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REVIEW ARTICLE

Acupuncture and the Emerging Evidence Base: Contrived Controversy and Rational Debate

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Abstract
The rising incidence of chronic disease and stress-related illness in the West, coupled with an expanding awareness of the unwanted side effects of pharmaceutical treatment, has led to an increased utilization of acupuncture as a contemporary health care option. This increase in utilization, in turn, has paralleled a response to the call for evidence, with the result that acupuncture is now supported by a broad range of surveys of safety, clinical trials and basic science studies of physiologic action. The combined impact of these studies is linked to a growing acceptance of this traditional medical practice. The present review takes a wide-angle look at these three major areas of acupuncture research, namely: safety and the risks of serious adverse events; clinical efficacy and effectiveness; and physiologic action. We identify advances in knowledge and present a point counterpoint approach to controversial issues, with the aim of offering clarification if not a measure of resolution.

1. Introduction

Over the major portion of its several millennia history, acupuncture and its traditional sister modalities have evolved as "experience-based medicine." Through astute and iterative observations combined with inductive reasoning, what "worked" was retained and often modified; what did not work was discarded. This pattern of continuous use of acupuncture in East Asia and more recently throughout the world, involving what must be thousands of millions of treatments, has led to the assumption that acupuncture is a relatively effective and safe procedure. Only recently, with the call for evidence based medicine, has acupuncture been tested at the forges of modern medicine: systematic evaluation of effectiveness, monitoring of adverse events, and exploration of underlying physiology. In this review we highlight a number of controversial issues and identify potential resolutions in the context of the evidence base for acupuncture.

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2. Acupuncture and the risks of serious adverse events

Given that acupuncture is already in widespread use, determination of its safety should be one of the initial tasks in establishing an evidence base [1]. We know that acupuncture can cause serious adverse events. A prime example, it can be recalled, was a hepatitis B outbreak in the United States in the 1980s, which was tracked down by public health officials as involving cross-infection due to unsterilized acupuncture needles. This was prior to the 1996 classification of the acupuncture needle in the United States as a safe and effective medical device, which applied solely and specifically to single-use disposable needles [2]. However, in the development of a strategy for assessing the incidence of acupuncture-related adverse events, it should be noted that case reports, while an important means of communication within the health care community, are not necessarily a reliable source on which to base current generalizations regarding either clinical effectiveness or clinical safety. Such case reports of benefits or harms most often serve as useful alerts but must be carefully examined to assess the likelihood that outcomes were truly related to acupuncture rather than, for example, to a concurrent life event of the patient. As a cautionary tale, authors of a systematic review documented case reports of individuals whose lives seemed to have been put at risk by acupuncture [3]. This was picked up by Men's Health (UK), which ran an article with the headline, "Can Complementary Medicine Kill You?" [4]. When tracking down the original reports of serious adverse events, it became clear that not all events were associated with the practice of acupuncture. For example, in one case from 1965, an 82-year-old Hungarian émigré, who was found dead in her home in New York, had self-inserted a sewing needle, which had then pierced her own heart [5]. Journalists who have an interest in manufacturing controversy about the safety of acupuncture continue to cite this case as a death caused by acupuncture [6] but without presenting the relevant context, namely that this tragic event had nothing to do with the modern day practice of acupuncture.

A second major concern about case reports of acupuncture adverse events arises when they are presented with no attention to frequency of occurrence. It is essential when quantifying risk to relate it to a denominator, in order to estimate frequency [7]. Without such data, case reports on acupuncture adverse events can appear to exaggerate the risks. For example, a paper titled, "Acupuncture — a treatment to die for" has content that includes the speculation, "Thus, the true number of fatalities is anybody's guess. Arguably, the published data merely depict the tip of the iceberg" [8]. A more recent paper in the journal *Pain* continues to amplify concerns about acupuncture safety by highlighting five individual fatalities [9]. By citing only the evidence on individual cases, the authors are misleading in their use of data relating to the safety of acupuncture. The five fatalities referred to above need to be understood in terms of how often such events occur. Is it five out of five hundred or five out of five million? Without providing an estimate of risk based on frequency or incidence rates, the reader can be left with a questionable impression of the prevalence of acupuncture harms.

The recent reviews of case reports of serious adverse events are even more disingenuous in light of the substantive literature, spanning more than a decade, which has quantified the incidence rates of such occurrences. Reliable data is available from independent prospective surveys of acupuncture safety conducted in the United Kingdom [10,11], Germany [12,13], Japan [14], Norway [15] and Australia [16]. In two surveys from the United Kingdom, which covered a total of more than 60,000 acupuncture sessions, no serious adverse events were associated with acupuncture, either when provided by traditional acupuncturists [10], or by physicians and physiotherapists [11]. In a larger-scale survey in Germany, 9,429 German physicians providing 760,000 acupuncture treatments reported two cases of pneumothorax, one of an exacerbation of depression, one acute hypertensive crisis, one vasovagal reaction, and one asthma attack with hypertension and angina [12]. In another large survey with 2.2 million consecutive acupuncture treatments provided for 229,230 patients, two patients were found to have had a pneumothorax (life threatening for neither patient), and one lower limb nerve injury that persisted for 180 days [13]. These prospective surveys, which provide a considerably higher level of evidence than case reports, confirm that serious adverse events after acupuncture are uncommon and patient deaths resulting from them are extremely rare.

When comparisons are made between the safety of acupuncture and the safety of prescribed medication, the inappropriate focus on individual cases instead of incidence rates can lead to highly misleading claims. For example, an editorial in *Pain*, which reviews a report on individual cases [9], concludes that acupuncture "can be dangerous" because, "If the 57 systematic reviews had been for a prescription drug and a similar list of serious adverse effects had been reported for that drug, we would hesitate to prescribe that drug" [17]. Basing such an assertion on individual case reports is unmerited. Once again, in the absence of frequency estimates, no meaningful comparison can be made with the safety of prescribed medication. In a review of deaths in the United Kingdom from chronic usage of NSAIDs causing internal bleeding or perforated gastroduodenal ulcers, a rigorous study found that, "On average, one in 1200 patients taking NSAIDs for at least 2 months will die from gastroduodenal complications, who would not have died had they not taken NSAIDs" [18]. The authors extrapolated these data to estimate that NSAIDs cause the deaths of 2000 people a year in the United Kingdom [18], a number that clearly contradicts the above cited claim that acupuncture is not as safe as prescribed medication. The continued reporting of individual cases might have its uses, for example highlighting specific concerns, but it provides no basis for assessing the safety of acupuncture in everyday practice.

While not the focus of this review, we note that reporting rates for non-serious adverse events of acupuncture are also remarkably low. Though there has been variability in definitions and methods of collecting these data, nevertheless we can estimate that non-serious adverse events, such as fainting, local needle pain and exacerbation of existing symptoms, occur at a frequency of 10 to 100 per 10,000 treatments [10—13,16,19].

To conclude, individual case reports have been used to amplify concerns about the safety of acupuncture. By contrast, the available evidence on incidence rates from large-scale prospective surveys shows that serious adverse events and fatalities appear to be rare. A clear conclusion from such an evidence-based approach is that acupuncture remains safe in competent hands [20].

3. Efficacy and effectiveness of acupuncture

Concerns about safety are often linked to questions regarding the risk/benefit ratio; at one extreme, "if there is no benefit, any risk is too much" [17]. As might be expected, the controversy around safety discussed above is paralleled by uncertainties as to whether acupuncture is beneficial. The concerns are reflected in two main questions: Is acupuncture associated with any overall benefit? And, does acupuncture have any effect beyond a placebo? With regard to the first, a recent overview of systematic reviews by Ernst and colleagues concludes: "Numerous reviews have produced little convincing evidence that acupuncture is effective in reducing pain" [9]. With regard to the second, Madsen and colleagues [21] have stated that "the effects of acupuncture cannot be clearly distinguished from bias and that it is unclear whether needling at acupuncture points relieves pain independently of the psychological impact of the treatment ritual." This implies that acupuncture might simply be a placebo. The validity of these assertions regarding overall benefit and benefit beyond placebo is important, since an unbiased assessment of the evidence base is essential if we are to inform patients, practitioners and policy makers with sound judgements about acupuncture.

To clarify the discussion, it is useful to distinguish between efficacy and effectiveness. Effectiveness is a measure of the overall impact of an intervention on outcome, as would be expected to occur in routine care, with an emphasis on generalisability. Efficacy is a measure of the impact of an intervention on outcome in as ideal conditions as possible, with an emphasis on controlling for placebo effects, thereby limiting the effects of bias. When evaluating effectiveness, a comparative design is commonly used, in which acupuncture is compared to another active treatment. It should be noted that many trials have three-arm designs, including both sham and an active comparison treatment, because the researchers are attempting to address the questions of efficacy and effectiveness in the same trial. The effectiveness/efficacy dichotomy provides a useful perspective on the evidence base, since it provides a framework for exploring the extent to which acupuncture treatment has an effect beyond the placebo as well as real-world benefit.

Looking first at the question of effectiveness, it is best to begin by examining results of meta-analyses, an evaluative approach that pools data from multiple trials with similar designs. This approach generates a higher level of evidence than when data is not pooled, as is usually the case in systematic reviews of individual trials or even in systematic reviews of systematic reviews, the approach used by Ernst and colleagues [9]. When using such meta-analyses, where there is sufficient homogeneity between trials, sound evidence has been found that acupuncture is more effective than non-acupuncture controls (wait-list, standard care, usual care, or no treatment) for the conditions of low back pain [22], migraine/headache [23,24] and osteoarthritis of the knee [25]. While effect sizes were moderate, of the order of 0.5, they can be regarded as indicative of clinical relevance [26]. As the number of clinical trials of acupuncture continues to increase, it can be expected that meta-analyses will also become available for conditions beyond chronic pain.

On the question of efficacy, we can draw on the evidence from acupuncture trials that have included at least one sham-controlled arm, thereby assessing the difference between verum and sham acupuncture. Once again the pooled data from meta-analyses provide the best evidence, subject to the caveat outlined above, that such analyses require at least two sufficiently high quality trials with adequate homogeneity. What has been found in a recent review [27] is that outcomes of sham-controlled trials provide evidence for the efficacy of acupuncture over the short and longer term for osteoarthritis of the knee [25,28,29] and headache [23,30,31] and, over the short-term only, for low back pain [22]; longer-term evidence for low back pain is equivocal. A small yet significant difference in favor of verum over sham acupuncture was again found for a range of pain conditions [21]. Across these reviews, the effect sizes associated with acupuncture when compared to sham acupuncture are small, often in the range of 0.15—0.25. As one might expect, the effect sizes related to efficacy are smaller than those related to effectiveness - around half the size. The difference (between 0.5 and 0.2) can be ascribed to "context effects," namely the impact of the ambiance of the practice setting, the time and quality of attention provided by the practitioner and the expectations of the patient, which in other fields are known to be associated with effect sizes of around 0.3 [32].

In summary, while uncertainty remains for many conditions, the growing evidence on acupuncture for chronic pain indicates that acupuncture is effective with an impact that is clinically relevant. When comparing acupuncture to sham acupuncture, again the emerging evidence indicates that, at least for several chronic pain conditions, acupuncture is significantly associated with improved outcomes. It is possible to distinguish these benefits from bias because the evidence is based primarily on pooled data from meta-analyses.

4. Physiology of acupuncture

Understanding the physiological basis of acupuncture is a long-standing goal of laboratories and clinics both East and West. Such research appears to have taken two main paths: the search for biochemical and physiologic endpoints ("biomarkers") whose concentrations and/or activity change in response to needling, and the exploration of how the biomedical model can describe and explain phenomena based in the traditional paradigm of acupuncture. While each path is notable for its progress and promise, each has been constrained by its methods and models.

The first of these research paths has led to numerous identifications of acupuncture-related biomarkers,

including antinociceptive endogenous opioids [33,34], immune system markers [35,36], cardiovascular activity [37], gastrointestinal function [38] and fMRI-detected brain activity [39]. Biomarker outcomes, however, are more revealing of correlations (i.e. when needling occurs, changes can be detected) than mechanisms. Reviews of acupuncture from China [40,41] and the West [42,43] continue to use the overarching term 'mechanism' but focus almost entirely on "correlates." For example, while the call for "a complete and plausible mechanism through which to understand its [acupuncture's] clinical effects" is representative of a generally held goal, the major focus of most reviews is on downstream biomarkers with little attention to the sequence of needling-initiated steps that result in the biomarker changes. Such a stepwise approach was followed to a limited extent to map pathways related to acupuncture-induced analgesia [33] and cardiovascular regulation [43].

The second research path, more directly aimed at defining mechanisms, has involved a search for anatomical, biochemical and physiological bases of acupuncture phenomena, including those associated with acupuncture points and meridians. Questions guiding these research efforts include: what is an acupuncture point; what does the needle initially stimulate; and, what local and systemic changes occur in response to needling? And, do meridians have a physical basis and what is the nature of the 'acu-signals' they carry?

This general approach holds considerable promise but a cautionary note seems warranted: the frequently stated conviction that a 'neurocentric' model can best explain acupuncture's actions may prove too limited a perspective. For example, as recently opined, "In this view [the neural hypothesis], meridians and their associated acupoints would be considered as simply road maps that help guide the practitioner where to stimulate to achieve the best clinical results. However, it is the stimulation of the underlying neural pathways that can account for the physiological effects and clinical responses to acupuncture in patients" [44]. For the present review, evidence in support of the neural hypothesis will be presented, where feasible, together with data supportive of the emerging view of loose connective tissue (fascia) as an alternative biomedical underpinning of acupuncture's traditional landmarks.

While no unique anatomical structure, e.g., a specialized type of nerve ending, has been identified at cutaneous sites corresponding to acupuncture points, several studies have described an association of known morphological structures with acupoints. A large proportion of traditional acupuncture points have been identified as sites at which underlying nerve-vessel bundles wrapped in a loose sheath of connective tissue penetrate the fascia to reach the outer dermal layers [45,46]. A subsequent study of 24 acupoints on 6 meridians demonstrated a high correspondence between the sites of acupuncture points and the location of loose connective tissue planes [47].

Acupuncture point structures *per se* have been reported in studies utilizing high-intensity ultrasound, with ovoid images proposed as acupoints localized in connective tissue [48,49]. In light of the several lines of evidence suggesting a connective tissue basis for acupoints, the oft-cited findings that injection of local anesthetic into an acupoint blocks responsiveness of the point to needle stimulation [50,51] should be re-examined by testing for effects of local anesthetics on connective tissue function.

On the broad spectrum of research aimed at the characterization of acupoints, electrodermal activity (EDA) continues as one of the more frequently examined and controversial endpoints. Becker's use of a 36-electrode square grid, revealing acupoints as the summits of individually contoured conductivity fields, remains one of the seminal contributions to this field [52]. Recent reviews have highlighted the experimental and physiological confounders to such measurements [53] and have systematically evaluated studies comparing EDA at acupoints relative to non-acupoint sites in healthy volunteers [54]. In this latter review, five of nine studies that met inclusion criteria for design and reporting showed a positive association for acupuncture points as sites of lower electrical resistance and impedance. The relation of acupoint EDA to pathology is described in a recent narrative review [55]. Among the included trials was a blinded study in which EDA at auricular acupuncture points distinguished patients with recent or prior cardiopathology from healthy controls [56].

The abundance of sensory nerve endings in the skin, the experimental recording of neural activity following needle insertion, and numerous correlations between neuromodulatory endogenous opioids and acupuncture-induced pain modulation were major factors that led researchers to develop elegant models depicting pathways of acupuncture analgesia through the peripheral and central nervous systems [33,34]. Such research had a strong influence on the thinking that acupuncture effects in general, not just its analgesic activity, could be mapped onto the nervous system [44,57]. Striking confirmation of neural involvement in acupuncture stems from medical imaging research [39,58]. Patterns of fMRI and PET signals have been detected following acupuncture that are distinct from patterns evoked by simple sensory stimuli or expectation (placebo) [59,60]. Nonetheless, while detection of brain activity consequent to needle stimulation reveals the brain as an endogenous monitor of acupuncture actions, it does not necessarily follow that neural activity, including sensory nerve ending activation, is the initiator of these physiological events.

As mentioned above, considerable evidence has accumulated for an interstitial connective tissue-based system as an additional or alternative mediator of acupuncture activity. Indications of superficial fascia as the initial 'response element' to needle stimulation include an apparent wrapping of collagen fibers around the needle that may explain the 'needle grasp' phenomenon of acupuncture practice [61], as well as a weakening of mechanical and clinical responses to needling (in rats) following acupoint injection of collagenase [62]. Observations that needling also induces local changes in blood flow [63], which may result from acupuncture-related peripheral increases in nitric oxide [64,65], and the proposed role of needling-induced peripheral release of ATP as an intermediary signal molecule between connective tissue and sensory nerve endings [66,67] await future research to clarify the sequence of events underlying the transduction of acupuncture stimulation to acupuncture signaling.

In summary, the neural hypothesis of meridians rests in large part on observations that a number of key acupoints and significant linear portions of meridians overlie major peripheral nerves [44]. Additionally, an intriguing model explains the subjective phenomenon of "propagated sensations along the meridians" as a resultant of neuronal connectivity in the spinal cord during the relay of presumed "acu-signals" to the brain [68].

The connective tissue hypothesis of meridians, for its part, is based on the observation that traditional pathways of acupuncture meridians correspond to ultrasound images of connective tissue planes [47]. Moreover, such bands of meridian-oriented collagenous structures are associated with lower electrical impedance [69], as was also detected in seven of nine studies of electrodermal activity along acupuncture meridians at both subcutaneous and intermuscular depths [54]. The proposal that triple-stranded collagen fibers support a rapid flow of hydrogen ions (protons) along water molecules bound to the fibers' outer shell has intriguing implications for acupuncture-related information signaling [70]. Further elucidation of the mechanotransduction events by which needling perturbs connective tissue elements and initiates signaling is a key area of acupuncture mechanism research [71,72].

Further questioning of the primacy of the neural model comes from proponents of the Bonghan intravascular system (primo vessels) [73,74] and from those who favor a biophysical model in which endogenously generated electromagnetic fields form standing waves that comprise an energetic representation of meridians [75,76].

In summary, while no anatomical or biochemical features have yet been unambiguously identified that uniquely identify acupuncture point sites and meridians, the balance of evidence favors quantitative differences in electrodermal properties between acupoints and surrounding skin [54,55]. In addition, evidence of correlations between loose connective tissue anatomy and the acupuncture system is emerging as a viable alternative to the prevailing neurobiological models [62,69]. A cautionary note regarding translational research bridging physiology and efficacy of acupuncture is that lack of a clear understanding of the events initiated by acupuncture needle insertion confounds the design of an appropriate sham acupuncture procedure for clinical trials [77,78].

5. Conclusions

In this review we have identified a number of areas of controversy in relation to the domains of acupuncture safety, clinical benefit and physiology. By focusing on these areas we have aimed to provide a balanced assessment that offers a measure of clarity and, where possible, a degree of resolution. In this manner, we hope our review helps to inform a range of stakeholders, from patients to practitioners to policy makers as to the current status of acupuncture research. Moreover, we hope our contribution highlights the pitfalls of misinterpretation and misdirection, and encourages the acupuncture research community to explore approaches that build on a sound interpretation of the evidence base.

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