

Unanticipated Insights into Biomedicine from the Study of Acupuncture

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Abstract

Research into acupuncture has had ripple effects beyond the field of acupuncture. This paper identifies five exemplars to illustrate that there is tangible evidence of the way insights gleaned from acupuncture research have informed biomedical research, practice, or policy. The first exemplar documents how early research into acupuncture analgesia has expanded into neuroimaging research, broadening physiologic understanding and treatment of chronic pain. The second describes how the acupuncture needle has become a tool to enhance biomedical knowledge of connective tissue. The third exemplar, which illustrates use of a modified acupuncture needle as a sham device, focuses on emergent understanding of placebo effects and, in turn, on insights into therapeutic encounters in treatments unrelated to acupuncture. The fourth exemplar documents that two medical devices now in widespread use were inspired by acupuncture: transcutaneous electrical nerve stimulators for pain control and anti-nausea wrist bands. The final exemplar describes how pragmatic clinical trial designs applied in acupuncture research have informed current general interest in comparative effectiveness research. In conclusion, these exemplars of unanticipated outcomes of acupuncture research comprise an additional rationale for continued support of basic and clinical research evaluating acupuncture and other under-researched therapies.

Background

WITHIN THE HISTORY OF MEDICINE, there are examples of scientific discoveries that emerged from unrelated or marginally related research. Such events often result from cross-fertilization of ideas, as for example when the emergent

concept of autoimmunity catalyzed the shift in understanding of type 1 diabetes from a genetically determined endocrine imbalance to an organ-specific autoimmune disorder.¹ New ideas also arise when research efforts to target specific questions reveal unexpected findings, for example, the effectiveness of sildenafil for treating erectile dysfunction

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(observed during its testing for coronary artery disease) and iproniazid, an early treatment for depression (during testing as a chemotherapeutic agent for tuberculosis).² The present paper examines results from acupuncture research that have affected biomedicine.

A major impetus to acupuncture research in the United States occurred in 1998, when the National Center for Complementary and Alternative Medicine (now the National Center for Complementary and Integrative Health) was established within the National Institutes of Health (NIH). This support has led to important research findings regarding acupuncture's effectiveness,³ as well as advances in the understanding of acupuncture's mechanisms of action.⁴ Despite this considerable progress, debate remains regarding the interpretation and acceptance of the evidence base for acupuncture and the value of future research.^{5,6} Missing from these reviews and discussions is a consideration of the often unexpected and broad-reaching discoveries that emerge when the traditions of biomedicine and acupuncture meet in the context of objective and systematic scientific exploration.

This paper documents how ripple effects of acupuncture research have traveled beyond the field of acupuncture to affect several aspects of biomedicine. Specifically, acupuncture research has (1) expanded scientific and clinical knowledge in the fields of chronic pain, connective tissue, and placebo effects; (2) spawned the design of novel medical devices, which have increased treatment options in the areas of pain control and nausea suppression; and (3) furthered the development of research methods through the design and implementation of pragmatic clinical trials for chronic pain. Few are aware of the origins and pathways of these developments because they are now sufficiently integrated within the knowledge base and practice of biomedicine. The paper concludes by proposing that these exemplars provide evidence that acupuncture research has broadened biomedical understanding with regard to research, practice, and policy, as well as strengthening the case for continued support of basic and clinical research evaluating acupuncture and other underresearched therapies.

Exemplars

Acupuncture, endorphins, and analgesia research

Among the earliest research findings pertinent to both acupuncture and biomedicine are the demonstrations in animal models and humans that acupuncture analgesia is mediated in part by endogenous opioids.^{7,8} These findings, including similar pharmacologic sensitivities of morphine analgesia and acupuncture analgesia and results indicating that different types of "endorphins" are released by different frequencies of electro-acupuncture, generated substantial interest within the biomedical community. Timely reviews appeared in high-profile journals,^{9,10} and the acupuncture/endogenous opioid connection was endorsed at the 1997 NIH Consensus Conference on Acupuncture.¹¹

More recently, biomedical research on pain has seen significant contributions from acupuncture neuroimaging research.^{4,12} For example, positron emission tomography detected an increase of mu-opioid receptor-binding potential in multiple brain regions that correlated with acupuncture-associated reduction in fibromyalgia pain.¹³ This specific

demonstration of altered brain activity in patients with fibromyalgia has been cited as an important precedent in studies on the pathophysiology of other chronic pain conditions.^{14,15}

In a functional magnetic resonance imaging study, patients with carpal tunnel syndrome whose subjective and objective symptoms improved following acupuncture demonstrated a return to normal mapping of their carpal tunnel syndrome-affected digits on the primary somatosensory cortex (S1).¹⁶ This finding of central nervous system-related peripheral pathology has been referenced in publications on neuroplasticity in carpal tunnel syndrome^{17,18} and neuropathic pain.¹⁹

Acupuncture neuroimaging research has also identified a novel brain-based marker for clinical pain perception. Patients with fibromyalgia show elevation of an intrinsic brain connectivity marker that correlates significantly with pain intensity²⁰ and is normalized following successful acupuncture analgesia therapy.²¹ This research has been cited in several recent reviews for its importance as an objective biological marker for pain neuroimaging research.²²⁻²⁴

The translational acupuncture research examples summarized above have contributed to the development of broader clinical guidelines and reimbursement policies related to pain, and to the use of acupuncture as an intervention within mainstream medicine. With an increased public profile and insurance reimbursement, pain is now the leading indication for acupuncture use, as revealed in surveys from the United States²⁵ and Europe.²⁶ Use has increased in parallel with greater acceptance of acupuncture by physicians and allied specialists. For example, in the United Kingdom about one third of the 4 million annual acupuncture sessions are provided (free at point of delivery) within the National Health Service by biomedical practitioners (doctors and physiotherapists).²⁷ In Germany, around 30,000 physicians, some of whom contributed to high-profile randomized controlled trials of acupuncture for chronic pain,²⁸ currently provide acupuncture, which is reimbursed by public health insurance.²⁹

Connective tissue in health and disease

Connective tissue has long been the orphan child of medicine. Although it is part of the musculoskeletal system, connective tissue is basically absent from orthopedic and rheumatology textbooks, which are principally concerned with bones, muscles, and cartilage. In current textbooks, the nonspecialized connective tissues forming the fascia that envelop all muscles, nerves bones, and blood vessels are typically allotted a short paragraph, if mentioned at all. Although the consequence of connective tissue injury—scarring and adhesion formation—is well recognized, the secondary effects of these adhesions, in particular their relevance to chronic pain, is little discussed.³⁰

However, interest in connective tissue has been growing, and acupuncture research has contributed to this trend within biomedicine. One area that has attracted researchers to this field has been the study of mechanotransduction, or the mechanisms by which cells perceive, interpret, and respond to mechanical forces present in tissues.³¹ Through specialized protein complexes, cells sense outside forces and "transduce" these mechanical signals into cellular responses, such

as activation/deactivation of signaling molecules, translocation of transcription factors into the nucleus, and changes in gene expression. But current research on mechanotransduction has a well-recognized limitation: Almost all of its knowledge is derived from cultured cells. Extension of this work into whole, live tissue has resulted from studies in which the acupuncture needle provides a method to deliver a precise mechanical signal that can produce dose-dependent responses in areolar connective tissue fibroblasts.^{32,33} Sustained stretching of tissue is inherent to this response and has been shown to cause local purinergic signaling and active, cell-mediated tissue relaxation.³⁴ Before experiments with the acupuncture needle, these functions of fibroblasts were unknown. Thus, novel insights gleaned from acupuncture-related research have led to an improved understanding of basic mechanobiology.^{31,35–37}

Acupuncture-related studies on connective tissue also have contributed to a resurgence of interest and greater understanding of connective tissue pathology associated with chronic musculoskeletal pain and fibrotic diseases.^{38,39} The areolar connective tissue layers that wind around the needle and respond to acupuncture needle manipulation are the same layers that normally allow gliding between adjacent layers of fascia during normal movement and become abnormal in musculoskeletal pain.⁴⁰ Recent ultrasound studies have shown that the connective tissues surrounding the muscles of the back are thicker in people with chronic low back pain than in control participants without back pain⁴¹; similar results have been reported in patients with chronic pelvic pain.⁴²

These insights and new avenues of investigation into mechanobiology and connective tissue pathophysiology are not likely to have occurred without the initial research that used acupuncture needles to interact specifically with loose connective tissue.

Toward a better understanding of placebo effects

Placebo effects, or nonspecific treatment effects, occur in preclinical research, clinical practice, and randomized controlled clinical trials, with large effect sizes in functional disorders such as chronic pain⁴³ and depression.⁴⁴ This section highlights how acupuncture research on chronic pain has contributed to the understanding and potential clinical use of placebo effects in biomedicine.

The use of the sham acupuncture needle as a unique placebo device has assisted researchers in identifying key components of treatment that may enhance the effect of placebo. In a seminal study by Kaptchuk et al., patients with irritable bowel syndrome reported increasing symptom relief with escalating “doses” of placebo: observation alone, observation plus sham acupuncture, and observation plus sham acupuncture plus positive patient-provider relationship.⁴⁵ This study has significantly affected the field of gastroenterology, enhancing appreciation of the doctor as a “walking placebo,”⁴⁶ and highlighting the potential that arises from placebo research for patients with chronic abdominal symptoms.⁴⁷ This specific line of research in irritable bowel syndrome also set the stage for exploring genomic effects on placebo response,⁴⁸ addressing ethical questions related to placebo effects,⁴⁹ the first open-label placebo pill study,⁵⁰ and other novel placebo study research designs.⁵¹

Acupuncture research has also been credited with identifying serum and genetic biomarkers associated with the placebo response.⁵² These markers include serum osteoprotegerin and tumor necrosis factor–related weak inducer of apoptosis⁵³ as well as catecholamine O-methyl transferase functional val158met polymorphism.⁴⁸

In summary, acupuncture research has contributed to the renewed interest in the role of placebo in clinical care and has helped advance placebo research in three major areas: (1) the rate and the degree of response to placebo, which can be high, leading to prolonged symptom (often pain) relief in up to half of the participants^{52,54}; (2) the important role of the provider-patient relationship in the therapeutic response to placebo^{45,55}; and (3) identification of additional biomarkers associated with placebo response.^{53,56} These innovative findings provide a scientific basis for ethically enhancing the placebo effect in the clinical setting by strengthening the provider-patient relationship (e.g., communications and clear explanation of possible benefits of a treatment^{46,54}) and by optimizing the therapeutic environment and rituals.⁴⁹

Acupuncture-related devices that have affected biomedicine

The development of several currently used biomedical devices has clear links to acupuncture-related research. This section highlights two widely used devices: transcutaneous electrical nerve stimulation (TENS) units for analgesia and acupressure bands for relief of nausea.

Acupuncture and TENS. The modern TENS unit as a means of pain relief was developed from a technique of dorsal column electroanalgesia by C. Norman Shealy, MD, in the early 1970s.^{57,58} According to Shealy, “I began stimulating acupuncture needles with electrical energy in the mid 60’s. Later, without needles, I introduced TENS.”⁵⁹ This led to a TENS patent issued to Medtronic in 1974.⁶⁰

In the United States, TENS is a reimbursable medical procedure for pain relief in both private and public insurance sectors. In the private sector, TENS is coded based on the American Medical Association (AMA) Current Procedural Terminology (CPT 97014 or 64550) and in the public sector based on the AMA’s Healthcare Common Procedure Coding System (HCPCS- G0283).⁶¹ The effect of TENS on the medical field at large is also reflected in U.S.-based insurance guidelines; for example, Blue Cross–Blue Shield Association currently supports the use of this device for chronic spinal pain (neck or back).⁶² TENS devices have received U.S. Food and Drug Administration (FDA) approval for both pain relief and the prevention of pain.⁶³

Acupuncture and acupressure bands. Numerous acupressure devices (e.g., Sea-Band® Sea-Band Ltd., Leicestershire, United Kingdom) are available on the open market, most often sold as a means to relieve nausea and vomiting. The history of these devices is inseparably linked to the clinical practice of acupuncture and acupressure, with clinical research reinforcing their acceptance. The earliest research trials were initiated in Ireland by J.W. Dundee, who had observed physicians in China teaching patients to press on acupuncture point PC6, located on the inner wrist.⁶⁴

Dundee and colleagues were among the first to conduct randomized controlled trials to demonstrate the antiemetic effectiveness of acupuncture,⁶⁵ a finding replicated with manual acupressure using a wristband device.⁶⁶ Numerous subsequent acupuncture and acupressure trials have been evaluated in systematic reviews of nausea and emesis associated with postoperative recovery⁶⁷ and chemotherapy.⁶⁸

The 1997 NIH Consensus Conference on Acupuncture reported promising results from stimulation of PC6 for postoperative and chemotherapy-related nausea and vomiting.¹¹ Several PC6 acupressure stimulation devices have received FDA approval for nausea control and are now available on the open market.⁶⁹

The common use of these acupressure devices, combined with clinical research results, has translated into several international clinical guidelines within biomedicine recommending acupressure. Such guidelines include those of the Society of Obstetrics & Gynecology of Canada on the management of nausea and vomiting in pregnancy,⁷⁰ the U.S. Agency for Healthcare Research and Quality,⁷¹ and the United Kingdom's National Institute for Health and Care Excellence (NICE).^{72,73}

Pragmatic clinical trials

The evolution of clinical research in biomedicine toward more pragmatic randomized controlled trials, a method often encouraged in comparative effectiveness research,⁷⁴ was informed by earlier research involving pragmatic trials of acupuncture for chronic pain conditions in the United Kingdom with recruitment starting in 1999^{75,76} and in Germany starting in 2001.²⁸ The need for a more pragmatic approach was supported in 2003 by Tunis and colleagues,⁷⁷ who argued that there was a paucity of published research designed to directly answer questions faced by policymakers, clinicians, and patients. Most trials, they observed, used efficacy or explanatory designs that evaluated the degree to which a specific component of an intervention can outperform a placebo or sham procedure. Their recommendations to increase the value of clinical research for decision-making in health policy and practice included placing a higher priority on pragmatic (practical) clinical trials.

The York Acupuncture for Back Pain trial provides an example of how a pragmatic acupuncture trial has been influential beyond the field of acupuncture research. The trial, in which 241 patients received a short course of up to 10 acupuncture sessions plus usual care or usual care alone, provided evidence that acupuncture is both clinically effective and cost-effective at 24 months after randomization.⁷⁵ This study was cited as the exemplar of a "highly pragmatic" trial in the Consolidated Standards of Reporting Trials statement extension for pragmatic trials, published in 2008.⁷⁸

Since 2009, comparative effectiveness research, which compares at least two interventions, each with the potential to be "best practice," has been promoted by the U.S.-based Institute of Medicine, much along the same lines as the United Kingdom and German trials, with a focus on assisting consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve healthcare at both the individual and population levels.⁷⁴ To this end, pragmatic trials are featured by the Institute of Medicine as one of the

most important research methods within comparative effectiveness research. The recently created Patient-Centered Outcomes Research Institute, which directly supports large pragmatic trials to evaluate patient-centered outcomes,⁷⁹ reflects the expanding interest in pragmatic trials.

The United Kingdom pragmatic trials of acupuncture for back pain⁷⁵ and for chronic headache and migraine⁷⁶ both demonstrated clear evidence of cost-effectiveness as well as clinical effectiveness.^{80,81} As a result, these trials contributed to a major shift in health policy within biomedicine. Both were cited by NICE as providing key evidence for the NICE recommendations that acupuncture should be offered within the National Health Service as an option for both persistent low back pain⁸² and headache/migraine.⁸³ The findings of the German acupuncture trials²⁸ contributed to a 2006 decision by that country's health authorities in favor of insurance-based reimbursement to physicians providing acupuncture for osteoarthritis of the knee and chronic low back pain.²⁹

Discussion

To the authors' knowledge, this is the first attempt to consider the effect of acupuncture research beyond the field of acupuncture itself, in particular its effect on research, practice, and healthcare policy within contemporary biomedicine. This article sought not only to identify the clearest examples of this scientific cross-fertilization but also to present a variety of topic areas not limited to different conditions for which acupuncture efficacy or effectiveness has been assessed. Thus, while this article described the effect of acupuncture research on biomedical understanding of chronic pain conditions and on the emerging role of connective tissue, it also documented clear instances of effects in the disparate areas of medical devices, placebo effects, and research methods.

Central to this paper is the question of how to define and recognize "effect." An initial realization was that the varied nature of the included topics would preclude an across-the-board application of a single criterion. Nevertheless, the consensus position was to seek tangible indications that information gleaned from acupuncture research had broadened the biomedical framework in regard to research, practice, or policy. Following this guideline, this article described, for example, how research on connective tissue has been advanced by use of the acupuncture needle as a probe in intact tissue. In the realm of practice and policy, we described two acupuncture-related devices that have received FDA approval as effective treatment options within mainstream medicine.

Similar findings of significant insights have been reported in other areas of research, especially in the scientific evaluation of poorly understood phenomena. Promise of novel "spin-offs" was a key argument underlying funding and investment in the NIH Office of Rare Diseases.⁸⁴ As an example, the Wyss Institute for Biologically Inspired Engineering, on the Harvard Medical School campus, has consciously fostered cross-disciplinary research by assembling a diverse faculty that "uses Nature's design principles to develop bio-inspired materials and devices that will transform medicine and create a more sustainable world."⁸⁵ Similarly, the Media Lab on the Massachusetts Institute of

Technology campus actively promotes an “antidisciplinary culture, encouraging the mixing and matching of seemingly disparate research areas” to create “disruptive technologies.”⁸⁶ In light of such institutional efforts to foster “silo-busting” research, conscious efforts to engender unanticipated insights should be considered as future research investment strategies for acupuncture and other under-researched therapies.

This review has limitations. It is a narrative one based on exemplars rather than a systematic review or an exhaustive presentation on all such instances of acupuncture influencing biomedicine. The authors are potentially influenced by their own research and clinical expertise. Additionally, this article has not explicitly explored the many ways that biomedicine has influenced acupuncture.

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