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Issues affecting the validity of a network meta-analysis of acupuncture and other physical interventions for the relief of chronic pain due to osteoarthritis of the knee

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Introduction

A network meta-analysis (NMA) requires the assumption that indirect and direct evidence is exchangeable. Additional assumptions of the model include a common between-study variance (BSV) across all the comparisons in the network, and the absence of bias. Poor model fit occurs when an individual trial estimate is highly inconsistent with the predictive distribution of the comparison derived from the model. It suggests the presence of outliers, inconsistency or an inappropriate common BSV assumption. Outliers may be due to chance or publication or study bias. Inconsistency may be due to bias, chance or an inappropriate BSV assumption. We investigated whether the assumptions required for a NMA were valid in the context of our network meta-analysis of acupuncture and other physical interventions for the relief of chronic pain due to osteoarthritis of the knee was undertaken.[1]

Table 1: Interventions included in the systematic review of physical interventions for osteoarthritis of the knee

Acupuncture	NMES
Sham acupuncture	Pulsed electrical stimulation
Balneotherapy	Pulsed electromagnetic fields
Braces	Static magnets
Exercise - Aerobic	Tai Chi
Exercise - Muscle strengthening	TENS
Heat treatment	Weight loss
Ice/cooling treatment	Standard care
Insoles	Placebo
Interferential therapy	No intervention
Laser/light therapy	
Manual therapy	

Methods

Twenty-two interventions were included in the review (Table 1). Trial quality was assessed using an adaptation of a checklist used in a previous review by the Centre for Reviews and Dissemination, using 14 questions. Separate analyses were run for all trials 'all-quality' and for higher-quality trials. Pain outcomes were converted to standardised mean differences (SMDs). The appropriateness of a common BSV was assessed by comparing the BSVs derived from the pairwise meta-analyses of each comparison, and the impact on the deviance of the model estimates from the trial estimates. The expected deviance of the estimate for a trial is 1 for a well fitting model. If the common BSV is less than the comparison's pairwise BSV then you would expect the average deviance to be greater than 1. The presence of publication bias was assessed using funnel plots where sufficient studies were available. The possibility of the presence of between-trial effect-modifiers was investigated through calculating deviance estimates, through pairwise meta-analyses, and the overall distribution of SMD estimates to identify outliers; and by performing consistency tests for the direct and indirect evidence for each evidence loop. The inconsistency degrees of freedom (ICDF) was derived for each analysis. This represents the number of independent loops of evidence on which consistency can be tested. Sensitivity analysis was performed excluding trials considered likely to be extreme outliers. Model fit was calculated as the percentage difference of the residual deviance over the number of data points (%dd).

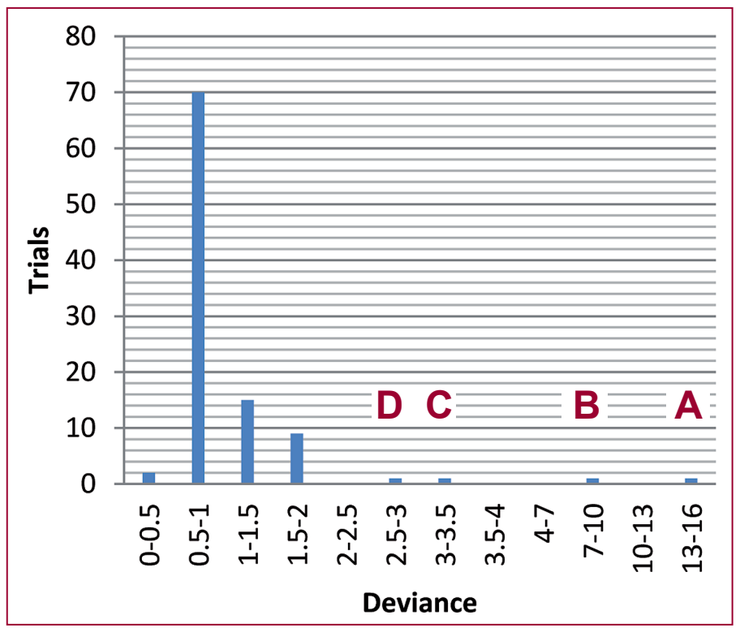

Figure 1: Histogram of the number of trials for each band of deviance for the analysis including all-quality trials

Results

There were 87 trials in the analysis of all-quality trials (results for a subset of interventions compared to standard care in Table 2). The BSVs calculated from the pairwise meta-analyses varied from 0 to 0.34, while the common BSV estimate was 0.185. The size of the pairwise BSVs relative to the common BSV was reflected in the average deviances of the trials for the comparison. Muscle-strengthening exercise vs standard care had a pairwise BSV of 0 (average deviance: 0.75). TENS vs placebo had a pairwise BSV of 0.34 (average deviance: 1.82). There was no evidence of publication bias for the one comparison with adequate trials. Figure 1 shows 2 trials (A and B) very likely to be outliers. The pairwise meta-analyses confirmed this. Trials C and D also look like potential outliers, but trial C was just one of 2 trials for the comparison and trial D did not show up as exceptionally outlying in the pairwise meta-analysis. Trials A and B along with two trials with potentially significant clinical differences were excluded in the sensitivity analysis. Excluding A and B improved the model fit from 16 %dd to 2.9 %dd, although the SMDs were not greatly affected (Table 2).

In the all-quality analysis, there were two comparisons with an inconsistency p-value<0.05, and 3 others < 0.1. Two of these comparisons included placebo; four included placebo in the evidence loop. The identified inconsistency remained in the sensitivity analysis. The exclusion of poor quality studies left only 19 trials for analysis. The ICDF was only 2 compared to an ICDF of 15 including poor quality studies, so there was little potential for inconsistency due to few evidence loops and lower power in the analysis.

Table 2: The standardised mean difference estimates and their 95% credible intervals

Intervention Comparator: standard care	**Trials of any quality** SMD (95% Cr I)	**Sensitivity analysis** SMD (95% Cr I)	**Higher-quality trials** SMD (95% Cr I)
Interferential therapy	-1.08 (-2.07 to -0.10)	-1.12 (-2.02 to -0.22)	N/A
Static magnets	-0.8 (-1.95 to 0.33)	-0.89 (-1.90 to 0.11)	N/A
Acupuncture	-0.79 (-1.12 to -0.47)	-0.86 (-1.16 to -0.55)	-1.01 (-1.42 to -0.62)
PES	-0.72 (-1.36 to -0.07)	-0.78 (-1.35 to -0.20)	-1.57 (-2.56 to -0.57)
TENS	-0.7 (-1.16 to -0.25)	-0.57 (-0.99 to -0.15)	N/A
Aerobic exercise	-0.59 (-1.06 to -0.16)	-0.32 (-0.71 to 0.07)	0.12 (-0.61 to 0.85)
	%dd: 16 ICDF: 15 Between-study standard deviation: 0.43	%dd: 2.9 ICDF: 15 Between-study standard deviation: 0.37	%dd: -0.7 ICDF: 2 Between-study standard deviation): 0.33

Conclusions

In the sensitivity analysis the presence of at least two trials with relatively high deviances and the identified high levels of inconsistency in places suggest that the uncertainty around at a least a few of the estimates is underestimated. There is uncertainty around the similarity of placebo effects in some trials and whether they are true placebo effects, and whether patient bias can be avoided where blinding is impossible. The lack of evidence loops and low power in the higher-quality trial analysis limited an analysis of inconsistency.

References

1. Corbett M, Rice S, Slack R, Harden M, Madurasinghe V, Sutton A, McPherson H, Woolacott N. . *Acupuncture and other physical treatments for the relief of chronic pain due to osteoarthritis of the knee: a systematic review and network meta-analysis*; In Press.

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