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Roundtable Discussion

Resolving Paradoxes in Acupuncture Research: A Roundtable Discussion

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Peter M. Wayne: We're going to be discussing the workshop that we held at the North American Research Conference on Complementary and Integrative Medicine (NARCCIM) in May 2009. The workshop was designed to present the findings from a Society for Acupuncture Research (SAR) board retreat, which focused on "Paradoxes in Acupuncture Research: Strategies for Moving Forward." The paradoxes, in turn, had emerged during the 2007 SAR International Conference that reviewed the progress in our field in the decade since the 1997 NIH Consensus Development Conference on Acupuncture. The conference was a great success, with more than 300 attendees and support from the National Institutes of Health (NIH), conventional medical schools, schools of acupuncture and Oriental medicine, and a variety of other national and international organizations. The conference concluded that the field of acupuncture research had made great progress since 1997. Many rigorous phase II and III randomized controlled trials were completed for acupuncture treatment of a wide variety of medical conditions, and some very strong basic research was performed with state-of-the-art tools to examine biochemical and physiologic correlates of acupuncture. Important progress was also made with respect to control procedures and other aspects of clinical research design. Summaries of the conference have been published in the *Journal of Alternative and Complementary Medicine*.[1–3]

But in putting together this work, we identified two paradoxes. Paradox One is that *an increasing number of large clinical trials have reported that true acupuncture does not significantly outperform sham acupuncture, a finding apparently at odds with traditional theories regarding acupuncture point specificity and needling techniques*.

Paradox Two is that *while many studies with animal and human experimental models have reported physiologic effects that vary as a function of needling parameters, the extent to which these parameters influence therapeutic outcomes in clinical trials is unclear*.

As the SAR board prepared a White Paper to highlight these paradoxes and discuss research directions to resolve them, the opportunity arose to present our thinking at the NARCCIM conference.

Richard Hammerschlag: That gives us a good sense of where we're at: How we came to focus on these paradoxes, our work in clarifying them, and the research we're proposing as necessary to resolve them.

Regarding the first paradox, many people, and especially practitioners, were quite disturbed after the 2007 SAR Conference by the conclusion, especially on the basis of the large-scale German trials[4] that were presented, that it either doesn't matter where we place acupuncture needles or that something is amiss with the research design of such studies. As researchers, we need to be open to exploring both possibilities.

For me, the question with regard to this paradox is twofold. First, sham needling is not inert and appears to produce a level of benefit that is procedure related. Second, inclusion of a sham-treatment arm in a randomized controlled trial may reduce the level of effectiveness of the active-treatment arm (by reducing patient expectancy of receiving an effective treatment from 100% to 50%).

My concern is that by utilizing a control procedure that has treatment benefit and by following a research design that may decrease the effectiveness of a verum or active treatment, we're generating type II errors and getting false-negative results. For example, sham needling—especially if it's invasive—may induce microtrauma through local physiologic changes in microcirculation or cytokines that promote healing in the body. A recent review indicates that in acupuncture trials that have had both a sham arm and a nontreatment arm in addition to the active-treatment arm, the difference between the sham and nontreatment arms seems to have been greater than that between the placebo and nontreatment arms in conventional pharmaceutical trials.[5] So this again raises a possibility that sham treatment is not inert, and that some

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type(s) of physiologic effect(s) occurs no matter where you insert a needle in the skin.

Another approach to the "sham problem" is to consider that a sham procedure is based, at least in theory, on two different factors. The first is a need to mimic what the patient sees and experiences. I think sham needling procedures have done quite a good job of this. But a second factor is that sham treatment must *not* mimic the physiologic effects of a verum treatment. Drug trials deal with this problem adequately since there is usually a very good idea of how the drug being tested is absorbed and metabolized, what receptor it is targeted to, and how it is inactivated, all of which permits the rational design of a placebo that doesn't do any of those things.

But because we don't know what happens in verum needling in terms of local effects when the needle is inserted, we don't know how to avoid these effects with sham needling. I think that's what we have to realize: We need a much clearer understanding of the local mechanism of acupuncture before we can develop an appropriate sham procedure.

If this is why a sham procedure may turn out to have a beneficial effect in its own right, we should also consider the possible deleterious effect of including a sham arm on the effectiveness of the verum treatment. When you tell patients, as part of the informed-consent process, that they have a 50–50 chance of getting a sham treatment, you may well be reducing their expectation of receiving an effective treatment from 100% (in clinical practice) to the 50% level.

Again, this is why I believe we're getting type II errors in many sham-controlled acupuncture trials.

Rosa N. Schnyer: I have a few things to add to what Richard said. One has to do with the problem of making the patients in each arm of a sham-controlled trial believe that they're receiving active treatment. Second is that in conventional clinical trials, it is also important whenever possible that the practitioner be blinded to the type of treatment intervention that they're providing. Third, it's important to recognize that the intent of practitioners may be skewed when we put them into experimental settings, as a consequence of the ethical dilemma of their being used to providing authentic acupuncture care, whereas they know that they may not be providing such care in the blinded setting of a clinical trial, with its inclusion of a sham-treatment arm.

That's a point we rarely discuss, but if the intent in study design is to create a placebo that truly blinds the practitioner or other person providing the treatment in the study, it's important to consider whether we're enhancing a placebo effect by increasing the concern and attentiveness of the practitioner to the patient in the administration of a sham control.

Another thing I want to say is that the use of the term "sham" for a control is problematic, because we haven't yet proven that these actually are sham interventions.

Richard Hammerschlag: Can you clarify what you mean by that?

Rosa N. Schnyer: When you use the term "sham," it implies that what is being done or given is false, and does not really have any kind of clinical effect. Here we have to consider that sham treatments have been developed on the basis of a preconception of what a verum or active acupuncture treatment really is, and whether it is based on the location of an acupuncture point or the type of needling or type of stimulation being provided, and we have not yet actually proven that sham or shadow needling at known acupuncture points does in fact constitute a noneffective, false treatment. Therefore, redefining sham interventions as "acupuncture-like controls" would probably help us to demystify the belief that we're actually providing sham or placebo controls, because we don't know that yet.

Richard Hammerschlag: I think you're right, Rosa, because the term "sham," I believe, comes from surgery, whereas the term "placebo" comes from drug trials, and there have been several dramatic examples of sham surgery being found to work as well as real surgery, as in the classic study of ligating the mammary artery as a treatment for angina,[6] and the more recent trial in which arthroscopic surgery for osteoarthritis of the knee performed no better than sham surgery.[7]

I'd also like to comment briefly on Rosa's point about practitioner intention. If you're allowing practitioners to apply sham needling with the same intention as verum acupuncture, the only difference is what the needle is doing, and in that case trials are really testing the effectiveness of the needle rather than the effectiveness of acupuncture. If we want to test whether *acupuncture* is effective, which I think is the relevant clinical question, we not only need to find some way of shamming the needling, but also of having practitioners block their intention, which is a major challenge.

Vitaly Napadow: I want to tackle the first point that Rosa brought up. Isn't the matter of intention just an issue of proper training? In a trial such as one of the very large German trials, where hundreds of practitioners were involved, it's very difficult to control what each practitioner does. But in most clinical trials it seems to me to be an issue of training practitioners to fix their intent on a certain location and dial up or dial down the factors that are specific to the intervention at that location.

Rosa N. Schnyer: That's why it would be important to define the factors that we consider to be specific to both needling and to acupuncture treatment, in order to understand why the so-called sham treatments are not differentiating themselves from valid acupuncture treatment.

Peter M. Wayne: I'd like to ask Helene to say a few words here, because one of the key conclusions that emerged in drafting our White Paper was the importance of clearly defining the key terms we use in our field, so that we can minimize confusion in our work and enhance communication of ideas.

Helene M. Langevin: Thank you, Peter. It does seem that a lot of confusion in the acupuncture literature is due to the ambiguous use of terms. The first and most fundamental term that is used ambiguously is the term "acupuncture" itself. People use "acupuncture" to describe a procedure that involves the insertion of a needle, and stimulation by some manual or electrical manipulation of the needle. People also use the term acupuncture to refer to the more complex intervention of acupuncture treatment, of which needling is only one of many different components. Such components include, for example, Traditional Chinese Medicine diagnosis, contextualizing of the patient's illness within a particular framework, and palpation for tenderness along acupuncture meridians or at acupuncture points. In this treatment context, the insertion of needles and perhaps other measures, such as moxibustion, are only one component.

Our first need, then, is to encourage the entire field of acupuncture to be very specific in defining what is meant by

"acupuncture" within a research study, whether it is meant to describe a needling procedure or a whole treatment.

Our second need, deriving from this first need, is to precisely state the hypothesis for which an "acupuncture" treatment is being tested, either in a basic science experiment or in a clinical trial. For example, in a basic science experiment where the hypothesis is that electrostimulation is having an effect, a logical control would be insertion of the same needles at the same depth and at the same places as the electrostimulation needles, but without the electrical stimulation. Alternatively, if the hypothesis is that it is the location of the treatment points that matters, an appropriate control would be insertion of the needles at a different location but with the same insertion depth and stimulation method.

On the other hand, if an investigation is testing the hypothesis in a clinical trial that it is the whole treatment that is having an effect, then the appropriate control would be a procedure that does not have the full totality of components of the complex treatment that are hypothesized to be active, including the diagnostic component, the intention of the treatment, or any needling or other components. A careful statement of the hypothesis for using a particular acupuncture treatment in a particular experiment or clinical trial, and specification of the treatment components being tested in the experiment or trial, will result in greater clarity in interpreting the outcome and will help us to move forward.

Richard Hammerschlag: I think that's a great clarification, and I'd like to offer, as a short example of what Helene described, the recent Cherkin and Sherman trial on acupuncture for chronic low back pain.[8] One of the several questions the trial sought to answer was whether an acupuncture needle has to be inserted to achieve a treatment effect. The use of a toothpick in a guide tube in that trial was not a sham, as many have misinterpreted it as being. Rather, the toothpicks were tapped at the same points used in the verum acupuncture to test the importance of skin penetration.

Helene M. Langevin: The toothpick in the guide tube controlled for just that. It included location and stimulation but *not* penetration.

Richard Hammerschlag: Yes.

Jongbae J. Park: I would like to view the findings of the past several decades from a rather bright side. I think we have realized that we don't know as much as we presumed through the findings of clinical trials of acupuncture. We now realize that the rather negative findings in many such studies may have been the result of a failure to differentiate the nature of what we have aimed at observing from what can be detected by available methods. If so, we may in the future be able to better define our questions for clinical research studies, based on what we have learned and the careful interpretation of our findings, and hopefully, that will lead us to more meaningful analysis of our findings.

Vitaly Napadow: Another important consideration is our assumption that sham effects and verum effects, however we define them, are going to be synergistic or additive. But I think it's possible that separate mechanisms underlie these effects. Thus, even though you might see, either clinically or behaviorally, a similar outcome with so-called sham or minimal acupuncture and verum acupuncture, there may actually be different mechanisms underlying the clinical efficacy observed in the two groups, as has been suggested in several recent neuroimaging studies.[9,10] If we can have a better mechanistic understanding of how these interventions might be working, we might be able to more specifically apply or even optimize various treatments for specific conditions.

An important caveat is that different mechanisms might apply in different conditions. The mechanisms that operate in acupuncture for low back pain or fibromyalgia, for instance, could be very different from those operating in acupuncture for carpal tunnel syndrome.

Jongbae J. Park: I completely agree. That's a great point.

Rosa N. Schnyer: I would like to add to that the issue of duration of follow-up. The differences in mechanisms between sham and verum procedures may very possibly not be evident either clinically or behaviorally over the very short term in which trial outcomes are generally evaluated, whereas if indeed sham and verum acupuncture do work through different mechanisms, such differences could become more evident, and more clinically significant, in the long term. It is possible that patients would respond similarly to short-term sham and verum treatment over 8 or even 12 weeks, but that differences in the effects of the two procedures would become more pronounced over a longer period.

Vitaly Napadow: Can you be more specific about what you consider a longer term?

Rosa N. Schnyer: It would probably be condition dependent, because clinically speaking, one would expect a different prognosis, a different treatment dosage, or different results depending on the chronicity of the condition being treated, and also depending on any other treatments the patient is using for her/his condition. All of this makes the issue of evaluation time a very difficult question to answer in a general way. It needs to be determined on the basis of the condition being treated and how it is treated clinically, and also in terms of the rates of remission and relapse in general for that particular condition.

We need to examine short-term treatments and then do follow-up of patients over a long period, and to look at the differences in the mechanisms of control procedures and active treatments, and also to look for correlates of these mechanistic differences with behavioral and clinical changes. These are important issues for acupuncture research.

Vitaly Napadow: I would agree. I think we also need to know more about the conditions that we're trying to treat; that we frankly just don't know enough about the pathophysiology of depression, for example, or the pathophysiology of low back pain, or of many chronic conditions. What that means is that people engaged in acupuncture research need to be current with the latest findings about these conditions as reported in the pathophysiology literature.

Peter M. Wayne: That's an important point, Vitaly, and I think that it is one of the themes that emerged from our discussion during the writing of the White Paper. It also parallels another key theme, which is the need for objective markers of outcome. Many of the outcomes we are evaluating in acupuncture research, and pain research in general, tend to be subjective. A better understanding of the pathophysiology of the conditions we're treating would bring a better understanding and choice of objective biomarkers for these conditions.

So I think that the processes of more fully understanding pathophysiologies and of identifying effective biomarkers have to evolve in parallel, and that this may require another level of collaboration between basic scientists and people

interested in clinical research issues in acupuncture. I believe that would be an important effort for advancing the field of acupuncture research.

Rosa N. Schnyer: I'd like to add to what Peter just said. Biological markers are a very important component of clinical change in patients with chronic disorders, but so are behavioral changes in patients' use of medication and need for services. I think that we need to expand the questions we're asking about acupuncture to include whether acupuncture may play a direct role in the management of chronic disorders, rather than being an alternative to such management. Acupuncture provides a step-by-step intervention in the chronic disease process, with utility as an initial intervention and also as an intervention over the long term for patients whose condition may be severe or difficult to manage, and for whom you want to reduce their need for services, increase their adaptability, and decrease their utilization of medications.

Peter M. Wayne: I fully agree with that. Markers needn't necessarily be useful only for following biochemical or physiologic processes. A broadened concept would include their use for following psychologic well-being, as long as they are relevant and validated indicators. I think that Rosa's point about what we would call translational research, with utility extending out to the practice community in terms of cost-effectiveness and the practicality of various interventions, is an important point.

Richard Hammerschlag: I also like the breadth of Rosa's statement. But I would ask whether it means challenging researchers to expand their concept of research design so as to enable them to follow the trajectory of care wherever that leads, rather than establishing a fixed treatment protocol from the outset. Do you see that as a possible new direction in acupuncture research?

Rosa N. Schnyer: I think it's very important that we not continue to explore research without questioning the current disease-centered model on which it is based, and as we move closer to developing biomedically based, patient-centered interventions, that we not go backwards by evaluating acupuncture merely as a disease-centered intervention, but rather look at the role of acupuncture as a new paradigm for care beyond the setting of complementary and alternative medicine alone.

Richard Hammerschlag: I think we should ask Helene to begin a discussion of Paradox Two, which focuses on the parameters of acupuncture needling in relation to therapeutic outcomes of clinical trials.

Helene M. Langevin: Basically, Paradox Two emerged from the SAR 2007 Conference on the Status and Future of Acupuncture Research, as did Paradox One. To begin, there seems to be a discrepancy between the effects of needling found in basic science experiments, both with animals and with humans, and those found in clinical trials. In basic science studies, it's not difficult to show that acupuncture needle stimulation is doing something. It has undeniable, measurable physiologic effects in many systems that have been examined, starting from the central nervous system and extending to the cardiovascular system, gastrointestinal system, and connective tissue. Yet in many clinical trials, it seems not to matter whether needles are even inserted—that similar clinical effects can be obtained with needles and with noninserted devices such as toothpicks or sham needles that don't penetrate the skin. In a lot of clinical trials, the location of needle insertion also doesn't seem to be particularly important, because the same effects can be obtained with needles placed at irrelevant sites.

Why is there such a disconnect or apparent discrepancy between the findings in basic science experiments and the findings in clinical trials? We have identified several potential reasons for this, one of which is that some of the phenomena observed in basic research may have no or limited relevance to the observed clinical effects.

On the other hand, it is possible that physiologic effects observed in basic science experiments do contribute to clinical effects in trials of acupuncture, but that in clinical trials these physiologic effects are overshadowed by other, greater effects of non-needle-specific components and/or the more general nonspecific treatment components that we discussed earlier.

Consequently, acupuncture needles may really be doing something, but we may not be able to perceive these effects in clinical trials because other factors are causing background noise in the system that increases the variability of the patient's response and decreases the magnitude of specific effects.

A further possibility is that we're really not homing in enough on the right outcome measures in clinical trials because as we mentioned earlier, we don't fully understand the pathophysiology of the conditions being studied, and are therefore not collecting the data needed to detect differences between active treatments for these conditions and nontreatment or control or sham procedures. These are the three main categories of factors that we discussed at the symposium. In the White Paper, we will be making some specific recommendations about ways in which to remedy these gaps in our knowledge so that we can resolve this paradox of the findings in basic versus clinical research and allow further progress in therapeutic acupuncture.

Richard Hammerschlag: Does anyone have follow-up questions about the second paradox?

Vitaly Napadow: I have a question. Given this paradox, what do we feel is the current role of animal research in acupuncture? It has been very interesting that a lot of animal research in acupuncture has demonstrated effects of needling at different acupoints, possible effects of deep versus shallow stimulation, and even effects in animal models that correlate with clinical outcomes. How does that translate to clinical trials? Is there simply a fundamentally different placebo mechanism or placebo effect (e.g., conditioning more than expectancy or vice versa) in rats than in humans?

Helene M. Langevin: Yes, that is certainly an interesting issue. Part of the answer seems to be that outcomes in animal studies tend to be measured in periods of hours to days rather than weeks to months. Also, when we say that we demonstrate point specificity in animal controls, this is sometimes not so clear-cut, and instead represents what is more likely a regional specificity. It's very difficult in a study with rats, for example, to know whether you're at a true acupuncture point, because the limb of the animal, for example, is so small. As a result, control needling often occurs at varying sites within a body region, or in different regions, and a study may therefore really not be demonstrating acupuncture point specificity as much as regional specificity. This needs to be taken into consideration.

Translating the interpretation of an effect observed in an animal to that observed in a human must also be done very carefully. Again, I think that the bridge between them can be made by careful physiologic studies in humans, which attempt to replicate animal experiments as closely as possible. Clearly, some of the outcome measures that we use in animals cannot be used in humans because they're too invasive. But that's where we need minimally- or non-invasive biomarkers that can be used in both animals and humans to translate observations made in animal studies to those in human studies. Once we can do that, we can move on to a more complex situation, such as a full treatment situation. But I think we have to look at the outcome measures one at a time and very specifically.

Vitaly Napadow: I completely agree.

Richard Hammerschlag: I agree that we need more immediate measures of short-term outcome and that animal studies can be used to develop these, with further study to see if they translate into effects in humans. Valid measures of immediate outcomes will enable us to more clearly examine different experimental variables as well as interventional and treatment variables in studies of human acupuncture.

I also think that some animal studies have shown clear differences between sham and active needling, but these studies have used one or two acupuncture points, and have used only one or two sham needles, whereas some of the recent German trials, in which verum acupuncture was modeled closely on real practice and individualized care, typically used 10–20 needles, and therefore also used 10–20 sham needles,[11,12] and when you use that many sham needles you may be getting a "ceiling effect" resulting from what is inadvertently activated in the body. So we need to look at whether two sham needles may be a sufficient control procedure in human trials, even when using 10 or more true acupuncture points. Do we need to balance the number of sham and treatment needles? Would we get a different outcome if we used only two sham needles instead of the same number as that used in the verum arm of a study?

Rosa N. Schnyer: I think that part of the reason why the same number of needles are used in the sham as in the verum arm of a study is that you're trying to blind the patient to any association between treatment technique and outcome. You can probably manipulate such a thing in your informed consent process, but if you have patients who know each other and discuss their treatments with one another, or who have the belief that acupuncture involves getting lots of needles as opposed to just two, that can have a nonspecific effect by differentiating a sham from an active treatment or one treatment from another. I think that from a mechanistic viewpoint, it makes a lot of sense to try to distinguish sham- from active-treatment effects, but I think that part of the reason that studies have maintained similarities in their sham- and active-treatment arms is to maintain the perceptual and physiologic effects of the two procedures as equally as possible.

Helene M. Langevin: Then what we may need to do is to conduct animal experiments, for example, in which we insert 15 or 20 needles rather than 2 needles, for example, and see whether that makes a difference.

Richard Hammerschlag: That sounds like a good concept, especially in the context of the kinds of studies that are needed to resolve the paradoxes we've discussed, and the kind of agenda that will help accomplish that.

Peter M. Wayne: I think that what we've tried to share here is a candid summary of our experiences and views, and I think our discussion today has captured the spirit of a roundtable discussion. But before we end, there are two issues that are worth making explicit.

First, why do we think that the SAR is uniquely qualified to pull together this White Paper and use it to propose an agenda for the future of acupuncture research? Second, what do we hope will be the impact of this paper? Since these questions will not be directly addressed in the White Paper itself, this roundtable discussion provides a unique opportunity for us to express our thoughts about these matters.

Helene M. Langevin: First of all, SAR has been in existence as an organization since 1993, and has witnessed the evolution of acupuncture as a field of healthcare practice. Because of that, the current board of the SAR, on the basis of its cumulative historical experience, feels that it is in a good position to provide a unique overview of the field and define it in a comprehensive way that will be useful to all those engaged in acupuncture and in acupuncture research.

Richard Hammerschlag: I also hope that what we'll do when we issue our agenda for the future direction of acupuncture is to call for a temporary halt to sham trials until we get a better idea of how they should be designed. That would dovetail nicely with the increased interest throughout the NIH, and certainly at the National Center for Complementary and Alternative Medicine, in trials designed to assess "comparative effectiveness." From our perspective, this translates not as comparative effectiveness of sham versus active acupuncture, but of acupuncture relative to biomedical usual care. Arguably, this latter research design is considerably more appropriate than sham-controlled designs for assessing clinical options from both the patient's perspective and the practitioner cross-referral perspective. The White Paper can help to influence the choice of research design, and I think that's a strong point for the role of the SAR.

Peter M. Wayne: I would also say that, in addition to its historical perspective, the SAR is composed of a unique group of people with unique experience, including seasoned practitioners of acupuncture in both the biomedicine and East Asian medicine professions, people involved in acupuncture education and organization of future research in the field, bench scientists, and clinical investigators. It's a unique confluence of experience and skills that places SAR in a valid position to issue a White Paper on acupuncture research.

I personally hope that once this White Paper is published, it will generate discussion and debate that begins to influence funding agencies' choice of research priorities, and also helps to better interpret the research that has already been done in acupuncture.

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