ADVANCING ACUPUNCTURE RESEARCH
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Since the early 1970s, acupuncture has been the subject of multiple animal experiments and randomized clinical trials. Our understanding of acupuncture from both the clinical and mechanistic perspectives has, as a result, grown tremendously. Yet the final word on acupuncture as a therapy remains mixed, largely due to the contradictory nature of the evidence. With some exception, what clinical conditions would benefit and how acupuncture physiologically operates remains unclear. The impediment to progress is found in three disjunctions in acupuncture research: (1) the biomedical need to standardize treatments creates uncertainty about whether we are studying acupuncture appropriately; (2) the variability in acupuncture styles creates ambiguity about whether we are studying the right style; and (3) the discrepancy between animal and human studies creates questions about whether we truly understand the underlying mechanism responsible for acupuncture's therapeutic effect.

We propose that these disjunctions are best addressed with the use of "manualized" protocols in clinical trials that are linked with mechanistic studies. Through this approach, we can create a healthy dialogue between the medical and acupuncture communities and recognize the unique physiologic properties that may be found in each acupuncture style. To illustrate how this proposal may fundamentally change acupuncture research, we present diabetic neuropathy as a particularly interesting model because of its complex heterogeneous pathophysiology.

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Since the early 1970s, more than 500 randomized controlled trials (RCTs) investigating acupuncture have been performed in the Western world. A National Institutes of Health (NIH) Consensus Development Panel on Acupuncture held in 1997 sifted though this mountain of evidence and reached the conclusion that “needle acupuncture is efficacious for adult post-operative and chemotherapy-induced nausea and vomiting and probably for nausea of pregnancy... There is evidence for efficacy for postoperative dental pain.” For all other conditions, the evidence was inconclusive or contradictory.

Despite the numerous clinical research trials on acupuncture, three major disjunctions persist: the gap between biomedicine and Eastern medicine, the gap between acupuncture styles, and the gap between animal and human studies. Unless these challenges are addressed, the contradictions in acupuncture research will remain inscrutable, and progress may be sluggish.

GAPS IN ACUPUNCTURE RESEARCH: BIOMEDICINE VERSUS EASTERN MEDICINE

The continued efforts to evaluate acupuncture solely on the grounds of Western research methodology may not provide the objective assessment needed to determine the effectiveness of acupuncture. Given that biomedicine and Eastern medicine (eg, traditional Chinese medicine or Japanese medicine) are different paradigmatic perspectives on illness and health, it is possible that our tools, particularly standardized protocols required for RCTs, are not tackling acupuncture directly, but rather evaluating a semblance of it. A number of acupuncture researchers have voiced this concern. The whole process can
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Biomedically identified diseases generally correspond to a heterogeneous collection of Eastern-medicine-defined conditions. What is one disease or condition in biomedicine can be equated to asking a sculptor to sculpt with a paintbrush to prove he is an "artist." The need to conform to an existing tool can undermine the very process we are trying to evaluate. In the case of the sculptor, the need to use the paintbrush undermines his or her ability to demonstrate his or her artistic skills, and in the case of the acupuncturist, the need to use standardized interventions (as in most RCTs) may undermine his or her ability to effectively treat the patient.

Patterns are perceived or "constructed" through a process of examination that involves observation, palpation, questioning, listening, and smelling. Once these patterns are constructed, they are used to guide treatment with the use of therapies such as acupuncture and herbs. Because these patterns often do not conform to known biomedically identified diseases, one can understand the dilemmas encountered by acupuncture researchers who are required to choose a treatment for a biomedically defined disease. For an acupuncturist, this task is probably no easier than it is for a biomedical physician to identify a drug to treat "failure of kidney to receive qi."

GAPS IN ACUPUNCTURE RESEARCH: ACUPUNCTURE STYLES

To further complicate the issue, acupuncture itself is varied in its treatment styles and diagnostic approaches. Unlike biomedicine, Eastern therapies such as acupuncture value experience and even intuition over reproducible and definitive facts. According to this principle, experience is the currency by which one accumulates proficiency and wisdom. Acupuncturists are encouraged to build upon these experiences and create a style that works best for them. For this reason, 2,000 years of use and dissemination, along with the accompanying cultural and political influences, have led to many divergent paths in acupuncture practice. In addition, the lack of transparency in original textual sources has compounded this diversification because of multiple interpretations of the texts. In the US alone, at least eight different styles of acupuncture are taught in the various accredited schools and endorsed by the national credentialing examination. This historical trajectory can be likened to martial arts. There are countless numbers of martial art forms, and, much like the contrast between tai chi and karate, the differences in styles can be so marked that there are few similarities between them. This variability explains the lack of consensus (even within the acupuncture community) on the proper acupuncture approach for an individual. Differences exist on such fundamental basics as what points are to be needled, how the needle should be manipulated, how long the needle should be kept in, and the appropriate response by the patient. The acupuncture community has been divided over these matters for centuries. Thus, to perform a clinical trial to evaluate acupuncture begs not only the question of whether we are really testing acupuncture, but also whether we are testing the right type of acupuncture.

GAPS IN ACUPUNCTURE RESEARCH: ANIMAL VERSUS HUMAN STUDIES

Basic research in acupuncture has played an important role in establishing credibility for acupuncture as a therapy. Numerous animal studies have not only demonstrated mechanisms for the acupuncture effect, but also have revealed the surprising consistency and reproducibility of certain acupuncture's beneficial effects on animals. In addition, these beneficial effects have been demonstrated in a large array of health problems from pain to diabetes. There is one large caveat, however: despite the promising research in animal models, the high success rate has not been duplicated in human clinical trials. One explanation for this disparity is the differences in interventions between the two models. As pointed out by some academic acupuncturists, most, if not all, animal studies involve either strong electrostimulation or powerful manual manipulations that are considered too painful for humans to tolerate. The common 1 to 3 milliamperes (mA) electrostimulations or 0.3 mm needles used in animal trials are much too intense when the intervention is extrapolated to a human scale. In addition, the stressful lab environment induces changes in animal physiology that fail to reflect the often relaxing acupuncture encounter. The neurophysiologic mechanisms elicited from animal trials (ie, diffuse noxious inhibitory complex, gate theory, proprio spinal inhibition) are also short-term often lasting 10 to 20 minutes.

Animal models, while necessary and helpful, are incomplete paradigms for acupuncture treatments. First, as previously mentioned, the interventions used in animal models do not accurately replicate human acupuncture interventions. Second, acupuncture treatments are complex, employing a sophisticated diagnostic pattern recognition followed by corresponding needle treatments. The needle treatments themselves often require feedback from the patient to assess for efficacy; eg elicitation of de qi, an aching sensation associated with needling (for Chinese acupuncture) and relief of tenderness (for Japanese acupuncture). Such complex protocols are difficult to replicate in an animal model. Third, acupuncture may involve psychosocial outcomes, such as reduction of stress or sense of wellness, which are difficult to measure in animals. Such qualitative measures are not infrequent in providing incentives for patients to seek alternative modalities such as acupuncture. The physiologic models are, therefore, insufficient explanations for human acupuncture models. While the proposed mechanisms may partially explain the human acupuncture model (especially acupuncture analgesia, which requires strong stimulation), there is a clear need for a more relevant human-scaled physiologic explanation.
BRIDGING THE GAPS

These three gaps—the gap between biomedicine and Eastern medicine, the gap between acupuncture styles, and the gap between animal and human studies—may largely explain the continued ambiguity encountered in acupuncture research. When a clinical trial is performed, even with rigorous scientific standards, we have little idea how to interpret the results. If it is negative, we do not know whether the choice of intervention or the choice of acupuncture style played a factor. If it is positive, we cannot be confident that the finding is reproducible given the history of conflicting RCTs and lack of responsible mechanism. The tools presently used in clinical acupuncture research need to be refined to transcend these gaps. To advance acupuncture research, adequate and reliable tools are needed to forge lines of communication between biomedicine and Eastern medicine and between the acupuncture styles. Two potential “bridges” that are capable of promoting dialogue are manualized protocols and human mechanistic explanations. Manualized protocols permit understanding from a biomedical standpoint on how acupuncture is performed in actual clinical practice, while the human mechanistic explanations permit understanding of why acupuncture may or may not work, thereby increasing confidence in its reproducibility.

Manualized protocols

Manualized protocols are carefully constructed treatment manuals designed for a specific biomedical disease. They outline both the diagnostic processes (ie. “pattern construction”) and accompanying treatment interventions according to the principles of an Eastern medicine style. The manuals allow acupuncturists to select from an ensemble of treatment options that best correlates with their diagnostic evaluation. This allows the flexibility and individualization that are considered important for an effective acupuncture intervention. At the same time, the diagnostic and treatment steps are predetermined, explicitly described, and rationalized in the manual, enabling researchers to identify interventions and the reasons for their use. Importantly, these manuals allow for the replicability and standardization necessary for rigorous scientific research.

The manuals are constructed to accurately reflect the teachings of both clinical texts and experienced acupuncturists. They are created to represent a specific acupuncture style’s treatment for a defined biomedical disease, (eg. Japanese acupuncture for depression). Manualized protocols were developed over the past four years and evolved from a creative collaboration between a psychologist and acupuncturists to assess the effects of acupuncture on depression. The details in the design and implementation of such protocols have already been outlined. Manualized protocols perform two other important tasks. One, permitting flexibility while maintaining standardization, creating a solution that is sensitive to the needs of both biomedicine and Eastern medicine. Two, they provide a venue for acupuncturists to discuss the merit of the determined treatment. Through the process of manual creation, acupuncturists are expected to consult texts and acupuncture experts to provide rationale for a treatment.

This helps to preclude the amorphous treatment selections often used in present research that leaves many readers wondering why the treatments were selected. In addition, these manuals allow different acupuncture schools to understand treatment rationale and to discuss and possibly dispute its merit. As a result, through the use of manualized protocols, communication between acupuncturists who practice different styles is fostered.

Human Mechanistic Explanation

While the physiologic processes involved in therapeutic acupuncture are not completely known, basic research in human and animal models has done a tremendous job of revealing candidate explanations. These candidates include changes in autonomic nerve functioning, hormones (such as oxytocin and cortisol), neuropeptides (such as serotonin and β-endorphin), cytokines, relaxation response, and alterations in collagen network communication.

These potential mechanistic explanations (and any unmentioned mechanistic explanations) are best understood when linked to a clinical trial. Whereas drugs undergo validation with molecular and animal studies, acupuncture treatments do not, and consequently, acupuncture RCTs face the unique challenge of convincing skeptics that a positive result is attributed to the acupuncture intervention and not to poor methodology, such as insufficient blinding, biased investigators, or even chance. No matter how persuasive the clinical result, there will be lingering doubts about the efficacy of acupuncture without a direct mechanistic explanation. Simultaneous basic science mechanistic findings, if detected, would strongly refute this claim by revealing reproducible and consistent physiological explanations. While animal studies have played a pivotal role in identifying candidate explanations and thus increasing the credibility of acupuncture, the contradictory clinical human evidence has revitalized many of the reservations held by skeptics in the medical community. To identify the pertinent physiologic mechanisms involved in the human model, clinical trials that simultaneously evaluate clinical efficacy and mechanism may provide an important methodological improvement and provide more rigorous scientific controls.

As many clinical researchers have recognized, the response to acupuncture treatments are likely embedded in a complex, multifactorial equation, including the nature of the disease, the attitude toward acupuncture, the points selected, the manner in which the needles are manipulated, and the patient’s prior experiences with acupuncture, and expectations and beliefs, and so on. Each factor can act in cooperation with or in opposition to the other factors, ultimately leading to a degree of responsiveness to treatment. To decipher this complex process, a mechanistic approach may be helpful.

Elucidation of the mechanisms of acupuncture in humans serves several important roles. It can enhance biomedical acceptance of acupuncture if a positive effect is found. As importantly, and perhaps as surprisingly, it could also create a means for dialogue between various styles of acupuncture. Present research methods do not provide common grounds for communication.
between practitioners of different acupuncture styles. These mechanistic explanations, however, may establish a "currency" to determine the worth of a particular treatment. For the first time, instead of relying on different interpretations of texts or the inertia of styles, acupuncturists would have new information to determine the worth of particular treatments, for the first time, mechanistic explanations may establish a "currency" between practitioners of different styles. These literally means "obtaining de qi," Japanese and Chinese styles.

**MECHANISTIC DIFFERENCES BETWEEN ACUPUNCTURE STYLES**

Clinical trials in acupuncture could be greatly enhanced by the use of manualized protocols and mechanistic explanations. Such a strategy could help bridge some of the gaps in acupuncture research. But in our attempt to do this, it is important to respect the variability in acupuncture and to consider the possible unique physiological effects of each style. Like tai chi and karate, each style may provide health, but by different means. To illustrate this point, we use Chinese and Japanese acupuncture as examples.

The interpretation of de qi is one of the fundamental reasons for the divergence in acupuncture approach between the Japanese and Chinese styles. De qi literally means "obtaining qi" and is an important aspect of the acupuncture discussion in The Book of Yellow Emperors: A Classic of Internal Medicine (HuangDi Neijing), the Chinese canonical medical text written circa 200 BC. The Chinese have long asserted that de qi is an acheing sensation essential for a therapeutic response. Western scientists studying acupuncture in China and their traditional colleagues theorized that de qi is mediated by the nervous system and have fortified their stance with mechanistic research demonstrating the importance of nerve stimulation in the therapeutic effect of acupuncture.

Acupuncture needling, as a result, tends to be deep and relies on manipulation techniques that elicit this de qi sensation, which can be accompanied by a tug of the needle. Japanese researchers and their traditional colleagues, on the other hand, have interpreted the Chinese texts differently and assert that de qi is a subtle signal sensed by the practitioner and not the patient. An acheing sensation is not required at all. The therapeutic effect of acupuncture, according to this physiological theory, is mediated through electrical pathways outside the nervous system. This is reflected in Japanese treatment techniques that emphasize extremely minimal interventions (such as small magnets) and aim to affect the electrical milieu of acupuncture meridians. The Japanese acupuncturist is expected to affect this electrical milieu with extreme delicacy, as if to "needle a sleeping cat without waking it."

Although it is possible that different styles function through common physiologic pathways, it is more likely that different styles affect different physiologic processes. Mechanistic studies should examine this potential for distinct mechanisms in different acupuncture approaches. Acupuncture technique may be an important determinant in the physiologic pathway involved in the healing process. Ignoring the diversity of acupuncture techniques would contribute further to our misunderstanding of acupuncture physiology.

**DIABETIC NEUROPATHY AS A MODEL**

To illustrate the usefulness of applying these principles to acupuncture research, we use diabetic neuropathy as an example. Diabetic neuropathy is a distal symmetric polyneuropathy that affects more than 30% of people who have diabetes. It presents with pain and tingling and can lead to sensory loss in the distal extremities. It generally is considered to be the most symptomatically distressing complication of diabetes. Unfortunately, present medications are largely ineffective and limited by adverse effects. For this reason, if acupuncture were proven effective, its widespread adoption into the treatment regimen would be immensely helpful for those patients needing relief. Thus far, the evidence regarding the efficacy of acupuncture for diabetic neuropathy in both human and animal studies has been encouraging. The animal studies in particular have demonstrated nerve restorative capabilities of acupuncture—a property that no present medical treatment for diabetic neuropathy can claim. Yet the call for adoption or for further studies of acupuncture is faint. The resistance to consider acupuncture as an added treatment for diabetic neuropathy stems not only from possible inherent biases but also from fundamental scientific barriers to acupuncture research.

The animal studies in acupuncture for neuropathy have been highly suggestive of acupuncture’s efficacy in treatment of diabetic neuropathy. Electroacupuncture applied to experimental diabetic rats with neuropathy resulted in a statistically significant increased pain threshold and decreased (and sometimes reversed) motor nerve conduction velocity slowing compared to both no-treatment and the transcutaneous electrical nerve stimulation (TENS) group. In other studies, electroacupuncture stimulated nerve regeneration in rats with transected or crushed sciatic nerves as demonstrated by histological evaluation and evoked electromyogram (EMG). When acupuncture was evaluated in 46 human patients with diabetic neuropathy, however, the results were encouraging, but not as impressive as the animal studies would suggest. While 77% of patients showed significant improvement in their primary or secondary symptoms, no improvement in vibration perception threshold or neuropathy disability score was noted. One possible source of the inconsistency becomes evident when the interventions are evaluated in detail. The rats in the animal studies were immobilized while an electrical current was applied to a predetermined acupuncture point. The intensities of electrical current ranged from 0.7 to 1 mAmp “to produce a visual muscle contraction.” These currents were often performed for 15 minutes every day or every other day for four to six weeks. Certainly, few patients would be willing to tolerate such stimulation.
to go through this rigorous regimen, and few acupuncturists can claim it reflects their daily practices. Conversely, the human study that evaluated acupuncture for diabetic neuropathy chose four predetermined acupuncture points as treatment. In this case also, few acupuncturists can claim this standardized intervention reflects their practices. The less than impressive results might easily be ascribed to the incomplete treatment. Either way, both acupuncturists and conventional researchers can declare that the true efficacy of acupuncture as treatment for diabetic neuropathy remains unclear despite these studies. How one acupuncture style would perform relative to another remains unanswered as well. These difficulties once again highlight the gaps described above.

A clinical trial that simultaneously evaluated the clinical efficacy and physiologic effects of various acupuncture styles for treatment of diabetic neuropathy would be useful. This combined approach would help clarify some unanswered questions, such as, what is the effect of acupuncture on neuropathic pain? What is its effect on lower extremity sensation? What mechanisms are responsible for both of these situations if acupuncture is demonstrated to be helpful? In addition, by evaluating more than one style, it is possible to study whether different styles have maximal effect in different disease presentations.

To test this hypothesis, diabetic neuropathy is an exceptionally rich model. Diabetic neuropathy is a heterogenic process that involves multiple pathophysiologic causes. The putative causes include autoimmune, vascular, and metabolic processes, which, over time, contribute to damage to nerve fibers.56 Diabetic neuropathy is also unique in that it is one of the few conditions (other than heavy metal toxicity and HIV neuropathy) in which both small and large nerve fibers are affected.4 Small fiber damage leads to neuropathic pain, while large fiber damage leads to loss of sensation. This heterogeneous presentation allows us to evaluate the effect of each acupuncture style on the various aspects of disease. Pain diaries and quantitative sensory testing can be used to measure neuropathic pain and lower extremity sensations, respectively. These outcome measures may reveal whether traditional Chinese acupuncture works best to relieve pain, while the Japanese meridian acupuncture works best to increase nerve sensation, or vice versa. Conceivably, modern physiology could significantly contribute to a debate about two important interpretations of "de qi." If differences are observed between styles, then physiologic markers, such as interleukin-2, interleukin-6, and C-reactive protein for inflammation; endothelin-1 for vascular physiology; or heart rate variability for autonomic nerve function may reveal why these differences occur. One style may more readily affect a particular physiologic process and thus affect the clinical presentation. These markers may have the additional advantage of identifying acupuncture points or other variables responsible for the changes in clinical outcome.

CHALLENGES TO ADOPTING AN EXPANDED MODEL OF ACUPUNCTURE RESEARCH

The incorporation of multiple acupuncture styles, manualized protocols, and mechanistic explanations into acupuncture trials possesses serious challenges. First, the use of multiple acupuncture styles presents challenges in the design of an appropriate control. Given the varied interventions used by different styles, the designation of a control that matches both styles will be difficult but theoretically achievable. A control that incorporates inactive representations from both styles is a potential option, but further exploration and investigation are warranted. Second, the proper selection and interpretation of mechanistic markers are crucial to ensure that these markers link directly and specifically to the symptoms and diseases investigated. Given the many physiologic effects of acupuncture, markers have the potential to confound rather than enlighten. Researchers are encouraged to select and interpret the markers carefully. Modern technologies, such as functional magnetic resonance imaging, are potent tools for providing mechanistic insights, but should be subject to the same standard. Last and foremost are the extenuating resources required to complete this type of trial. It requires multiple arms and thus more patients, use of basic science tools, recruitment of experts who can create manualized protocols, and recruitment of acupuncturists from various styles, which all translate to higher costs and more time. We must ask whether this increased experimental burden is balanced by the increased rigorous scientific knowledge that these methods can provide. The lack of substantial progress in acupuncture research (despite the large funding already provided for acupuncture research compared to other complementary therapies) may suggest that the extra research resources are best served producing useable data as opposed to more contradictory evidence. One possible solution is to use these methods to research conditions that have demonstrated modest benefits in previously well-designed animal or human studies. This ensures that resources are not being spent unnecessarily on trials that have low probability of success.

CONCLUSION

Research in animal and human models has greatly enhanced our understanding of acupuncture. It can be argued, however, that despite our continued efforts, we have reached an evidence impasse. Our present track has left fundamental gaps unaddressed, and as a result, each additional study simply adds motion to the cogwheel of contradictions. To advance our understanding of acupuncture, the gaps between biomedicine and Eastern medicine, between acupuncture styles, and between animal and human studies need to be addressed. With the use of manualized protocols and clinical trials linked with mechanistic testing, we can bridge these gaps and create healthy, respectful dialogues between biomedical practitioners and acupuncturists and among acupuncturists themselves.

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