

Evidence for acupuncture – updated Aug 2016

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Evidence for acupuncture relevant to primary care

Chronic low back pain

A Cochrane review by Furlan et al of acupuncture and dry needling for low back pain, which included 35 RCTs, concluded that 'for chronic low back pain, acupuncture is more effective for pain relief and functional improvement than no treatment or sham treatment immediately after treatment and in the short term only'.[1] A systematic review published in the same year by Manheimer et al also found acupuncture to be significantly more effective than sham acupuncture in chronic low back pain.[2] More recent systematic reviews have not included meta-analysis. The Cochrane review (including meta-analysis) is being updated under the new title *Acupuncture for (sub)acute non-specific low-back pain*, and will be published in due course.[3]

Since these reviews there have been several relevant studies published. The ART (Acupuncture Randomised Trial) study (n=298) from the Charité University Medical Center in Berlin of acupuncture for chronic low back pain shows a trend in favour of verum over minimal (superficial non-point) acupuncture, but a significant difference between verum and the no (additional) treatment control group.[4] The standard deviation in the primary outcome measure in this trial exceeded the estimate in the sample size calculation by 50%, which reduced the intended statistical power of the trial considerably.

Thomas et al reported positive results in their pragmatic trial of acupuncture in chronic low back pain in primary care (n=241). They demonstrated effectiveness and cost-utility at 24 months – the cost per additional QALY was £4241.[5,6] The primary outcome for additional

acupuncture over routine GP care was significant at 24 months but not at 12 months. This is a surprising result following a short course of acupuncture, since the systematic reviews demonstrate a short term effect only.[1,2]

The results of the very large pragmatic ARC (Acupuncture in Routine Care) study on chronic low back pain (n=3093 randomised; 11 630 total cohort) confirm effectiveness and cost effectiveness of acupuncture, with the cost per additional QALY of €10 526.[7]

The GERAC (German Acupuncture trial) trial on low back pain (n=1162)[8] found acupuncture and minimal (sham) acupuncture to be superior to guideline-based standard treatment, however, acupuncture was not statistically superior to minimal (superficial non-point) acupuncture. On the basis of this, the German health authorities have decided that acupuncture will be included in routine reimbursement by social health insurance funds for the treatment of low back pain. One of the key findings in this trial was that the minimal (sham) acupuncture (often viewed as a 'placebo' control) was superior to guideline-based standard care (twice as good in the primary outcome measure). This calls into question the validity of making judgements about the clinical relevance of the difference between acupuncture and minimal (sham or 'placebo' control) acupuncture.

A large (n=638), four-arm sham controlled and comparative trial performed in the US demonstrated no difference between individualised acupuncture, standardised acupuncture or simulated acupuncture (using blunted cocktail sticks) on mechanical low back pain, but all three groups were more than twice as effective as usual care alone.[9]

An individual patient data meta-analysis (IPDM) reported by Vickers et al in 2012 (see below), [10] includes pooled data from 5 of the best quality trials of acupuncture in low back pain in a sensitivity analysis. This includes data from the ART & GERAC trials described above,[4,8] but not the four-arm US trial.[9] Acupuncture was significantly

superior to sham and to no acupuncture with pooled effect sizes of 0.20 and 0.46 respectively.

The NICE clinical guideline (CG88) for the early management of persistent non-specific low back pain (between 6 months and 1 year) include consideration of 12 sessions of acupuncture over 3 months.[11] Unfortunately the update of this guideline, titled 'Low back pain and sciatica',[12] due to be published in September 2016 is unlikely to recommend acupuncture, as NICE are now applying minimal clinically important difference (MCID) as a new criterion applied to the difference of an intervention over sham or placebo.

Chronic headache

The first Cochrane review on acupuncture for idiopathic headache was tentatively positive.[13]

Vickers and Wonderling show definitive effectiveness (not efficacy) and cost effectiveness – the cost per additional QALY was £9180.[14,15]

Efficacy was still in some doubt following the results of the German ART studies in migraine and TTH.[16,17] Responder rates were good for needling but the rates in the minimal (sham) needling groups were also high. Responder rates were confirmed in a large epidemiological study (n=2022).[18] The ARC study on headache confirmed effectiveness compared with usual care alone (n=3182 randomised; 15 056 total cohort),[19] and confirmed cost effectiveness (n=2682), with the cost per additional QALY of €11 590.[20]

The GERAC trial on migraine (n=960) showed that outcomes do not differ between acupuncture, minimal (sham) needling, and standard therapy (1st beta-blocker; 2nd flunarizine; 3rd valproic acid).[21] The responder rates at 26 weeks after randomisation were 47%, 39% and 40% respectively. When reanalysed in the IPDM by Vickers et al, the difference between acupuncture and minimal (sham) acupuncture became statistically significant.[10]

In 2009 the Cochrane review was updated and split into acupuncture for migraine prophylaxis,[22] and acupuncture for tension-type headache.[23] The authors' conclusions were as follows:

Acupuncture for migraine prophylaxis[22]

In the previous version of this review, evidence in support of acupuncture for migraine prophylaxis was considered promising but insufficient. Now, with 12 additional trials, there is consistent evidence that acupuncture provides additional benefit to treatment of acute migraine attacks only or to routine care. There is no evidence for an effect of 'true' acupuncture over sham interventions, though this is difficult to interpret, as exact point location could be of limited importance. Available studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered a treatment option for patients willing to undergo this treatment.

Acupuncture for tension-type headache[23]

In the previous version of this review, evidence in support of acupuncture for tension-type headache was considered insufficient. Now, with six additional trials, the authors conclude that acupuncture could be a valuable non-pharmacological tool in patients with frequent episodic or chronic tension-type headaches.

The NICE clinical guideline (CG150) on diagnosis and management of headaches in young people and adults recommends the use of acupuncture for prophylaxis of tension type headache and migraine,[24] although there is some debate over the network meta-analysis that showed acupuncture to be only half as good as topiramate,[25] when the same data seems to show that sham acupuncture is marginally better than real topiramate.

An update to CG150 was published in November 2015, and the recommendations for acupuncture remain.

Subsequently the Cochrane reviews have been updated,[26,27] and the

conclusions remain positive. Data from the IDPM was used,[10] and for the first time acupuncture has been shown to be marginally superior to sham, as well as medication in migraine prophylaxis.

Knee osteoarthritis (OA knee)

The largest sham controlled trial to date is the GERAC OA knee trial (n=1007).[28] This trial used off-point superficial acupuncture in the sham, and a third arm of conservative treatment only (physiotherapy and NSAIDs). Both acupuncture groups (traditional Chinese acupuncture and sham acupuncture) were significantly better than conservative treatment alone. The improvement in WOMAC index in the real acupuncture group was very similar to that in the ART OA knee trial (around 20% reduction at 26 weeks).[29] The key difference between ART and GERAC appears to be the effect size in the minimal acupuncture group (it was markedly higher in the GERAC trial than in the ART trial).

An SR by White et al included 13 RCTs.[30] The results from the five high quality trials (n=1334) were pooled in meta-analysis for the primary outcome, and demonstrated a significant effect of acupuncture versus sham in short term pain. A subsequent SR by Manheimer et al found very similar results in their meta-analysis,[31] although their interpretation differed in terms of clinical relevance.

The pragmatic ARC study on acupuncture for OA in the hip and knee (n=712 randomised; 3633 total cohort) has demonstrated marked clinical improvement, which is maintained at six months, from a 15 session course of treatment.[32] The economic analysis performed alongside the ARC study (n=421) demonstrated cost effectiveness of €17 845 per additional QALY.[33] A further health economic assessment in the UK, that formed part of the APEX trial,[34] provides a more favourable figure of £3889 per additional QALY for an intervention including advice, exercise and acupuncture.[35]

The most recent Cochrane review of acupuncture for peripheral joint OA (lead

by Manheimer)[36] included 16 trials and 3498 participants. Twelve trials were on OA knee, three on OA hip and one included both. The authors concluded:

Sham-controlled trials show statistically significant benefits; however, these benefits are small, do not meet our pre-defined thresholds for clinical relevance, and are probably due at least partially to placebo effects from incomplete blinding. Waiting list-controlled trials of acupuncture for peripheral joint osteoarthritis suggest statistically significant and clinically relevant benefits, much of which may be due to expectation or placebo effects.

We (White & Cummings)[37] argue that you can only test the biological plausibility of acupuncture against sham acupuncture, not its clinical relevance.

The NICE clinical guideline (CG59) on osteoarthritis recommends that electroacupuncture should not be used on the basis of the perceived cost derived from health economic modelling.[38] This guideline was much debated,[39–41] and an alternative economic analysis seemed to favour acupuncture,[42] however, the updated guideline did not recommend acupuncture,[43] despite evidence of efficacy over sham, effectiveness and cost effectiveness within threshold. The difference beyond sham is the sticking point, and the wording of the Cochrane review above is repeated as the excuse. Acupuncture did not achieve a standardised mean difference (SMD) of 0.5 over sham acupuncture; however, few interventions if any in osteoarthritis do achieve this.

Further evidence that suggests acupuncture can play a useful role in osteoarthritis comes from a network meta-analysis (NMA).[44] This was a comprehensive NMA of physical treatments for pain relief in osteoarthritis of the knee (OA knee). A total of 114 trials including 22 different interventions in 9709 patients provided data suitable for NMA. The higher quality trials were of acupuncture (11 trials) and muscle strengthening exercises (9 trials). The latter is recommended in national clinical guidelines as a core treatment in OA knee.[38] Acupuncture was significantly

better than muscle strengthening exercises with an effect size of 0.49 (SMD). This seems to raise questions about why acupuncture is not recommended as a treatment in OA.[40]

A further small but rigorous study published in JAMA again raised the question of MCID over sham.[45] There was a significant difference for needle acupuncture over a no treatment control who were not aware of the trial (Zelen design), and therefore not disappointed. The paper has raised some debate over interpretation of the results.[46]

Neck pain

The first SR of acupuncture for neck pain was neutral,[47] but this was based on relatively small trials with methodological drawbacks. The ARC study on neck pain (n=3766 randomised; 14 161 total cohort) clearly demonstrates effectiveness,[48] and combined with confirmed efficacy over sham for acupuncture in chronic low back pain [see above], it seems reasonable to postulate that there is also specific efficacy for acupuncture in neck pain. The economic analysis that formed part of the ARC study found the cost per additional QALY of acupuncture in chronic neck pain was €12 469.[49]

A Cochrane review was published in 2006,[50] although this does not include the ARC study above. It found moderate evidence that acupuncture relieves pain in chronic mechanical neck disorders. Interestingly the 10 trials included had a total of only 661 subjects – one fifth of the size of the randomised element of the ARC trial.[48]

Shoulder pain

The Cochrane review on acupuncture for shoulder pain in 2005 was inconclusive but suggested that there may be a short term benefit on pain and function.[51] Since then there have been two interesting trials. Vas et al demonstrated the advantage of manual acupuncture to a single point (ST38) versus sham (mock TENS) along with physical therapy rehabilitation for shoulder pain in 425 subjects.[52] More recently the GRASP

trial (German Randomized Acupuncture trial for chronic Shoulder Pain) tested acupuncture against a distant superficial off-point sham and conventional orthopaedic care in 424 subjects with chronic shoulder pain.[53] Acupuncture proved to be superior to sham and conventional orthopaedic care, although the dropout rate in the sham group was rather high at 45%.

Individual patient data meta-analysis

The Acupuncture Trialists' Collaboration have performed the first individual patient data meta-analysis (IDPM) of chronic pain trials.[10] This meta-analysis includes individual data on 17 922 patients, and clearly demonstrates efficacy of acupuncture over sham in chronic pain, and effectiveness over non-acupuncture controls. A further analysis of this data with meta-regression attempted to define the characteristics of treatment associated with better or worse outcomes.[54] Better outcomes were observed when more needles were used when acupuncture was compared with non-acupuncture controls. A sensitivity analysis (excluding three outlying RCTs with very much larger effect sizes than the others) showed that trials allowing electrical stimulation had a significantly stronger effect of acupuncture compared with sham and those with a longer average treatment session duration had a smaller effect compared to sham. The patient level analysis showed a small but highly significant association between better outcomes and a higher number of treatment sessions.

Nausea & vomiting

This was the first area with a positive SR.[55] The best evidence is for post-operative nausea and vomiting (PONV), in which the NNT is estimated to be between 4 and 5 for early PONV.[56] Not so relevant for primary care, but even [Bandolier](#) said it was probably worth using!

The latest Cochrane review on the subject concludes:[57]

P6 acupoint stimulation prevented PONV. There was no reliable evidence for differences in risks of postoperative nausea or vomiting after P6 acupoint stimulation compared to antiemetic drugs.

Overactive bladder

A trial of electroacupuncture (EA) to SP6, referred to by urologists as PTNS (percutaneous tibial nerve stimulation), has demonstrated efficacy of this intervention compared with sham (including the Streitberger needle) in 220 subjects with overactive bladder symptoms.[58] Other studies suggest that the technique compares favourably to the drug tolterodine,[59] and that it appears to be a viable long term therapy.[60]

Allergic rhinitis

Acupuncture for allergic rhinitis (mixed perennial and seasonal) was evaluated as part of the large trial programme funded by the health insurers in Germany from the late 1990s – the Modellvorhaben Akupunktur.[61,62] A pragmatic trial of acupuncture in addition to usual care compared with usual care alone in 981 patients over a three-month period found that a significant benefit occurred in the acupuncture group, and the ICER was estimated at €17 377 per QALY gained.[62]

Seasonal allergic rhinitis was evaluated subsequently in a large sham controlled trial (n=422).[63] The trial compared 12 sessions over 8 weeks of real acupuncture with a sham that involved gentle needling of points that were not recognised as acupuncture points. A third group had no acupuncture initially but received real acupuncture in the second part of the trial, after 8 weeks. All groups were allowed rescue medication in the form of up to two doses of cetirizine per day, and if their symptoms were not adequately controlled, they could be treated with an oral corticosteroid. The primary outcome was a change in symptoms (Rhinitis Quality of Life Questionnaire [RQLQ]) and need for medication (Rescue Medication Score [RMS]). Secondary outcomes included responder rates, where a responder was

defined by a change in RQLQ of at least 0.5 compared with baseline. Real acupuncture was associated with a statistically significant benefit over sham at 7 to 8 weeks (end of treatment), but not at 15 to 16 weeks (approaching the end of the season), when the sham group caught up. Interestingly, the real acupuncture group was still significantly improved in the following year compared with the sham group, regarding both symptoms and medication use. Despite this longterm effect, the economic analysis was restricted to the primary endpoint at 8 and 16 weeks. The ICER for each additional QALY gained by using acupuncture to treat seasonal allergic rhinitis was between €31 241 and €118 889 from a societal perspective, and between €20 807 and €74 585 from a third-party payer's perspective. This does not look likely to be cost effective using contemporary thresholds for cost effectiveness (approximately €50 000 per QALY gain).[64]

The trial was featured in NICE Eyes on Evidence in September 2013,[65] and it was comforting that their editors recognised the clinical significance of the results, a detail that the editors of *Annals of Internal Medicine* felt necessary to caution against.

The future

In a review paper in the journal *Nature* in 2002,[66] Tracey discussed the anti-inflammatory role of the vagus nerve, focussing on the anti-TNF effect of peripheral acetylcholine release and implied that acupuncture might be a possible method of stimulating this homeostatic response.

In 2014 a team in the US published an experimental trial in a mouse model of

sepsis that demonstrated a novel inflammatory mechanism of indirect vagal stimulation.[67] The intervention they used was 10 minutes of EA to the point ST36, and it saved the majority of mice in the experiment from an otherwise fatal outcome. The effect of EA on TNF lasted for 72 hours after just 10 minutes of stimulation at ST36.

Since vagal stimulators are now starting to be used in patients with severe inflammatory arthropathies,[68] it is tempting to wonder if self-applied EA to ST36 twice a week could have the same effect.

Key to abbreviations

ARC – acupuncture in routine care (large cohort studies, some with randomised elements; also part of the German Health Insurance Modellvorhaben; Berlin group)

ART – acupuncture randomised trial (part of the German Health Insurance Modellvorhaben – trial phases; Berlin group)

EA – electroacupuncture

GERAC – German acupuncture trial (part of the German Health Insurance Modellvorhaben; Bochum group)

GRASP – German randomized acupuncture trial for chronic shoulder pain

ICER – incremental cost effectiveness ratio

IDPM – individual patient data meta-analysis

MCID – minimal clinically important difference

NMA – network meta-analysis

NNT – number needed to treat

OA – osteoarthritis

PONV – postoperative nausea and vomiting

QALY – quality adjusted life year (parameter used in economic analysis of healthcare interventions)

SMD – standardised mean difference

SR – systematic review

TENS – transcutaneous electrical nerve stimulation

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