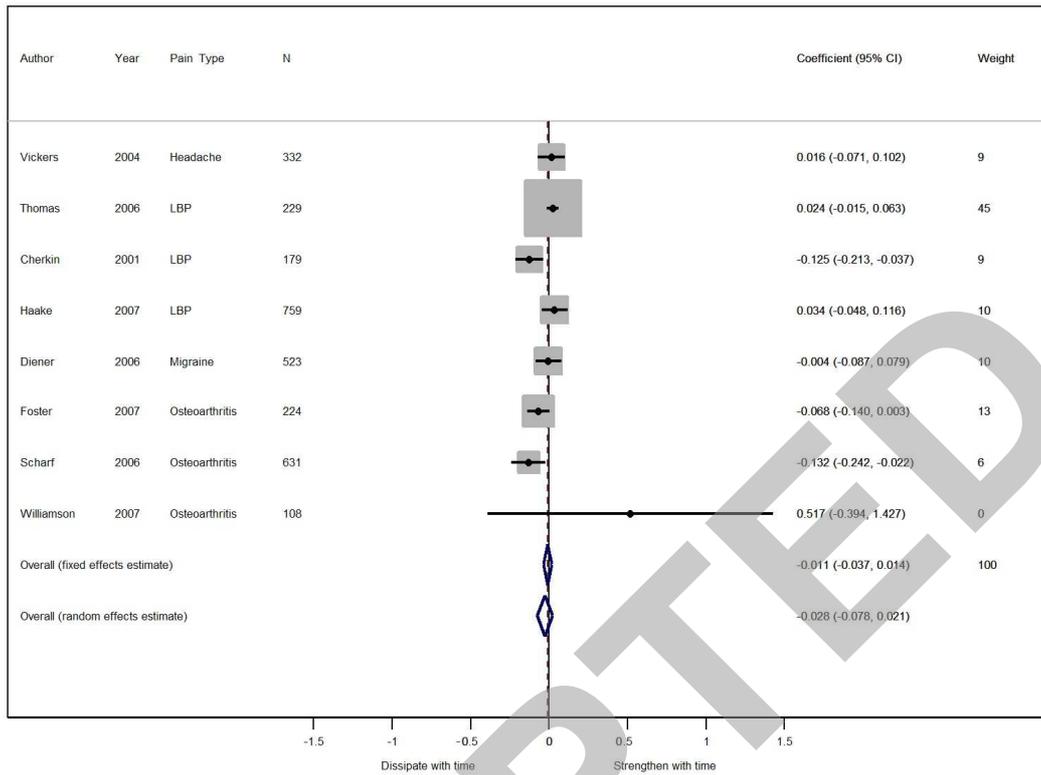
Trial Name	Pain Condition	Control patients offered acupuncture treatment (Crossover)	Average Length of Treatment	Time Points after End of Treatment	Included in meta-analysis
Foster 2007[10]	Osteoarthritis	No	3 weeks	Weeks 3, 23 and 49	Yes
Linde 2005[22]	Migraine	At 12 weeks	8 weeks	Week 4	No
Melchart 2005[25]	Headache	At 12 weeks	8 weeks	Week 4	No
Thomas 2006[30]	Low Back Pain	No	12 weeks	Weeks 1, 40 and 92	Yes
Salter 2006[26]	Neck	No	12 weeks	Week 1	No
Berman 2004[3]	Osteoarthritis	No	26 weeks	End of treatment	No
Cherkin 2001[6]	Low Back Pain	No	10 weeks	End of treatment and week 42	Yes
Diener 2006[8]	Migraine	No	6 weeks	End of treatment and weeks 7 and 20	Yes
Scharf 2006[27]	Osteoarthritis	No	6 weeks	Weeks 7 and 20	Yes
Haake 2007[15]	Low Back Pain	No	6 weeks	End of treatment and weeks 7 and 20	Yes
Vickers 2004[37]	Headache	No	6 weeks	Weeks 1 and 40	Yes
Williamson 2007[39]	Osteoarthritis	No	6 weeks	Weeks 1 and 6	Yes
Witt 2005[40]	Osteoarthritis	At 8 weeks	8 weeks	End of treatment	No
Witt 2006[41]	Neck	At 12 weeks	12 weeks	All measurements after crossover	No
Witt 2006[42]	Osteoarthritis	At 12 weeks	12 weeks	All measurements after crossover	No
Jena 2008[17]	Headache	At 12 weeks	12 weeks	All measurements after crossover	No
Witt ARC 2006[43]	Low Back Pain	At 12 weeks	12 weeks	All measurements after crossover	No
Brinkhaus 2006[4]	Low Back Pain	At 8 weeks	8 weeks	End of treatment	No

Table 2. Sham Controlled Acupuncture Trials.

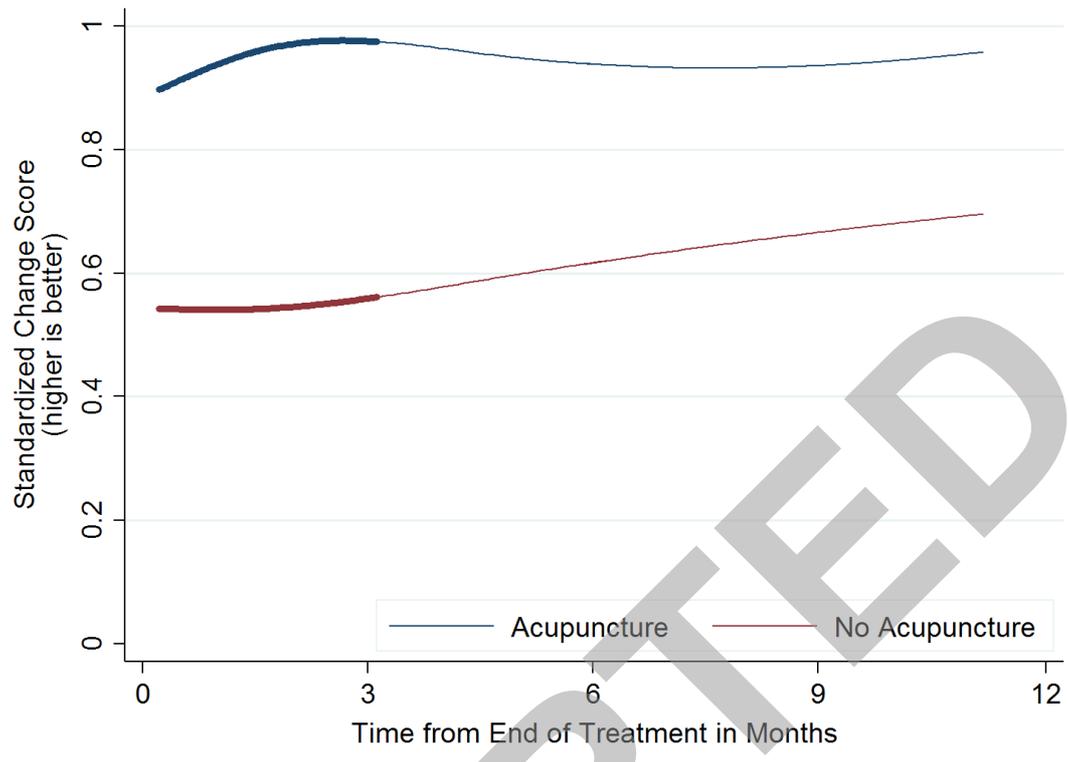
Trial Name	Pain Condition	Average Length of Treatment	Time Points after End of Treatment	Included in meta-analysis
Carlsson 2001[5]	Low Back Pain	8 weeks	Weeks 4, 12 and 26	Yes
Foster 2007[10]	Osteoarthritis	3 weeks	Weeks 3, 23 and 49	Yes
Guerra 2004[14]	Shoulder	8 weeks	Weeks 5 and 18	Yes
Irnich 2001[16]	Neck	3 weeks	Weeks 1 and 10	Yes
Kennedy 2008[18]	Low Back Pain	5 weeks	End of treatment and week 7	Yes
Kerr 2003[19]	Low Back Pain	6 weeks	None	No
White 2004[38]	Neck	4 weeks	End of treatment and weeks 1 through 8	Yes
Linde 2005[22]	Migraine	8 weeks	End of treatment and weeks 4 and 16	Yes
Melchart 2005[25]	Headache	8 weeks	End of treatment and weeks 4 and 16	Yes
Berman 2004[3]	Osteoarthritis	26 weeks	End of treatment	No
Kleinhenz 1999[20]	Shoulder	4 weeks	End of treatment	No
Diener 2006[8]	Migraine	6 weeks	End of treatment and weeks 7 and 20	Yes
Scharf 2006[27]	Osteoarthritis	6 weeks	Weeks 7 and 20	Yes
Haake 2007[15]	Low Back Pain	6 weeks	End of treatment and weeks 7 and 20	Yes
Endres 2007[9]	Headache	6 weeks	End of treatment and weeks 7 and 20	Yes
Vas 2004[32]	Osteoarthritis	12 weeks	Week 1	No
Vas 2006[34]	Neck	3 weeks	Weeks 1 and 25	Yes
Vas 2008[33]	Shoulder	3 weeks	Weeks 1, 10, 23 and 49	Yes
Witt 2005[40]	Osteoarthritis	8 weeks	End of treatment and weeks 18 and 44	Yes
Brinkhaus 2006[4]	Low Back Pain	8 weeks	End of treatment and weeks 18 and 44	Yes

Table 3: Effect size in SD for trials with follow-up longer than 6 months.

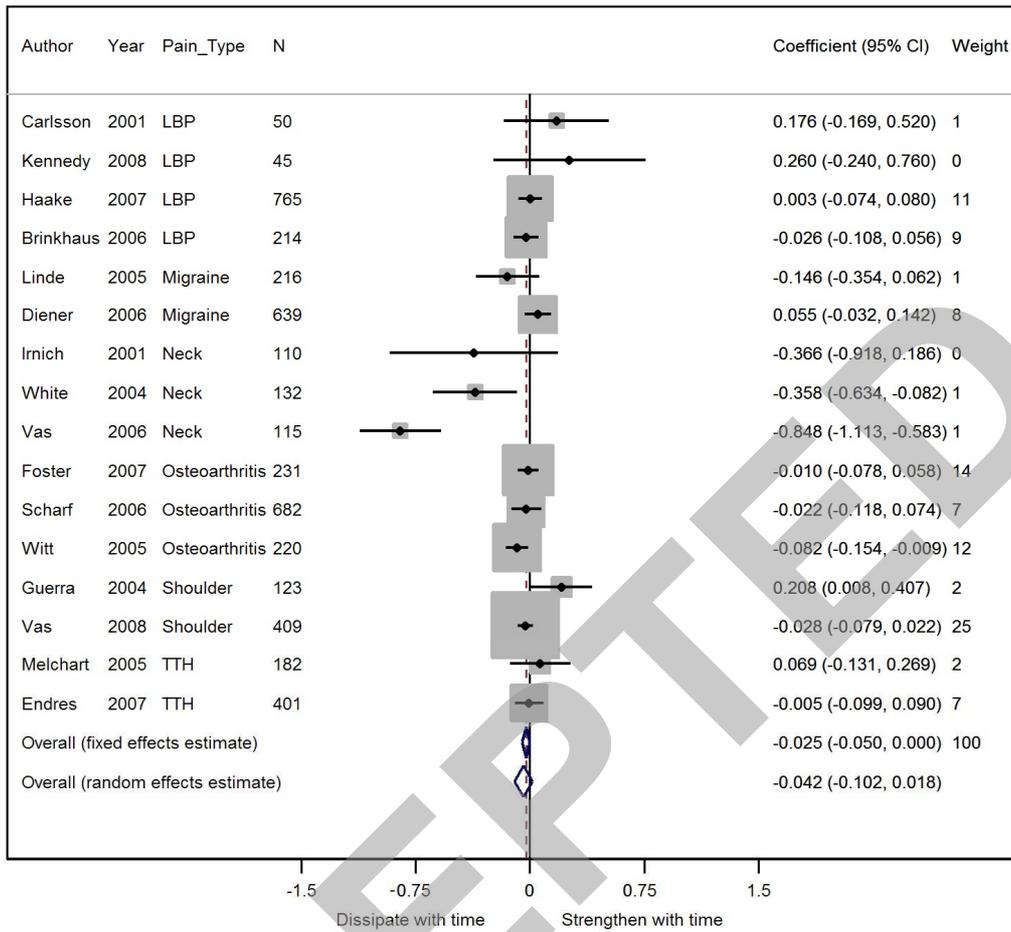
Acupuncture and no acupuncture control arms					
Trial	Arm	Week 40	Week 42	Week 49	Week 92
Foster 2007[10]	No acupuncture	-	-	0.60	
Foster 2007[10]	Acupuncture	-	-	0.55	
Thomas 2006[30]	No acupuncture	1.09	-	-	1.17
Thomas 2006[30]	Acupuncture	1.30	-	-	1.46
Cherkin 2001[6]	No acupuncture	-	0.91	-	
Cherkin 2001[6]	Acupuncture	-	0.85	-	
Vickers 2004[37]	No acupuncture	0.42	-	-	
Vickers 2004[37]	Acupuncture	0.80	-	-	
Acupuncture and sham acupuncture arms					
Trial	Arm	Week 23	Week 25/26	Week 44	Week 49
Carlsson 2001[5]	Sham		-0.30		
Carlsson 2001[5]	Acupuncture		0.91		
Foster 2007[10]	Sham	0.61	-	-	0.68
Foster 2007[10]	Acupuncture	0.56	-	-	0.57
Vas 2006[34]	Sham	-	1.03	-	-
Vas 2006[34]	Acupuncture	-	1.59	-	-
Vas 2008[33]	Sham	0.33	-	-	0.52
Vas 2008[33]	Acupuncture	1.02	-	-	1.22
Witt 2005[40]	Sham		-	0.72	-
Witt 2005[40]	Acupuncture		-	0.78	-
Brinkhaus 2006[4]	Sham		-	0.69	-
Brinkhaus 2006[4]	Acupuncture		-	0.76	-



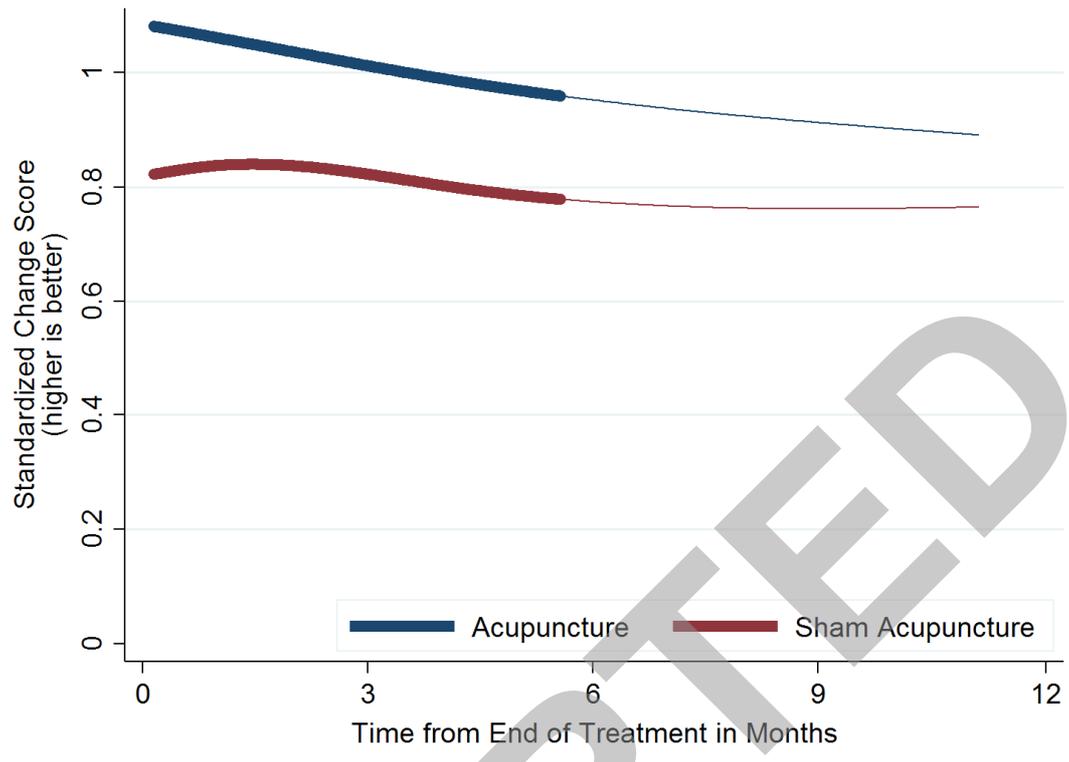
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