Appendix 1

Search strategy

MEDLINE (1950 to November 2007)
Retrieved 3945 articles

1 random:.ti,ab,sh.
2 randomized controlled trial.pt.
3 double-blind method/
4 single blind method/
5 placebos/
6 clinical trial.pt.
7 exp clinical trials/
8 controlled clinical trial.pt.
9 (clin$ adj25 trial$).ti,ab.
10 ((singl$ or doubl$ or trebl$) adj25 (blind$ or mask$)).ti,ab.
11 placebo$.ti,ab.
12. exp cohort studies/
13 cohort$.tw.
14. epidemiologic methods/
15. limit 14 to yr=1971-1988
16 or/1-13,15
17 ACUPUNCTURE/
18 exp Acupuncture Therapy/
19 ELECTROACUPUNCTURE/
20 acupunctur$.ti,ab.
21 electroacupunctur$.ti,ab.
22 electro-acupunctur$.ti,ab.
23 auriculoacupunctur$.ti,ab.
24 percutaneous electrical nerve stimulation.ti,ab.
25 PENS.ti,ab.
26 acupoint$.ti,ab.
27 meridian$.ti,ab.
28 dry needling.ti,ab.
29 or/17-28
30 16 and 29

EMBASE
Retrieved 3697 articles
1 exp ACUPUNCTURE/
2 acupunctur$.ti,ab.
3 electroacupunctur$.ti,ab.
4 electro-acupunctur$.ti,ab.
5 auriculoacupunctur$.ti,ab.
6 percutaneous electrical nerve stimulation.ti,ab.
7 PENS.ti,ab.
8 acupoint$.ti,ab.
9 meridian$.ti,ab.
10 dry needling.ti,ab.
11 or/1-10
12 random:.tw,sh.
13 double-blind method/
14 Single Blind Procedure/
15 placebos/
16 exp clinical trials/
17 (clin: adj25 trial:).tw.
18 ((singl: or doubl: or trebl: or tripl:) adj25 (blind: or mask:)).tw.
19 placebo:.tw.
20 or/12-19
21 case study/
22 case report.tw.
23 abstract report/ or letter/
24 or/21-23
25 exp cohort analysis/
26 exp longitudinal study/
27 exp prospective study/
28 exp follow up/
29 cohort$.tw.
30 or/25-29
31 20 not 24
32 Or/30-31
33 11 and 32

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AMED (1985 to November 2007)
Retrieved 3072 articles
1 exp Acupuncture/
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CINAHL
Retrieved 1068 articles
1 random:.ti,ab,sh.
2 random$.mp.
3 trial$.mp
4 placebos/
5 placebo$.mp.
6 clinical trial.pt.
7 exp clinical trials/
8 (clin$ adj25 trial$).ti,ab.
9 ((singl$ or doubl$ or trebl$) adj25 (blind$ or mask$)).ti,ab.
10. exp cohort studies/
11 cohort$.tw.
12 or/1-11
13 ACUPUNCTURE/
14 ELECTROACUPUNCTURE/
15 acupunctur$.ti,ab.
16 electroacupuncture$.ti,ab.
17 electro-acupuncture$.ti,ab.
18 auriculoacupuncture$.ti,ab.
19 percutaneous electrical nerve stimulation.ti,ab.
20 PENS.ti,ab.
The search strategy was developed to identify abstracts and papers of randomised controlled trials (RCTs), quasi-randomised trials (CCTs) and controlled cohort studies of acupuncture for the treatment of any medical or psychological condition in adults (≥18 years). Other study designs (e.g. case-control studies) were excluded as were studies of healthy volunteers or where all participants were children (<18), but trials were included when it was unclear whether the study was a CCT/RCT.

MEDLINE, AMED, CENTRAL, CINAHL, EMBASE and the Science and Technology Proceedings were searched in November 2007 with no language restriction (Appendix 1). An initial screening was conducted by one reviewer and rejected titles and abstracts were rescreened by a second. Due to resource limitations we were not able to translate foreign language papers or contact authors for clarification of data. A citation search for authors’ names of included studies was undertaken in MEDLINE in April 2010 to identify additional publications of relationship data arising from included papers dated post 2004.
Full papers were independently screened by two reviewers for mention of a relationship constraint. We defined this as any mention that communication between a practitioner and a conscious patient was constrained; studies of anaesthetised patients were excluded.

For all studies reporting a relationship constraint, the data pertaining to the reason for the relationship constraint, descriptions of constraint, monitoring and fidelity and debriefing in addition to general study data were extracted by one reviewer and checked by another, resolving discrepancies by discussion. We evaluated studies on two items related to quality; the reporting and adequacy of allocation concealment where applicable [1] and blinding of outcome observer. Data were presented as a narrative synthesis, presenting both the percentage of all trials reporting each feature related to the constraint, and the percentage of chronic musculoskeletal or neuropathic pain trials (defined below). We compared trial characteristics between constrained and unconstrained trials using Chi-square, Mann-Whitney and Fisher’s exact tests; we restricted this to trials of chronic pain only as these data were not extracted for unconstrained trials that were not of chronic pain.

We undertook a meta-regression to determine the effect of constrained relationships on participant outcomes. To reduce heterogeneity arising from different conditions under study and varying outcome measures, we restricted this analysis to reports of RCTs for the treatment by acupuncture of chronic (≥2 weeks duration) musculoskeletal or neuropathic pain. This we defined as pain associated with arthritic conditions, muscle pain, joint pain or fibromyalgia, any neuropathy or chronic post-operative pain, or pain of unknown origin. Tension-type headache was considered to be muscular in origin.[2] Musculoskeletal or neuropathic pain was not considered to be pain associated with neoplasms, acute trauma or fractures.

Studies were included when there was no mention of chronicity for a condition that could be acute or chronic. We further restricted trials to those that reported a pain outcome using a continuous measure after the end of the treatment, using the time point closest to the end of the treatment. For cross-over trials, this outcome needed to be reported before the treatment switch. If the trial
took multiple pain measures the hierarchy of visual analogue scale (VAS), over a non-VAS, over a condition specific pain outcome was implemented, taking the first usable outcome reported in the paper. To select which control arm to use in trials with more than two control arms the following selection criteria was used: a sham was selected; if there was more than one sham arm the sham arm with the better outcome was selected; if there was no sham arm but more than one non-sham arm the arm with the better outcome was selected. Data reported as intention to treat was preferred over completers over per-protocol analysis. Unadjusted outcomes were preferred over data adjusted for baseline characteristics or other covariates over imputed data. We imputed missing variance estimates using the mean (by trial arm) of variance estimates from similar measures in other acupuncture studies. Where the number of participants at outcome was not reported we imputed the number randomised, included, or followed-up at a previous time point, whichever was smaller. RCT’s that fulfilled all these criteria and did report a relationship constraint were included as ‘constrained’, those that fulfilled the criteria but did not report a relationship constraint were included as ‘comparators’ and this classification was used as the covariate in the main meta-regression. To explore the effect of different trial designs and a marker of trial quality we repeated the meta-regression also including the binary covariates of whether the trial was controlled by sham acupuncture, and the adequacy or otherwise of allocation concealment.[1]

We used a random effects meta-analysis,[3] as we expected between-study variability (heterogeneity).[4] Because a variety of pain rating scales were used, we standardised the unit of outcome measurement across trials by calculating the standardised mean difference (SMD) in each trial using Hedge’s adjusted g. We quantified heterogeneity and its confidence interval (CI) as $I^2$, calculated using a non-central (Chi-squared) approach.[5] An $I^2$ point value of 25% or less was considered to be low, 20-75% moderate and 75% and over high [6] and the 95% CI used to interpret the precision of the estimate.[5, 7] Due to the moderate and high levels of heterogeneity present we reported prediction intervals (PI) to indicate the range of possible summary effect [8] and not confidence intervals (CI) for the estimation of variance around the SMD. A random-effects meta-
regression was used to assess the effect of the covariates on heterogeneity,[9] using an iterative restricted maximum likelihood (REML) estimator for $r^2$ (tau-squared) [10] and conservative quadratic Knapp-Hartung estimator for the variances of the effect estimates.[9] The proportion of heterogeneity explained by the covariate ($R^2_{\text{Adj}}$), (the relative reduction in between-study variance [9]) was presented along with the coefficient and two-tailed P value (alpha=0.05). The proportion of residual heterogeneity after adjustment with the covariates not due to sampling variation was presented as $I^2_{\text{Res}}$. As an interpretative note, it is possible for the $R^2_{\text{Adj}}$ to be negative, this indicates that the proportion explained is no greater than what would be expected by chance.[11] The metan,[12] heterogi,[13] and metareg [11] modules of STATA 12 (StataCorp LP, Texas) were used to generate the meta-analysis and meta-regression.

References

8 Riley DR, Higgins JPT, Deeks J. Interpretation of random effects meta-analysis. BMJ. 2011;342:549.