

# Developing a Research Strategy for Acupuncture

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**Abstract:** This strategic overview revisits some of the basic assumptions that relate to the clinical evaluation of acupuncture. We look at the evidence available to estimate both the specific and nonspecific effect size of acupuncture (efficacy and effectiveness) and consider the placebo within acupuncture trials, as well as the value of both placebo controlled trials and pragmatic acupuncture studies. We argue for an augmented, mixed methodology that integrates basic mechanism studies, including modern imaging techniques such as functional magnetic resonance, quantitative and qualitative research, as well as safety and health economic data to obtain a more rigorous understanding of acupuncture. We hope that by taking a broad, patient-centered, and rigorous approach we may arrive at a realistic and thoughtful evaluation of its relative value in comparison to placebo treatment, conventional medicine, and its potential for integration into conventional clinical care.

**Key Words:** acupuncture, controlled trials, imaging, placebo

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Acupuncture trials before the 1980s were haphazard and unstructured producing a plethora of information from which it was almost impossible to interpret a coherent picture. The evidence produced was largely equivocal and contradictory.<sup>1</sup> One of the first methodologic papers published in complementary and alternative medicine (CAM), and addressing this chaos, were Lewith and Machin's<sup>2</sup> observations suggesting a conceptual framework through which the evaluation of acupuncture might proceed, both in terms of trial design and with respect to appropriate placebo control interventions for such studies. On the basis of data available in the early 1980s, Lewith and Machin<sup>2</sup> suggested that true placebo was likely to produce a 30% improvement in chronic

pain, sham acupuncture (SA) (a penetrating needle at a nonacupuncture point without needling sensation), a 50% improvement and real acupuncture (RA) (at an appropriate acupuncture point with needling sensation), and a 70% improvement from baseline pain. This article reexamines these approaches to acupuncture research given 25 years of additional collective experience with particular reference to the plethora of recent substantive papers and systematic reviews.

We also consider what might be nonspecific and specific clinical effects in the context of the clinical provision of acupuncture. Paterson and Dieppe<sup>3</sup> recently raised the issue that part of the specific effect of acupuncture may be related to the context and process of Traditional Chinese Medicine (TCM). Acupuncture as a "whole system" may be much more than the process of penetrating needling.<sup>4</sup> Indeed the use of a TCM diagnosis may in itself be therapeutic in chronic intractable pain.<sup>5</sup>

## WHAT IS ACUPUNCTURE AND HOW SHOULD IT BE DEFINED AND REPORTED?

In the 1980s, there was much confusion concerning fundamental definitions of acupuncture, with quite different treatment techniques receiving the same "label." Electro-acupuncture, manual stimulation of needles at trigger points, and an individualized TCM approach to point selection and needle stimulation, as well as fixed protocol acupuncture were all considered to be "real acupuncture." The details of the intervention were rarely accurately described in the trial methods section, consequently comparing or repeating studies was almost impossible. Similarly, different controls had been used against which to assess the clinical effects of RA in pain, many of which were referred to as "sham" even though they could be substantially physically and physiologically different, such as needling inappropriate points, minimal needle penetration, and even mock transcutaneous nerve stimulation (Table 1).

In 2002, subsequent to the publication of the Standards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) guidelines,<sup>6</sup> many of the recent large acupuncture studies demonstrate a dramatic improvement in the precision of reporting of the exact nature of the acupuncture intervention and associated controls, thus allowing the studies to be repeated accurately and independently.

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**TABLE 1.** Some Recent Major Studies Involving Acupuncture for Pain and Headache

Study	Condition	Trial Design	Patient Numbers	Intervention	Outcome Measure	Significance
Irnich et al <sup>63</sup>	Chronic neck pain	RCT	177	1. Massage 2. Sham laser 3. RA	Motion related pain	Acupuncture > massage ( $P = 0.005$ ) but not significantly different to sham laser
White et al <sup>19</sup>	Chronic neck pain	RCT	135	1. RA 2. Mock transcutaneous electrical stimulation	Pain (Visual Analogue Scale)	Acupuncture significantly better than mock transcutaneous electrical stimulation ( $P = 0.01$ )
Melchart et al <sup>35</sup>	Tension headache	RCT	270	1. RA 2. Minimal acupuncture (penetrating needling) 3. Waiting list control	Days with headache	No difference between acupuncture and minimal acupuncture ( $P = 0.58$ ) but significant difference between acupuncture and waiting list control ( $P = 0.001$ )
Linde et al <sup>34</sup>	Migraine	RCT	302	1. RA 2. SA (penetrating needling) 3. Waiting list control	Days with headache	No difference between RA and SA but both showed a significant improvement on waiting list control ( $P = 0.001$ )
Assefi et al <sup>70</sup>	Fibromyalgia	RCT	100	1. RA 2. SA (penetrating needling)	Pain	No difference between SA and RA
Witt et al <sup>37</sup>	Osteoarthritis knee	RCT	294	1. RA 2. SA (penetrating needling) 3. Waiting list control	Western Ontario and McMaster Universities Osteoarthritis Index	RA > SA ( $P = 0.0002$ ). RA > waiting list control ( $P = 0.0001$ )
Berman et al <sup>24</sup>	Osteoarthritis knee	RCT	570	1. RA 2. SA (penetrating and non-penetrating needling)	Western Ontario and McMaster Universities Osteoarthritis Index (pain)	RA > SA ( $P = 0.01$ )
Vickers et al <sup>44</sup>	Headache	Pragmatic RCT	401	RA vs. conventional medicine	Headache score	RA > conventional medicine ( $P = 0.0002$ )
Thomas et al <sup>43</sup>	Low back pain	Pragmatic RCT	241	RA vs. conventional medicine	SF36 (pain)	Acupuncture improved SF36 by 6 points more than conventional medicine at 12 months
Kleinhenz et al <sup>16</sup>	Rotator cuff tendonitis	RCT	52	RA vs. Streitberger needle	Constant-Murley Score	Acupuncture > Streitberger needle ( $P = 0.01$ )

RA indicates real acupuncture; SA, Sham acupuncture.

### PLACEBO CONTROLS FOR ACUPUNCTURE STUDIES?

With the evidence available to both practitioner and patient alike, the perceived effectiveness of acupuncture is in no doubt.<sup>7-9</sup> The specific efficacy of this technique, however is in doubt especially if one considers the evidence available for the treatment of low back pain.<sup>10-14</sup>

The efficacy of acupuncture is often perceived as residing in the site of needling (the acupuncture point) and the specific needling techniques used at that site. The search for an ideal and physiologically inert acupuncture placebo began in earnest in the mid-1980s<sup>15</sup> and has involved a whole variety of different techniques including the “stage dagger effect” provided by the Streitberger needle.<sup>16,17</sup> Controls that do not involve needling, such as

mock transcutaneous nerve stimulation are seen as an unconvincing placebo,<sup>15</sup> even though evidence exists to suggest that they are convincing to patients and produce clinical effects equivalent to other acupuncture placebo/controls.<sup>18,19</sup> Because we are unclear about the exact mechanisms of acupuncture and how this may differ from placebo,<sup>20</sup> we cannot at this present time properly differentiate between an expectancy effect and acupuncture and placebo, in the context of treating pain. Therefore, although arguments may rage about “ideal” placebo for acupuncture studies, we have no sound basis upon which to define a true and physiologically inert placebo in relation to RA for pain. We are unsure exactly what differentiates RA from placebo in relation to their respective neural substrates. Consequently, interpreting

and defining efficacy accurately is impossible as we cannot reliably differentiate between specific and nonspecific effects in this context. As White<sup>21</sup> suggests, “some effects included in the term nonspecific may be peculiar to acupuncture.” This lack of definition is probably one of the central factors underpinning the confusion and contradiction that we find when reading different systematic reviews of the same research material.<sup>10–14</sup> Not only are we unsure about how to define the specific effect of RA, we also possess almost no information about the relative efficacy of specific acupuncture approaches, such as needling trigger points, the clinical value of obtaining needling sensation (*de qi*), and the use of a TCM approach to point selection in the treatment of pain. Each reviewer may therefore define placebo or control and SA quite legitimately in a slightly different manner, thus attributing specific and nonspecific effects to RA, SA, or placebo with no sound understanding of these interventions.

### DEVELOPING METHODOLOGY FOR RANDOMIZED CONTROLLED TRIALS (RCTS) OF ACUPUNCTURE

A second but closely related paper published in the mid-1990s<sup>22</sup> further developed the theoretical basis upon which acupuncture trials might be designed. The first related to the use of RA in chronic and acute pain where the specific efficacy of acupuncture has been difficult to demonstrate. It now seems that there is a small but significant treatment advantage (efficacy) for RA over placebo in osteoarthritis of the knee, neck, and low back pain,<sup>10,19,23,24</sup> although the systematic reviews of acupuncture in low back pain are confusing and difficult to interpret as Manheimer et al<sup>10</sup> convey in their most recent publication. A second type of acupuncture RCT began to be published in the mid 1980s, which investigated the use of acupuncture as a treatment to help addiction withdrawal from substance abuse.<sup>25</sup> These studies have been reviewed elsewhere.<sup>26,27</sup> Lewith and Vincent<sup>22</sup> suggest there is little point specific effect from using “the correct acupuncture prescription” in this context as they hypothesized that the effect of acupuncture in the treatment of all addictions may be largely non-point-specific and possibly entirely endorphin mediated.<sup>15</sup> This conclusion is supported by Avants et al<sup>28</sup> with respect to cocaine addiction when using a nonacupuncture control, but not by Margolin et al<sup>29</sup> when using similar techniques. Overall, however, particularly in the context of smoking, the evidence overwhelmingly supports a substantial non-point-specific clinical effect that is equivalent to other conventional treatments, but because of acupuncture’s lack of point specificity, and mistakenly assumed point specific effects, the systematic reviews conclude it is ineffective rather than “non-point-specific” in this context.<sup>26,27</sup> The third group comprises nonpainful, non-addictive conditions such as nausea, breathlessness, and irritable bowel. The systematic reviews of acupuncture (P6) in nausea demonstrate clear efficacy over sham and

other control treatments.<sup>30,31</sup> However, few trials have been published evaluating conditions other than the symptom nausea and those that have are often small and of poor methodologic quality. Although some studies do suggest that a TCM approach may have specific efficacy in these benign, chronic and nonpainful conditions,<sup>32</sup> others do not.<sup>33</sup> The latter 2 assumptions pertaining to the nonspecific effects of acupuncture in addictions and the potentially specific effects of TCM-based acupuncture in chronic, benign, nonpainful conditions have been inadequately evaluated to date.

### DEFINING AND INVESTIGATING THE EFFECT SIZE OF ACUPUNCTURE IN PAIN

In the light of recent publications, the hypothesis suggested by Lewith and Machin<sup>2</sup> in 1983 is substantially incorrect. These recent studies were complex to develop and difficult to fund, but are currently among the largest and most rigorous to evaluate treatment efficacy for acupuncture in chronic arthritic pain, back pain, and headache<sup>19,24,34–38</sup> (Table 1). The evidence for low back pain, neck pain, and osteoarthritis<sup>19,24,36,37</sup> suggests that acupuncture has a substantial effect size in the treatment of arthritic and spinal pain over the initial treatment period, but efficacy between RA and either minimal acupuncture or nonacupuncture controls (with good expectancy) is small and of the order of a 10% treatment advantage. The recent studies involve different conditions so a variety of appropriate and disease specific outcomes have been employed. As a consequence, direct comparisons of effect sizes between the studies are both complex and difficult to interpret accurately. This was not the case for fibromyalgia where Assefi et al<sup>38</sup> found no difference between RA and various sham controls. Melchart<sup>35</sup> and Linde<sup>34</sup> report 2 headache studies, which together recruited 572 patients. Both of these studies again demonstrate large effect sizes but no significant difference between RA and minimal acupuncture. However, acupuncture was significantly more effective than waiting list controls. This suggests that RCT of acupuncture for painful conditions (but perhaps not for headaches) using current models for placebo/controls should only predict a specific effect, attributable to site of needle and needle insertion, of the order of 10% at most.

Interestingly, the studies that showed a statistically significant difference between placebo/control and RA were not overwhelmingly reported in the media as a “positive” outcome for acupuncture. However, 10% efficacy is a common specific treatment effect in many chronic conditions. It is a similar effect size to that noted with selective serotonin re-uptake inhibitors for depression,<sup>39</sup> bronchodilators for asthma,<sup>40,41</sup> and the effect of topical nonsteroidal anti-inflammatory drugs in chronic long-term painful conditions.<sup>42</sup>

Thomas et al’s<sup>43</sup> pragmatic trial of acupuncture in back pain did not look at specific efficacy, but did suggest that the benefits derived from acupuncture need to be considered over a long period of time. Similarly, Vickers

et al's<sup>44</sup> pragmatic study on headache also shows a large effect size but was not designed to evaluate point specificity or efficacy.

In conjunction with the Vickers et al<sup>44</sup> study, Wonderling et al<sup>45</sup> conducted an estimate of the cost per QALY of providing acupuncture for headache and found that this was £9180. Thomas et al<sup>43</sup> also provided cost per QALY for back pain in her study (£4241). These costs are within those acceptable to the UK healthcare system purchasers and will provide, taken in conjunction with data on safety, important criteria for clinical decision making. The strength of both Vickers et al<sup>44</sup> and Thomas et al's<sup>43</sup> studies was that they involved long periods of follow-up and were able to detect improvement (in the case of Thomas's study) 2 years' posttreatment, thus suggesting that future clinical studies should not only be powered to detect small specific effects, but should also involve long periods of careful follow-up posttreatment, and economic data.

### QUALITATIVE STUDIES

Paterson and Britten's qualitative work<sup>46,47</sup> clearly demonstrates that patients and practitioners value many components of the "acupuncture experience," particularly, the TCM diagnosis and consultation, thus suggesting that these interventions are independently perceived as therapeutically valuable. Our current preliminary qualitative work reinforces this impression. People seem to continue to seek acupuncture for chronic painful conditions even though there may not be any demonstrable pain relief, an observation that has been previously reported in conventional medicine and CAM.<sup>48</sup> We therefore propose that the RCT model be supplemented with simultaneous qualitative research to understand the patient perceived benefit of treatment, basic science to enhance our mechanistic concepts, and sophisticated statistical methodology so that we can better define and understand acupuncture as a "Whole System."<sup>4,49</sup>

This points us in the direction of considering how we might reevaluate the acupuncture research agenda. It is abundantly clear that overwhelming numbers of people in the western industrialized nations seek CAM<sup>50-52</sup> and acupuncture for pain seems to be a particularly popular and a very safe choice of therapy.<sup>50,53,54-57</sup> Patients seem happy to part with their own money to fund these interventions which, on their own admission, make them feel better about their problem and seem to "help them" in ways that we find difficult to define with generic well-validated outcome measures.<sup>58-60</sup>

We should therefore consider nested and exploratory qualitative studies both before and within RCTs, which might address the reasons why people value these therapies. What is it about the standard outcome measures that fail to measure the patient perceived improvement, an issue that not only concerns CAM but also seems to be an important and unaddressed problem when comparing qualitative work and disease-specific

quality of life for conventional medicine in chronic conditions.<sup>48</sup> If outcome is so difficult to evaluate then how can we place the provision of this therapy into an appropriate and generalizable clinical context? Qualitative investigations could also be used in the initial design stages of future studies to develop a better understanding of the questions that should be asked at an individualized level about CAM from the patient's and also the practitioner's perspective. We also need to understand how patients value acupuncture and evaluate the risk, cost, and benefit of this intervention. Our argument is not to use qualitative research to impose "proof" that fits a belief system, but rather we would wish to look at why patients flock to CAM so that we may better understand their needs and therapeutic perceptions.

### MEASURING EFFECTS

Although it is clear that the specific effect size of acupuncture is likely to be relatively small, this does not make it an "irrelevant treatment" as implied by a recent editorial,<sup>61</sup> especially so if it is safe, economically viable, and accompanied by a very large nonspecific effects. It is entirely legitimate to suggest that small improvements in chronic conditions, derived at reasonable cost and with great safety, are appropriate and consistent with conventional evidence-based medicine. We must not ignore the substantial overall effect sizes obtained with acupuncture combined with minimal risk of adverse reaction.<sup>53-56,62</sup> Efficacy is a narrow and academic interpretation of benefit and, although entirely valid, often difficult for patients and many clinicians to fully comprehend. Patients consider overall effectiveness rather than specific efficacy as the important factor in deciding about treatment, combined with issues such as cost and safety. Healthcare purchasers may also increasingly consider cost and safety data as the mainstay of their strategic decision making in the treatment of chronic conditions. Such complexity demands larger, more complex studies with longer follow-up that includes patient-centered outcomes.

Methods of data analysis are also important for us to consider. Irnich et al's<sup>63</sup> initial report of their neck pain study simply involved a comparison of proportions and consequently a result that did not "properly" interpret the outcome with respect to acupuncture in an appropriate clinical context. Vickers et al's<sup>64</sup> subsequent reevaluation of Irnich et al's paper emphasizes the importance of comparing final outcome to baseline values for each intervention rather than simply comparing the interventions themselves at a given time posttreatment analysis of covariance, thus emphasizing the need for an appropriate pretreatment baseline "run-in" period. All too often, CAM studies have involved inadequate data analysis and interpretation, even when published in high quality general medical journals. The longitudinal modeling employed within White et al's<sup>19</sup> neck pain study maximizes data by including all the data in the analysis, even for those patients who failed to complete the study period. Although such statistical methods are not new,

they are frequently under used. They offer “extravalue” in the interpretation of data and may allow us to maximize the value of the data while potentially generating important hypotheses for further research.

### BASIC SCIENTIFIC MECHANISMS?

No RCT is ever perfect, especially single blind trials involving physical interventions such as acupuncture. It is easy to find reasons to be sceptical of a RCT result with which one disagrees. In acupuncture, this scepticism is compounded by the absence of a complete and plausible mechanism through which to understand its clinical effects. However, some recent neuroimaging studies focused on acupuncture seem to provide valuable insight and may begin to resolve this issue.

Cho et al's<sup>65</sup> initial work with neuroimaging suggested that we could identify visual stimulation triggered by specific peripheral acupuncture points. This specificity was entirely consistent with a TCM interpretation of the acupuncture point's function. Further work on nausea by Yoo et al<sup>66</sup> also identified specific areas of activation that are consistent with the function of acupuncture as an antiemetic but others have not always been able to reproduce these conclusions. On balance, however, it does seem that acupuncture points may create specific activation with respect to sight and vision and possibly nausea but further work is certainly required before we can be sure.

When considering the effect of acupuncture on pain the picture becomes very much more diffuse. The conclusions from a number of research groups suggest endorphin rich areas in the periaqueductal gray become activated by real acupuncture, but these areas are diffuse and form part of the pain matrix.<sup>67</sup>

Our recent work on imaging has focused on how this may contribute to the development of clinical trial methodology.<sup>20</sup> Specifically we wished to investigate whether we could differentiate acupuncture from a validated sham acupuncture device (Streitberger needle) and how the expectation of RA influenced brain activation. Expectation has a substantial “activating” effect on the endorphin rich areas which may underpin the significant nonspecific effect of acupuncture (and indeed placebo) in pain.<sup>68</sup> It is possible that acupuncture may be considered “a placebo-enhancing procedure,” reinforced by patient expectation<sup>69</sup> with small specific clinical effects attributable to a specific point prescription. Certainly, belief that one is receiving acupuncture activates significantly different neuronal substrates than simple touch. We believe that by developing our understanding of the neurologic mechanisms in conjunction with rigorous clinical trial methodology, we may ultimately be able to attribute specific clinical effects to particular neurologic substrates. This will resolve the confusing arguments surrounding placebo, efficacy, and effect in acupuncture studies. Furthermore, we will develop greater clarity about the effect of expectation and the placebo response in pain and may then be able to

enhance the therapeutic effect of other analgesic treatments.

### CONCLUSIONS

The combination of more sophisticated clinical trial methodology with the imaging techniques now available to us will allow us to understand more about acupuncture and its effect in commonly treated conditions such as chronic pain. This will provide substantial insights into the mechanisms that underpin both the placebo response and chronic pain itself. We should also be able to develop a sophisticated qualitative understanding of why people seek acupuncture and what they gain from it. The growth of CAM in western industrialized nations has been difficult for conventional physicians to accept, largely because it has developed in response to patient demand, and is not medically initiated. It is not an approach inspired by the development of new technology or one “discovered” by eminent scientists. It may therefore provide us with an environment that appropriately illustrates and emphasizes the essential dimension of the patient's perspective as part of treatment choice and the subsequent research agenda that engenders.

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