

ACADEMIC EXPLORATION

Recent Clinical Trials of Acupuncture in the West: Responses from the Practitioners

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ABSTRACT In the West, hundreds of randomized controlled trials (RCTs) have been performed testing acupuncture. They include two types: those that compare acupuncture to other therapies, usual care or no treatment (pragmatic trials), and those that have placebo controls (efficacy trials). Acupuncture has generally performed well against other therapies or no treatment, but until recently, the evidence from placebo controlled trials has been considered equivocal or contradictory. A recent series of large RCTs, mostly performed in Germany and also in the US have included both pragmatic and placebo comparisons. The evidence poses a conundrum for the profession of acupuncture. This essay first describes the two types of RCTs used to examine acupuncture and examine the results of two recent large RCTs for chronic low back pain as representative examples of recent large studies. The essay then presents the most common Euro-American acupuncture professions' interpretation of these results. Western responses have included: (1) methodological weaknesses; (2) inappropriateness of placebo controls; (3) questions as to whether acupuncture placebo controls are "inert"; (4) rejection of evidence-based medicine epistemology; (5) discrepancy between acupuncture performed in RCTs with real world acupuncture; (6) enhanced placebo effects of acupuncture; and (7) needs to re-evaluate acupuncture theory. The authors do not necessarily agree with all of these responses; they are presented in an attempt to foster critical discussion. The paper also looks at recent neuroimaging experiments on acupuncture that may point to some worthwhile new avenues of investigation. Finally, the Euro-American health care policy consequences of these recent RCTs are discussed.

KEYWORDS acupuncture, sham acupuncture, low back pain, randomized controlled trials, acupuncture neuroimaging



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Traditional acupuncture is based in the interpretation of classical texts, the accumulated clinical practice of thousands of years health care, mentorship from revered older teachers, and individual practitioner's clinical practice. In recent years, the profession of Chinese medicine (CM) has embraced the methods of biomedicine including the importance of evidence from randomized controlled trial (RCT). In the West, hundreds of RCTs have been performed evaluating the efficacy of acupuncture. Integrating the findings into a traditional acupuncture framework has been difficult. This essay reviews the two basic types of RCTs (pragmatic and efficacy) and focuses on two large RCTs of acupuncture for chronic low back pain as representative examples of the recent conundrum posed by recent acupuncture

trials in the West. The article then reviews the main responses that have come forth from the Western profession of CM. Recent neuroimaging experiments on acupuncture and placebo acupuncture that point to new approaches are described. Finally, some of the health policy consequences of the recent RCTs in the West are presented.

Two Types of Randomized Controlled Trials

RCTs come in two broad categories: pragmatic (also known as effectiveness or comparative effectiveness) trials and efficacy (also known as fastidious or explanatory) trials⁽¹⁾. Pragmatic trials

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compare two treatments under conditions in which they would be applied in routine care. They are not concerned with mechanism and explanation. The question is which works better? Placebo controls are not consequential. Generally, the research is carried out in normal or optimal environments with an emphasis on acquiring information necessary for making a clinical decision⁽²⁾. Recently, complementary and alternative medicine (CAM) or integrative investigators, among others, have labeled this method as "whole system" research^(3,4). In contradistinction, the efficacy approach asks is it better than placebo? It seeks to understand whether a treatment has effects beyond the context or ritual of the treatment. It is less concerned with clinical outcomes and privileges of causal pathways. Distinguishing whether the treatment has a "specific" impact on disease, as opposed to "mere" nonspecific effects, is the key issue. Placebos are the defining characteristic of such studies. The efficacy approach usually treats "nonspecific" as inconsequential or unnecessary noise in the experiment⁽⁵⁾. Western regulatory requirements for obtaining FDA labeling and scientific prestige reinforce the status and importance of such studies. The two types of RCTs manage to coexist although they embody implicit criticism of one another. Efficacy trials question the rigor of the science in pragmatic studies, while the pragmatic approach (even for pharmaceutical trials) implicitly raises questions about untested assumptions that "specific" and "nonspecific" effects are separable, noninteractive, stable, linear, and relatively constant during the duration of the trial⁽⁶⁾.

Results of the Latest Randomized Controlled Trials for Chronic Low Back Pain

In the last 20 years, there have been hundreds of both pragmatic and efficacy RCTs for acupuncture⁽⁷⁾. The results, with some notably exceptions like acupuncture for nausea and vomiting, have been inconsistent or contradictory⁽⁸⁾. More recently, there have been attempts to provide more definitive evidences with large RCTs. Especially noteworthy are two trials for chronic low back pain (cLBP): one initiated by the German government and funded by statutory health insurance grants for the purpose of determining reimbursement policy for acupuncture, and a recent NIH-funded trial performed by Seattle Group Health. What is remarkable about these two experiments is that they addressed a pragmatic

question and an efficacy question simultaneously. Both trials included the pragmatic comparison, "how does acupuncture treatment compare to optimal or usual mainstream care?" and the efficacy test, "is verum (genuine) acupuncture superior to a dummy control?"

The German trial randomized 1 162 patient with cLBP to three arms: (1) 10 verum acupuncture treatments according to the principles of CM over five weeks; (2) 10 sham (placebo) acupuncture treatments consisting of superficial needling at nonacupuncture points over five weeks; or (3) optimal usual care consisting of a combination of drugs, physical therapy, and exercise that included 10 contact visits with mainstream providers⁽⁹⁾. If patients had a partial response to acupuncture or sham acupuncture, they could elect to have five additional sessions. The comparison of verum acupuncture (arm 1) and optimal mainstream care (arm 3) answered the practical clinical question, while contrasting verum acupuncture (arm 1) and sham acupuncture (arm 2) addressed efficacy beyond placebo. At six months after randomization, the primary endpoint, acupuncture was almost twice as effective as optimal mainstream care (47.6% versus 27.4%, $P < 0.001$) and provided significant clinical benefits to patients. The answer to the efficacy question was not so comfortable for practitioners of East Asian medicine: verum and sham acupuncture had effects of identical magnitudes.

The Seattle story told a similar story. A total of 640 patients with cLBP were randomized to a total of 10 treatments over seven weeks to one of four arms: (1) standardized verum acupuncture treatment for cLBP, based on CM principles; (2) individualized verum acupuncture, based on a CM diagnostician's evaluation who then prescribed a unique treatment that could include any acupuncture points that could be needled with the patient prone (An acupuncturist different from the diagnostician performed the actual treatment.); (3) treatment using a toothpick in a guide tube that simulated acupuncture at the same eight acupuncture points used in the standardized treatment group; and (4) continued usual care involving medications (mostly nonsteroidal anti-inflammatory medicines, primary care, and physical therapy visits)⁽¹⁰⁾. At eight weeks, the primary endpoint, in the pragmatic comparison, 60% of those receiving acupuncture experienced clinically

meaningful improvements on a dysfunction scale compared to 39% in mainstream care ($P < 0.001$). This difference lasted through the entire one year follow-up period. For the efficacy question, acupuncture (either standardized or individualized) was no different than simulated acupuncture.

The Western Acupuncture Profession's Response to the cLBP Trials

The results of these two RCTs have raised a conundrum for the acupuncture profession in the West. The pragmatic comparison was easy to accept, but the efficacy comparison was very uncomfortable. Below, we briefly discuss several of the most common interpretations articulated by Western acupuncturists and acupuncturist-researchers in relation to efficacy acupuncture versus placebo acupuncture comparison. Our aim here is to describe the ongoing discussion around the issue of placebo-controlled trials and to think out loud; we do not claim to fully understand what these RCT results mean. Nor do we necessarily agree with all of the responses mentioned. We think that such a summary would be helpful for further discussion and future strategic planning both in China and the West.

Methodological Weakness and Inadequacies

If an experimental finding is inconsistent with deeply held a priori beliefs or principles, whether mainstream or CAM, it is usually treated with suspicion. Thus, an unexpected and unwelcomed result is initially apt to be considered an indication that an experiment was poorly designed or executed⁽¹¹⁾. For acupuncture in particular, the number of such potentially treacherous imperfections are almost endless. Examples of such potential pitfalls might include patient entry criteria, skill of practitioners, point selection, frequency and scheduling of treatments, style of acupuncture, and absence of ancillary treatments (e.g., moxibustion, massage, exercise, and herbs)^(12,13). One could challenge any of these particulars (and others) for any acupuncture RCT. Nonetheless, it should be noted that senior and experienced acupuncturists were extensively consulted for both of these RCTs and felt that the treatments and sham controls were good ones.

Placebo Controlled Acupuncture Trials Distort Acupuncture

Many acupuncturists argue that placebo

controls is not meaningful for complex interventions, such as acupuncture: acupuncture is not simply needling. "Elements that are categorized as incidental (nonspecific) in drug trials may be integral to nonpharmacological interventions."⁽¹⁴⁾ Besides, needling with acupuncture needles, acupuncture includes the benefits of diagnosis and interaction with the therapist. Therefore, the "sham acupuncture design is inappropriate because it delivers these other characteristics to both groups (and) consequently; the difference between the groups may be greatly underestimated."⁽¹⁴⁾ This argument of multiple essential ingredients is aligned to the notion that acupuncture must be treated as a "whole system" medicine and cannot be broken into components⁽¹⁵⁾. Efficacy studies are inherently invalid, and such complex systems can only be studied within a pragmatic approach "because of problems developing, identifying, documenting, and reproducing the intervention and their inherent multidimensionality"⁽¹⁶⁾.

Placebo Acupuncture Is Not Inert or It Does Not Exist

Another criticism of placebo controlled RCTs contends that sham acupuncture is not inert or innocuous. Indeed, most methods of sham acupuncture have somatosensory properties and stimulates mechanoreceptors^(17,18). Touching the skin anywhere "induces a certain amount of sensory stimulation and, thereby, a possible therapeutic effect."⁽¹⁹⁾ This line of reasoning call also point out that even the most gentle touch can be verum acupuncture, e.g., some Japanese styles of acupuncture⁽²⁰⁾. In fact, this argument can apply to placebo controls for other procedures beside acupuncture; for example, sham surgery is physiologically active and is hardly innocuous^(21,22). (Even sugar and saline are not without biological activity.) In fact, the key issue for RCTs is not the inertness of placebo but the placebo controls should lack the purported "active" ingredient of the genuine exposure. Following this line of reasoning, some acupuncture researchers, therefore, have called for a moratorium on placebo-controlled acupuncture RCTs until there is "a clear understanding of the mechanism by which acupuncture works."⁽²³⁾ This problem of imperfect placebos is not unique to acupuncture and plagues RCTs testing of many devices or procedures for cLBP⁽²⁴⁾, and even drug researchers have raised concern that "chemicals used as placebo (pills) may

have (undetected) specific effects."⁽²⁵⁾

Rejection of Evidence-Based Biomedicine

Some practitioners believe that any collaboration with RCTs betrays East Asian medicine's unique methodology of accumulated clinical experience, reflective observation and textual analysis. It is maintained that Asian medicine is "incompatible with the ethos of science"⁽²⁶⁾, and RCT evidence is "frequently inimical to the authenticity of the traditions that they claim to examine."⁽²⁷⁾ Some even speak of the "randomized controlled crime."⁽²⁸⁾ Others have suggested that "anthropological notions of evidence that include such concepts as "transcendent, transformational experiences, changing lived-body experience, and the gaining of meaning" are more compatible with Asian medicine⁽²⁹⁾. Still, others have argued for a middle position that believes that it is possible for RCTs to be "sufficiently flexible, so that it can match the expected variability in patients, that outcomes measures can capture the broader range of changes that can be experienced by patients, and that the therapeutic relationship is not compromised by the trial design."⁽³⁰⁾ This last position seems to be most comfortable with pragmatic trials.

RCTs Underestimates Real-World Effects

Researchers who study research methods generally agree that there is a "discrepancy" between the results of placebo-controlled trials and outcomes that are detected in clinical practice⁽³¹⁾. The argument is even the most unbiased methods that correctly use randomization and blinding have their own "bias". The blinding that placebo controls insures may have the consequence of underestimating effects sizes because of diminished expectancy, elimination of the impact of patients' personal preferences, increase of passivity and reduction of self-reliant behavior, intentionality, and personal investment⁽³²⁾. Evidence suggests that people who enroll in RCTs may be systematically different from those who do not create a "nonconsent" bias⁽³³⁾. Perhaps relating to these ideas, many acupuncturists have noted "the lack of resonance between many of the research findings and the every day practice of acupuncture"⁽³⁴⁾ and concluded that the poor results in RCTs are due to this underestimation of acupuncture's clinical impact⁽³⁵⁾.

Placebo Acupuncture Has Enhanced Effects

Just because something is equivalent to a

placebo control in a RCT does not mean that it is equivalent to the outcome of other placebo treatments found in other RCTs. Not all placebos are equal. Indeed, one argument for the absence of a difference between genuine acupuncture and sham treatment has been that acupuncture has inordinately high placebo effects. If a placebo effect is especially strong, it is difficult to detect an acupuncture-placebo difference. This argument is based on evidence from surgery, procedure, and device trials that suggests inordinately high placebo effect compared to placebo pills⁽³⁶⁾. Indeed, direct comparison of sham acupuncture and placebo pills shows that sham acupuncture is superior to placebo pills for pain outcomes^(37,38). (Alternatively, such evidence could be interpreted that sham acupuncture is not inert compared to pills and has similar properties to genuine acupuncture. However, recent neuroimaging evidence makes this second interpretation more problematic; see below.)

Acupuncture Theory Needs to be Re-Evaluated

To my knowledge, no acupuncturist has abandoned practice or dropped their commitment to East Asian medicine because of the RCT evidence. Also, few acupuncturists have come to agree with the segment of the biomedical community who see acupuncture as a glorified placebo⁽³⁹⁾. However, a small minority of acupuncturists seem to have taken the poor efficacy results to heart and begun to question their allegiance to traditional theory and ask "whether traditional theories for differential diagnosis as well as selecting points, locating them on the body, and choosing appropriate stimulation need to be re-evaluated."⁽⁴⁰⁾ They have argued that "if acupuncture does not depend on specific points or techniques, it significantly simplifies practice."⁽⁴¹⁾

Emerging Neuroscience Evidence

Two neuroscience teams, each led by highly trained acupuncturists, have produced new evidence that suggest new directions in acupuncture versus sham acupuncture dilemma. The first study performed acupuncture and nonpenetrating sham acupuncture on healthy volunteers over nonacupuncture points and examined the neuroanatomical correlates of these treatments using functional magnetic resonance imaging (fMRI). What they found was interesting: while both genuine and sham acupuncture equally reduced noxious stimuli,

needle stimulation inhibited incoming noxious stimuli with a peripheral-central bottom up somatosensory modulation, while sham acupuncture activated a top-down modulation of pain and worked through the brain's emotional circuitry⁽⁴²⁾.

The second study used positron emission tomography (PET) and a radioactive tracer in patients with fibromyalgia who were followed after eight weeks of acupuncture treatment. While acupuncture and sham acupuncture produced identical pain relief, two very distinct brain mechanistic patterns was observed. Verum acupuncture seemed to increase endogenous opioid receptors availability, while sham acupuncture produced decreased or no change in receptor availability and instead seemed to increase endorphin release. The pattern observed with sham acupuncture is consistent to previous placebo studies with creams or saline injections, where placebo treatment is associated with the increase in endogenous opioid release. The increase in receptors found with genuine acupuncture has not been observed previously with other treatments. This study "strongly implied divergent opioid receptor mechanisms for acupuncture and sham acupuncture."⁽⁴³⁾ Together, both studies suggest that the mechanism of acupuncture and sham acupuncture may be very distinct.

Western Health Care Policy Consequences

While acupuncturists try and understand the results of the two cLBP trial discussed here, the concrete consequences to the profession in the West have not been negative. The one that is most dramatical is what happened with regulatory agencies in Europe. In May 2009, the National Health Services' National Institute for Health and Clinical Excellence (NICE) in Britain recommended health care providers to offer cLBP patients a course of acupuncture for up to 10 sessions over a period of up to 12 weeks⁽⁴⁴⁾. Even earlier, the German Federal Committee of Physicians and Health Insurers authorized that acupuncture be included in the usual care package for cLBP⁽⁴⁵⁾. While American regulatory agencies have been more cautious, the American College of Physicians and American Pain Society has maintained their clinical guidelines that acupuncture should be considered as a therapeutic option for cLBP⁽⁴⁶⁾. All these recommendations imply that, for governmental or insurance agencies, pragmatic evidence may trump efficacy evidence. Also, all these recommendation were sensitive to patient preferences and were highly

influenced by cost effectiveness studies performed in Europe. For example, two parallel cost-effective studies for cLBP found that acupuncture treatments would save Germany €13 000 (\$19 600) per patient compared to usual care⁽⁴⁸⁾ and save £4 241 (\$7 000) in Britain⁽⁴⁷⁾. Furthermore, insurance data demonstrates that acupuncture is a substitute for more expensive medical care and not an additional cost⁽⁴⁹⁾. These recent clinical and insurance guidelines suggest that Western policy makers are more persuaded by patient outcomes and cost than the question of superiority over placebo.

Summary

The recent scientific evidence for acupuncture and cLBP has not been what the acupuncture profession expected or ideally preferred, but it has provided solid evidence that acupuncture significantly helps patients. Acupuncturists are engaged in a complex discussion on interpreting this data. Recent neuroimaging evidence seems to offer new ways of understanding acupuncture and sham acupuncture. The recent clinical guidelines concerning acupuncture in Europe and America suggests that pragmatic evidence outweighs efficacy evidence in illnesses where Western treatments are inadequate. This discussion is likely to continue.

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