

# Controlling for non-specific effects of acupuncture in clinical trials

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Placebo controlled trials are used to examine the relative size of the specific effects of a therapy. When the therapy is a manual treatment like acupuncture, placebo control models are very complex due to the range of non-specific effects that can occur and issues such as blinding. This article examines ten different research models that have been used to control for placebo or other non-specific effects in clinical trials of acupuncture. Through an examination of the different non-specific effects that can occur in acupuncture therapy, it explores the relative ability of these ten models to control for the placebo and other non-specific effects. Three models are eliminated as probably unable to adequately control for these effects and therefore unable to explore the specific effects of acupuncture. The strengths and weaknesses of the remaining seven models are analyzed. Finally, methods and assessments needed to control for non-specific effects are discussed so that these seven models can be used to control for these effects and thus the models can examine the specific effects of acupuncture treatment.

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## INTRODUCTION

Acupuncture treatments are thought to have two kinds of specific effects, those related to the sites at which the needling is applied and those related to the techniques of needling.<sup>8,10</sup> Various levels of evidence exist for these site-related and technique-related types of specific effects.<sup>18,64,65,76</sup> The theories of acupuncture also suggest that these two components will interact<sup>3,25,29,70</sup> so that depending upon the research question asked, it is important to modify study designs to address either or both effects. Studies might attempt to assess the combined effect of site-related and technique-related effects, or they may try to assess only the site-related or the technique-related specific effects. To test the extent of any specific effects of an acupuncture treatment it is necessary to design studies that can adequately control for placebo, and any other non-specific effects that may occur. This paper addresses and analyzes the multiplicity of designs by which

acupuncture researchers have attempted to tease out and control for the variety of non-specific effects of acupuncture.

## PLACEBO-CONTROL TREATMENT MODELS USED IN CLINICAL TRIALS OF ACUPUNCTURE

A variety of purported placebo-control treatments can be found in the published literature. Different needle insertion techniques, combined with different point location strategies and various methods of non-insertion treatment techniques have been used. Some of these have been used within more than one research model, so that there have been a number of different approaches to conducting placebo-controlled treatments. The following 10 represent the most important variations that this author has found:

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### Invasive procedures

- (1) *Sham acupuncture – type 1*: inserting needles at non-acupuncture points and using the same stimulation methods as those in the test treatment (AT).<sup>51</sup> This can include the addition of electrical stimulation<sup>6,16</sup>
- (2) *Sham acupuncture – type 2*: inserting needles at non-acupuncture points and using different stimulation methods from those used in AT<sup>21</sup>
- (3) *Minimal acupuncture\* – type 1*: shallow insertion of needles at non-acupuncture points with no further manipulation<sup>33,34,77,79</sup>
- (4) *Minimal acupuncture – type 2*: shallow insertion of needles to the same acupoints as those used in AT with no further manipulation<sup>30,85</sup>
- (5) *Minimal acupuncture\*\* – type 3*: shallow insertion of needles to irrelevant acupoints – points documented as being not useful for the condition being treated – with no further manipulation<sup>14</sup>
- (6) *Non-relevant acupuncture*: a control AT that is active but is not specific or hypothetically not useful for the condition being treated.<sup>2</sup>

### Non-invasive procedures

- (7) *Non-invasive acupuncture-like methods*: inserted needling is mimicked by use of needles taped to the skin,<sup>38</sup> pressing the points with an insertion tube,<sup>44</sup> pressing the sites with a probe,<sup>60</sup> pressing the sites with a cocktail stick,<sup>83</sup> or using a specially constructed dummy needle that retracts when pressed into the skin so as to appear to insert.<sup>62,71</sup>

### More complex designs

- (8) *Combining an invasive control acupuncture with a standard therapy and comparing this to AT combined with a placebo pill*<sup>74</sup>
- (9) *Combining a non-invasive control acupuncture with a standard therapy and comparing this to AT combined with a placebo pill*<sup>85</sup>
- (10) *Non-acupuncture like non-invasive methods*: the use of a sham or disconnected TENS unit,<sup>22–24,47,86</sup> or the use of an electronic diagnostic unit.<sup>52</sup>

\*The term ‘minimal’ acupuncture de facto presumes that non-minimal acupuncture is used as the active or test treatment. This idea is based on the claim that ‘de qi’ must be obtained for the test

acupuncture to be effective,<sup>3,11,13,65</sup> which involves deeper needling with more manipulation, hence the control ‘minimal’ acupuncture uses shallow needling with no further manipulation.

\*\*Here the term ‘minimal’ acupuncture refers to the use of shallow needling with no further manipulation, but in comparison to shallow needling as the ‘active’ treatment, AT.

After general discussions of the specific and non-specific effects of treatment, this paper will examine these different research models to determine which can be used in placebo-controlled studies of acupuncture, highlighting strengths, weaknesses and additional steps necessary to control for placebo.

### PLACEBO EFFECTS

Some authors have questioned whether the placebo effect is real<sup>41</sup> or what its power is<sup>36</sup>, however it is still generally acknowledged to be an important component of any therapy, with treatment effects that appear to be widespread and highly variable.<sup>40,49,67,75</sup> In the placebo effect, issues such as expectations, prior beliefs, treatment context, appearance of the therapy, interactions with the therapists, interactions with the research staff, explanations about the treatment, including informed consent, seem able to contribute to the placebo effect.<sup>28,42</sup> There also appear to be individual differences in whether and to what extent placebo responses may occur.<sup>49</sup> Additionally, the placebo effect of different therapies appears to be different and cannot be assumed to be uniform or comparable.<sup>40</sup> It is highly likely that placebo-related treatment effects occur in acupuncture therapy, some have even argued that the placebo effects in acupuncture treatment may be quite strong because of the exotic appearance of acupuncture,<sup>5</sup> which could enhance the placebo effects. There is preliminary experimental evidence about the possible role of belief in the treatment effects of acupuncture, but limitations with the few studies that have explored this<sup>17,19</sup> leave the issue inconclusive. There is thus much controversy and a wide range of opinions about the nature and size of the placebo effect. Until such time as a general consensus has emerged in the scientific community about the nature of the placebo effect, it is assumed here that placebo is a complex factor that contributes to the overall treatment effect of acupuncture. However, investigating the extent of placebo effects in any clinical trial is complicated by the possible interactions of the specific effects of a therapy with the placebo-related ef-

fects of that therapy.<sup>42,43</sup> We will return to this issue below.

## PLACEBO TREATMENT VS PLACEBO CONTROL

In the gold standard pharmaceutical study, the double blind randomized controlled clinical trial, where a test drug is compared to a truly physiologically inert pill that looks identical to the test drug, it has been assumed that any effects in the treatment group receiving the physiologically inert treatment are due only to placebo effects. The control treatment is considered to be a placebo treatment, and that the comparison of a treatment group receiving the test drug to the treatment group receiving the placebo pill is sufficient to determine the specific effects of the test drug beyond placebo, so long as appropriate design measures are used, such as randomization and double-blinding. Randomization and double-blinding are thought to ensure that any placebo effects will be roughly equal in the two treatment groups. However, recent proposals have identified the need to additionally control for other non-placebo non-specific effects such as regression to the mean, chance, or natural course of the disease in any study that attempts to control for placebo.<sup>26,41,59,66</sup> Thus there is now a shift in placebo research models away from the simple idea of administering a placebo treatment in the control group, assumed sufficient as a placebo control, to models that attempt to control for placebo using additional methods such as having a parallel group that receives no treatment.<sup>26,66</sup>

In acupuncture studies many of the control treatments listed above have been thought to be placebo treatments in the same manner that the inert placebo pill is a placebo treatment.<sup>6,34,58,69,72,74</sup> However, the situation in acupuncture studies is not so simple, and it is necessary to question the assumption that the control treatments are simply 'placebo treatments'. It is very difficult administering a truly physiologically inert treatment in acupuncture studies (as a parallel to the inert placebo pill). Any time that the control treatment involves insertion of needles, the possibility exists for the involvement of physiological non-specific effects that must also be controlled for.<sup>31,45</sup> The seven invasive control treatment procedures listed above must each deal with this issue. This is further complicated by the virtual impossibility of conducting true 'double-blind' studies. It is not possible to blind the acupuncturist,<sup>80</sup> thus the protection against bias from the interaction of the practitioner and patient cannot be immediately guaranteed. It

then becomes necessary to conduct single-blind clinical trials where the patient is blind to which treatment they receive.<sup>31,80</sup> However, differences in how the practitioner behaves while delivering the test and control treatments, any unusual or unexpected appearance of the control treatment, etc., will result in the control treatment and test treatment not being believably the same. Circumstances such as these can create the possibility that the placebo effects of the test and control treatments will not be equal. If the control treatment procedure produces physiologically non-specific effects and/or the placebo effects of the test and control treatments are not comparable, then it becomes impossible to claim that any of the control treatments can control for placebo effects.

These issues are further compounded by the need to control for any other non-placebo non-specific effects in placebo-controlled studies of acupuncture. Complex strategies thus become necessary if an acupuncture study is to be considered a placebo-controlled study, even when a placebo only control needling acupuncture is administered (e.g., a plausible non-invasive procedure such as some of those listed under 7 above). To understand what measures may be needed it is necessary to examine in more detail the range of treatment effects that might occur.

Table 1 summarises those treatment effects that can be reasonably expected to occur in the administration of acupuncture treatment, and is an expansion of a table by Hammerschlag.<sup>31</sup>

The non-placebo non-specific effects will include a range of different physiological responses to being needled and allowing the patient to wait quietly until the needles are removed.<sup>31</sup> These will be physiological effects that occur regardless of the site of insertion or the precise nature of the stimulation associated with it. Various anti-nociceptive mechanisms, both homosegmental<sup>57</sup> and heterosegmental<sup>7,46</sup> could be triggered, as can micro-circulatory changes.<sup>37</sup> Depending on the treatment context, it is likely that effects due to relaxation will also occur,<sup>4,55</sup> which can have a range of physiological effects. Various other physiological changes could also result from the insertion of the needles, regardless of the site of insertion or the precise nature of the stimulation given, including possible anti-inflammatory effects,<sup>65</sup> possible immunological effects, possible muscular-tonus and thus structural effects. Many of these physiological effects are already documented, and, since the principle purpose of conducting placebo-controlled studies is to investigate the size of the treatment effects associated with the specific effects of the therapy, it will be necessary to develop procedures to control for them if a clinical trial of acu-

Table 1 Expected components of treatment effects				
	Placebo non-specific effects	Non-placebo non-specific physiological effects	Non-treatment-related non-specific effects	Specific effects
Total treatment effect	e.g., beliefs, expectations, therapist interactions, diagnostic processes, therapeutic processes <sup>40,42,49,67,75</sup>	Various physiological non-specific effects such as anti-nociceptive effects <sup>45,50</sup>	e.g., regression to the mean, natural course of the disease, chance, etc. <sup>26,66</sup>	Proposed by different schools of acupuncture <sup>3,25,29,70</sup>
Site-related treatment effects	Same <sup>40,42,49,67,75</sup>	Non-specific <sup>45</sup> homo-segmental analgesic effects, <sup>57</sup> relaxation effects, <sup>4,55</sup> etc.	Same <sup>26,66</sup>	Specific actions of the points <sup>3,25</sup>
Technique-related treatment effects	Same <sup>40,42,49,67,75</sup>	Non-specific, <sup>45</sup> such as heterosegmental analgesic effects, e.g., diffuse noxious inhibitory control mechanisms (DNIC), <sup>46</sup> generalized micro-circulatory effects, <sup>37</sup> or relaxation effects <sup>4,55</sup>	Same <sup>26,66</sup>	Different techniques are claimed to produce different effects <sup>3,25,27,64,65</sup>

puncture is to be considered a valid placebo-controlled trial.

The non-treatment-related non-specific effects such as regression to the mean, chance and natural course of the disease<sup>26,66</sup> will occur regardless of the therapy. The nature of the disease and the inclusion and exclusion criteria will have effects on these factors. But as we will see below, controlling for them will generally not be difficult.

There will be an additional layer of treatment effects due to possible interactions between the specific and non-specific effects. In mainstream medical research, evidence has emerged for the interaction of specific, placebo and non-placebo non-specific effects.<sup>42,43,66</sup> There will likely be interactions between the various components of acupuncture treatment as well. For example, evidence exists for endorphin involvement in placebo effects,<sup>48</sup> for involvement of endorphins in acupuncture specific effects<sup>64,65</sup> and for involvement of endorphins in analgesic heterosegmental non-specific effects of acupuncture.<sup>7</sup> These findings imply a probable interaction of these three components in some acupuncture treatments. Interactions between treatment components blur the lines between those components, making it difficult if not impossible to fully control for them in controlled clinical trials, as one cannot assume that they may be roughly equal in each treatment group. These interactions thus make some of the research models listed above probably unusable for placebo-controlled trials of acupuncture.

The interactions of therapies and components of therapies make clinical trials of acupuncture more complicated, both trials in which placebo-related

and non-placebo-related non-specific effects are being controlled for, and especially in trials where patients continue to receive standard therapy or other therapies. It is quite likely that for conditions where acupuncture is normally used as an adjunctive treatment, such as in addictions, asthma, angina and stroke,<sup>1,12,39,61</sup> that the acupuncture treatment will interact with the standard therapy for those problems. Thus in controlled clinical trials of acupuncture for conditions where standard therapy must be continued, it may be impossible to separate out the specific and non-specific effects of the acupuncture treatment since each part of the acupuncture effects may be interacting both with themselves and the standard therapy. This leaves us with the logical conclusion that placebo-controlled studies may not be a viable strategy for testing acupuncture in conditions where the standard therapy is continued and acupuncture is used as an adjunctive therapy. Hence any study that combines acupuncture with a standard therapy and attempts to compare it to a control acupuncture plus the standard therapy [e.g.,<sup>4,14</sup>] will probably encounter these difficulties of data interpretation. The two models listed above (8 and 9) where acupuncture was combined with a placebo pill and compared to some form of control acupuncture combined with standard therapy may thus be unusable as placebo-control models.

Additionally, the variability of the placebo effect both within a therapy and between therapies,<sup>40,41</sup> makes it highly unlikely that a non-acupuncture control procedure can serve as a placebo control as there is no way of ensuring comparability of placebo effects in the two treatments. This also leaves us with the logical conclusion that model 10, where

**Table 2 Treatment effect components in acupuncture (AT) and possible placebo-control treatments**

	Hypothesized site-related specific effects A	Hypothesized technique-related specific effects B	Placebo non-specific effects C	Non-placebo non-specific effects not related to AT D	AT-related non-placebo non-specific physiological effects E
AT, acupuncture treatment	X	X	X	X	X
1. Sham (same stimulation at non-points)	?	X	X	X	X
2. Sham (different stimulation at non-points)	?	?	X	X	X
3. Minimal (minimal needling at non-points)	?	?	X	X	X
4. Minimal (minimal needling at same points)	X	?	X	X	X
5. Minimal (same shallow needling as AT but at irrelevant points)	?	?	X	X	X
6. Not specific (same needling at non-specific points)	?	?	X	X	X
7. Non-invasive (e.g., pressing points with tube or with sham-retractable needle)	0	0	X	X	0/?

X, effects are reasonably expected; ?, effects will probably be found but of entirely unknown dimensions; 0, depending upon the method, no or almost no effects are reasonably expected.

acupuncture is compared with a sham-TENS unit<sup>23</sup> or an electro-diagnostic device,<sup>52</sup> cannot serve as a placebo control since there is no way to determine if the placebo effects of the acupuncture and the device are comparable, a point raised by other researchers.<sup>45,73</sup> Thus models 8–10 shall not be considered further as they are each probably incapable of controlling for the placebo effects of acupuncture.

Table 2 lists those control treatments that could in principle be used in placebo-controlled acupuncture studies. This table also identifies which of five treatment effects will occur with AT and with each of the seven control treatments. This comparison is made so as to identify strengths and weaknesses of each control treatment model.

It is important to state clearly whether the study aims to control for placebo in order to investigate the total specific treatment effects of AT (AT-A + B), to control for placebo in order to investigate the contribution of the specific treatment effects of AT from the treated points (AT-A) or to control for placebo in order to investigate the contribution of the specific treatment effects of AT from the applied techniques (AT-B). In the case where the total specific effects of AT are being examined, more flexibility of control treatment can be used, but for an examination of the effects of point stimulation, it

would be ideal to compare the use of the same techniques at different acupuncture points, and for the investigation of the effects of the technique of treatment, to compare the application of different techniques to the same acupuncture points. Based on these considerations it is possible to examine issues important in the implementation of studies that compare AT to the control treatments 1–7.

In the comparison of these different control treatments to AT, the ideal model would:

- (i) Reduce effects 1A–7A and/or 1B–7B to zero, i.e., be comparable to a placebo pill in drug trials
- (ii) Demonstrate that AT-C is comparable to 1C–7C, as is expected in placebo-controlled drug trials
- (iii) Demonstrate that AT-E is comparable to 1E–7E, without which the specific effects cannot be examined
- (iv) Use proper randomization with, as necessary, stratification, and the use of an untreated control group. These are thought sufficient to help ensure that AT-D is comparable to 1D–7D.<sup>26,66</sup>

However, B and E may be related to each other. For example, the stronger the applied technique B, the stronger the DNIC related effects E.<sup>46</sup> Since the

**Table 3 Strengths, weaknesses and requirements of each placebo control**

Questions answerable	Strengths	Weaknesses	Requirements
1. Sham (same stimulation at non-points)	Could examine effect of point location (AT-A vs 1A)	Comparable techniques – easier to control for non-placebo non-specific effects	Need large sample size because of larger non-placebo non-specific effects (50)
2. Sham (different stimulation at non-points)	Could examine total specific effect (AT-A&B vs 2A&B), or specific effect point location or treatment technique (AT-A vs 2A or AT-B vs 2B)	Depending on technique, possibly smaller non-placebo non-specific effects – hence, may need smaller sample size	Technique comparability unclear – controlling for non-placebo non-specific effects may be difficult
3. Minimal (minimal needling at non-points)	Could examine total effect of treatment (AT-A&B vs 3A&B)	Probably smaller non-placebo non-specific effects – hence, may need smaller sample size	Not comparable techniques – controlling for non-placebo non-specific effects may be difficult, or requires use shallow insertion AT
4. Minimal (minimal needling at same points)	Could examine effect of treatment technique (AT-B vs 4B)	Possibly smaller non-placebo non-specific effects – hence, may need smaller sample size	Not comparable techniques – controlling for non-placebo non-specific effects may be difficult, or requires use shallow insertion AT. It may need larger sample size as it is an active treatment, also theories of point and technique selection may be different
5. Minimal (same shallow needling at irrelevant points)	Could examine total effect of treatment (AT-A&B vs 5A&B)	Possibly smaller non-placebo non-specific effects – hence, may need smaller sample size	Not comparable techniques – controlling for non-placebo non-specific effects may be difficult.
6. Not Specific (same needling at non-specific points)	Could examine effect of point location (AT-A vs 6A)	Comparable techniques – easier to control for non-placebo non-specific effects	Non-placebo non-specific effects probably large – hence need larger sample size (50)
7. Non-invasive (e.g., pressing points with tube or sham retractable needle)	Could examine efficacy AT compared to placebo [assume AT-D = 7D, then model could compare: AT-A + B + C + E vs 7C]	Little or no non-placebo non-specific effects – probably need smaller sample size	Technique not comparable so AT-E and 7E probably not comparable, possible difficulties with credibility and blinding (possibly AT-C and 7C not comparable) + depending on method, may have some non-placebo non-specific effects that need investigating*
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies
			Placebo-related assessments + non-placebo non-specific assessments + non-treatment group + pilot studies + special care needed to ensure comparability and integrity placebo control

\* The 'placebo' needle that has been developed<sup>71</sup> has been found difficult to use, as it must be taped onto the body. On hairy areas, the removal of the tape can create discomfort and possibly significant stimulation, thus adding possible additional non-placebo non-specific effects, so it will likely not be physiologically inactive [Richard Hammerschlag, personal communication].

same technique is used in AT, 1, 5 and 6, we can expect that AT-B is comparable to 1B, 5B or 6B and AT-E to 1E, 5E or 6E. This is not the case in the control treatments 2, 3, 4 and 7. In these, the treatment technique is intentionally different, or so far has been, and therefore may be harder to establish comparability. We can expect that AT-E > 3E, 4E and 7E, but comparability of AT-E to 2E is unclear. While it would be ideal to try to match E for the test and control treatments, this may result in a diminution of AT-B or an increase of B of that control treatment, both of which will decrease the effect size difference between the test and control treatments. Pilot studies will be necessary to explore these issues.<sup>53,55</sup> In cases where AT-E and 1E–7E are not comparable, it may be possible to run stepwise regression analyses of the measures of these differences and see if there is any significant correlation between those factors and treatment outcome.<sup>14</sup> But in an ideal model, the control treatment would use a similar technique as that in the test treatment, as this increases the likelihood of the comparability of AT-E with E of that control treatment.

Table 3 lists the principle types of questions that can be addressed by use of control treatments 1–7, their design strengths and weaknesses and design requirements if they are to be considered as viable placebo control models.

As can be seen from this table, a number of key issues emerge. Sample size requirements for a study may become too large<sup>50</sup> if B and E are comparable in the test and control treatments. When there is a clear difference in B and E between the test and control treatments, difficulties may emerge in being able to control for the effects of E. This will be especially so in model 7, where E is reduced ostensibly to zero. All control treatments need to be tested in pilot studies, something few researchers have done. Credibility and other placebo assessment instruments need to be used to ensure comparability of the placebo effects in the test and control treatment groups, assessment instruments need to be used to ensure comparability of the non-placebo, non-specific effects and additional design procedures may need to be used [see below].

## ASSESSMENTS AND PROCEDURES NECESSARY TO CONTROL FOR THE NON-SPECIFIC EFFECTS OF TREATMENT

### Placebo effects

In studies where patients are assigned to receive one of two acupuncture treatments, it is important that the patients be blinded as to which they re-

ceive. It is not enough to simply state that the patients were or were not blind to which group they were in,<sup>58</sup> it must be demonstrated.<sup>14,88</sup> Whether the patients were blind to which treatment they received or not should be determined by using a questionnaire to assess this. In addition, other placebo-related non-specific effects need to be assessed so that they can also be controlled for.<sup>4,8,14,55</sup>

The credibility of the AT and the sham acupuncture treatments should be assessed at intervals during the treatment phase using a series of standardized questions.<sup>14,55,63,78</sup> While there have been questions about the validity of the specific questions<sup>83,87</sup> used in the instrument validated for acupuncture studies by Vincent,<sup>78</sup> there is little disagreement about the need for some form of credibility measure.<sup>14,55,81,84,88</sup> It is possible that the perceptions about the credibility and efficacy of treatments might change over time, as the series of treatments continue, thus it would be useful to make these credibility assessments at intervals during the treatment phase. In addition, it may be useful to investigate other factors such as prior beliefs about treatment, expectations before treatment, prior experiences with treatment, these can be assessed at baseline or entry into the study using an appropriate instrument. It will also be useful to assess how the therapists are perceived; are they viewed as clinically capable? Is their behavior seen as the same in the different treatment arms? Are they liked more in one treatment arm than another? Are there more interactions between patients and practitioners in one treatment arm compared to the other?<sup>74,14,17,19,55,68</sup> The Yale team used a therapeutic alliance 10-item scale to examine the possible role of these factors.<sup>4</sup>

Making assessments so as to be able to control for the non-specific effects of treatment is further complicated by how the consent form for the study is worded. Some ethics committees or 'institutional review boards' (IRB) insist on full and explicit disclosure of what treatments a patient may be randomised to. The more explicit the description in the consent form, the more likely that the patient will be thinking about what treatment they are receiving,<sup>9,87</sup> some research has already demonstrated how the informed consent can affect treatment outcome.<sup>42</sup> Assuming that the wording of the consent form may have an impact on how patients perceive the treatments they receive and how they think about those treatments, especially when asked to consider them, variation in the explicitness of the consent form descriptions produce variations that may also need to be accounted for,<sup>9,55,87</sup> and, in certain cases could make it difficult to conduct the study at all because of perceived ethical issues<sup>42</sup>.

Careful studies exploring the role of belief, prior experience, appearance of the therapy, diagnostic

assessments, touch and palpation, training and appearance of the acupuncturist, consent form descriptions, etc. need to be conducted. A combination of qualitative and quantitative approaches would be useful. Some preliminary work has explored some of these areas,<sup>14,17,19,20,53,54,62,68,78,82,84,87,88</sup> but much more work is necessary. It would be ideal if a standardized set of validated instruments and methods could be developed for future studies.

### **Patient-related non-placebo non-specific effects**

Ernst and Resch have argued that a necessary component of any studies that attempt a placebo-control design, is the addition of methods that control for patient-related non-placebo, non-specific effects such as the natural course of the disease, regression towards the mean, chance, etc.<sup>26,66</sup> They propose use of proper randomization with an untreated control group, wherever ethically possible. Randomization is a necessary component of any high quality clinical trial, and while not without possible difficulties,<sup>40</sup> is important as a method for dealing with a number of items involved in the clinical effectiveness of any therapy. It can be augmented by use of appropriate exclusion criteria and/or stratification of any factors such as gender, prior experiences with treatment to ensure proper randomization occurs. Ernst and Resch state that use of an untreated control group is necessary whenever a study attempts to quantify non-specific effects separate from specific effects, as it allows quantification and thus control of the patient-related non-placebo non-specific effects.<sup>26,66</sup>

### **Treatment-related non-placebo non-specific effects**

Diffuse noxious inhibitory control (DNIC) mechanisms are thought to be heterosegmental pain control mechanisms that occur regardless of the location of treatment stimulation.<sup>46</sup> Many forms of acupuncture are naturally painful or noxious,<sup>82</sup> some more than others<sup>11,13</sup> and are likely to activate DNIC mechanisms. To control for these effects will require the use of a procedure that ideally has comparable DNIC effects to those of the test treatment,<sup>8</sup> or if not comparable, do not show significant association with treatment outcome.<sup>14</sup> To be able to make these judgements it is necessary to make assessments of possible DNIC effects, e.g., by evaluating the relative discomfort of both the control and test treatments.<sup>4,8,14</sup> Birch used two questions on a questionnaire to explore this,<sup>14</sup> the Yale team used a more developed series of questions.<sup>4</sup> A fully validated instrument needs to be developed in order to

assess these possible effects. To control for homosegmental effects, it may be necessary to ensure that part of the control treatment utilizes treatment points in the same relevant segments as those used in the test treatment. While an ideal solution, it may be difficult to achieve and needs further exploration in pilot studies. Further, controlling for only DNIC may not be sufficient to control for the range of possible non-placebo, non-specific physiological effects that may occur. It may be necessary to control for effects such as the relaxation response,<sup>4,55</sup> by use of a comparison group that receives a similar period of relaxation as the time the patient spends remaining still with needles inserted.<sup>4</sup> It will also be important to explore other physiological effects of the different needle techniques in pre-clinical studies in order to understand what other physiological changes might result from needle insertion.<sup>53-55</sup>

### **Blinding of staff**

Additionally, it is important in clinical trials that the evaluator be blind to treatment assignment. In acupuncture this is especially important, as it is not possible to conduct studies in a truly double-blind manner.<sup>15,80</sup> The use of a blinded evaluator, with blinded patients is a recommended feature for acupuncture trials.<sup>31,80</sup> Further, it is ideal if the personnel responsible for entering the data into a computer, checking the data for accuracy and completion, and the statisticians conducting the data analyses be blind wherever possible to patient assignment so as to eliminate any other potential sources of bias.<sup>32,55</sup> This is not always possible, but by eliminating or reducing potential bias it improves the credibility of the trial and its findings.

## **DISCUSSION**

Ten basic research models for conducting placebo-controlled trials of acupuncture have been explored. Unpacking the total treatment effect of an acupuncture treatment revealed five distinct contributing effects: (a) specific effects due to needling certain points, (b) specific effects due to applying certain treatment techniques, (c) non-specific effects resulting from placebo, (d) non-specific effects not related to the treatment such as regressions to the mean, and (e) non-specific effects due to physiological responses to the insertion of needles (see Table 1). When these 10 purported placebo-control treatment procedures were examined, it was found that they each contribute one or more of these five effects (see Table 2). Each requires either specific design and assessment features to



remain suitable as a placebo-control intervention (see Table 3) or they are unsuitable as placebo-control interventions. Three were found unsuitable, either because of the incomparability of the placebo effects of the acupuncture and the control intervention (mock-TENS) or the inseparable complexity of treatment effect interactions when the acupuncture is added to a standard therapy either out of necessity or by design.<sup>4,14,35,74</sup> The remaining seven placebo-control models were then analyzed in terms of their strengths, weaknesses and additional measures necessary for each.

Some researchers have argued that the possibility of interactions between the specific and non-specific effects of a therapy in general clinical research raises difficult questions about the use of the double blind randomized controlled trial effort to conduct placebo-controlled studies.<sup>40</sup> These probable interactions make a clear determination of the relative size of each effect quite difficult, if not impossible. As a consequence of this, it may be impossible to conduct a true placebo-controlled study of acupuncture. Since this is an issue in mainstream medicine that still needs to be resolved, it is not appropriate here to state emphatically one way or the other whether one should continue using trials that attempt a placebo-control model in acupuncture studies. But it does make the task of conducting studies that attempt to use placebo-control models quite difficult, and their conclusions only approximate at best. However, so long as ethics committees, funding agencies and the research community continue to use this as the 'gold standard' research model and require the continued use of this research model for testing acupuncture,<sup>1,15,56</sup> it is necessary to find the best approaches possible while recognizing these possible restrictions. The continued use of this model for acupuncture studies necessitates detailed exploration of a wide range of issues and effects in pre-clinical studies, and the design of better methods and assessment tools.

A common problem that is encountered in studies that compare acupuncture to some form of control needling is the faulty assumption that the 'sham' acupuncture is equivalent to placebo<sup>69</sup> and will have a treatment effect of about 30%.<sup>50</sup> Lewith and Machin estimated in 1983 that the 'sham' acupuncture is usually a complex combination of placebo and other non-specific effects, with an effect size of around 50%.<sup>50</sup> Thus studies using a 'sham' acupuncture control treatment model routinely under calculated the sample size requirements of the study as they assumed a 70 vs 30% difference rather than the 70 vs 50% difference that usually occurs in this design.<sup>50</sup> However, if the acupuncture is compared to one of the non-invasive placebo-control treatments listed

under 7 above, the sample size requirements will probably be smaller than when acupuncture is compared to some form of invasive treatment. It is also possible that the use of minimal acupuncture as a control treatment will reduce the sample size requirements since ostensibly it will have less physiological non-specific effects. However, in all these cases, it is essential that pilot studies be conducted to determine actual sample size requirements based on data and not projected estimates.

While recent non-invasive control treatment procedures<sup>62,71</sup> are appealing, they pose other problems in implementation and study result interpretation. It may be very difficult adequately controlling for the non-placebo non-specific effects due to the physiological effects of inserting needles using non-invasive control treatments. Placebo-controlled studies have historically been conducted in order to explore the extent of the specific effects of the test treatment. A study that administers a placebo treatment, but does not control for the physiological non-specific effects, is essentially in conflict with the reasons for conducting a placebo-control study: namely to investigate the extent of the specific effects. The question naturally arises that if a placebo (non-invasive) acupuncture intervention is administered as the control treatment, is this more than merely an academic exercise, when it is not possible to isolate or control for the placebo component itself? This question needs to be addressed before more research is conducted using these placebo needles,<sup>62,71</sup> as these studies may not be very useful for addressing the questions they have been designed for. It may be satisfactory to simply compare the test treatment to the non-invasive placebo treatment, so that the question: 'is acupuncture more effective than placebo?' can be answered. But if the specific acupuncture treatment is to be examined, so that one can answer a question like: 'is acupuncture administered in the manner described here more effective than the administration of any acupuncture procedure anywhere else on the body?' additional studies will probably still be necessary. But it is conceptually confusing to say that the use of a non-invasive control acupuncture treatment has controlled for placebo, since in pharmaceutical research the comparison to placebo is done to highlight the specific effects of the test drug. Here, it may not be possible to separate the physiological non-specific from the specific effects.

## CONCLUSION

A variety of different placebo controls have been attempted in clinical trials of acupuncture. This

review has examined the possible specific and non-specific effects that might be produced with these purported placebo-control treatments. It has found that 3 of the 10 models examined will probably be unsuitable as placebo-control interventions in clinical trials of acupuncture. Of the remaining seven, this review has examined the kinds of questions these controls can answer, what their particular strengths and weaknesses are and what steps will be necessary to ensure that each can be considered to have functioned as a valid placebo-control treatment. In the past, due to poorly conceived ideas about acupuncture, inadequate reading of the published literature, inadequate study designs, and the lack of necessary assessments, most studies using one of these seven models have not been adequately applied, and cannot be considered as having achieved a placebo control. For example, the need to make assessments of patient perceptions and beliefs was first suggested over 15 years ago, and a validated scale has been available for over 10 years, yet the majority of studies attempting placebo controls have not used these methods, making interpretation of their results difficult. The need to control for non-placebo non-specific effects has also been identified for over 15 years, but virtually no studies have developed a method for doing this, and many sham acupuncture models are inappropriate for doing this. Assessment methods for evaluating these effects are also necessary, and have been absent in all but a handful of studies to date.<sup>4,14</sup> More attention needs to be paid to these issues if valid placebo-controlled studies are to be conducted, and greater care is needed in selecting the control intervention procedure in answer to the study question.<sup>12a</sup>

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