Acupuncture: Specific and Non-Specific Effects

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As an alternative and complement to conventional or allopathic medicine, acupuncture has become a firmly established therapy in many countries. Despite this wide acceptance, the question of how acupuncture works, or whether it works at all, remains the subject of lively debate.

One problem in the discussion of acupuncture and its possible mechanisms is that acupuncture is not only used for the alleviation of acute or chronic pain but also for the treatment of nausea and vomiting following chemotherapy, for addictions, asthma, depression, etc. An article on the 1998 NIH Consensus Conference on acupuncture even suggests that ‘further research is likely to uncover additional areas where acupuncture interventions will be useful’ [1]. Given such a variety of applications, efficacy of acupuncture certainly cannot be explained by one single mechanism, unless we assume it acts exclusively through non-specific (placebo) effects. Furthermore, practitioners (in Germany, mainly physicians in private practice) follow a variety of protocols with regard to point selection and needling techniques.

The best evidence available to date shows that body needle acupuncture is effective as a symptomatic treatment of chronic pain. Several recent, large randomized controlled trials (RCTs) have demonstrated a strong therapeutic effect of acupuncture [2–9]. In all of these studies, patients who received sham acupuncture served as one control group, while the second control group consisted either of patients who received conventional, guideline-based treatment or of a waiting list.

The first direct comparison of acupuncture and conventional treatment was made in the GERAC studies [2, 4, 5]. This approach was taken from pharmaceutical research. The procedure is similar to that involved in testing a new drug against established standard medication. Direct testing is particularly useful to compare the value of ‘new’ therapies to ‘old’ ones. Trials may be designed to test whether the new treatment is

more effective than the old one (superiority design), or to prove that it is not inferior (non-inferiority design). In the latter case the new treatment must have other advantages, e.g. significantly fewer side effects.

The use of sham acupuncture as a control was designed to assess non-specific effects of acupuncture, which would also be expected in verum acupuncture (following the rules of traditional Chinese medicine [TCM]). In sham acupuncture, needles are inserted at non-acupuncture points, superficially, and without needle stimulation (i.e. no elicitation of the deqi sensation that indicates sufficient intensity of stimulus in the afferent fibers). Sham acupuncture is considered the most suitable control for verum acupuncture as far as patient blinding is concerned. Yet, it is not physiologically inert ‘placebo’ treatment [10], because inserting needles into the skin (‘minimal acupuncture’) produces specific physiological effects that may well be significant, especially in studies on pain treatment. This leads to an underestimation of the specific effects due to point selection, deeper needle insertion and stimulation of nerve fibers until deqi in verum acupuncture. Consequently, the specific effects of verum acupuncture may well be underestimated in sham-controlled RCTs [1].

The GERAC studies, the largest studies on acupuncture to date (about 300 patients per treatment group) and consequently those with the highest power to reveal differences between sham and verum acupuncture, failed to show any such difference. Still, perhaps the most surprising result of these studies, even to the authors, was that acupuncture was found to be as effective as drug interval therapy for the treatment of migraine and in fact significantly more effective than the conventional treatment for knee and back pain. Yet, this was equally true for verum acupuncture and for sham acupuncture.

How can this be explained? It is not sufficient to simply assume that there are additional, previously unknown active

points besides the classical TCM points, because the practice of sham and verum acupuncture differs fundamentally in a number of ways. Instead, it is important to recall that the therapeutic effect of any treatment – not just acupuncture – is made up of specific and non-specific effects. Non-specific effects are effects we cannot explain in terms of a direct, physiological (biological) mechanism. Therefore, non-specific effects also include all biologically active mechanisms that have not yet been discovered.

Non-specific effects can be divided into desirable (placebo) and undesirable (nocebo) effects. They include positive or negative patient expectations that affect every treatment process [11, 12] (expectations that in turn are affected by patient education), anxiety about pain [13, 14], higher intensity of care by the acupuncturist, the physician's enthusiasm (investigator effects), a 'healing ritual' that references East Asian culture/philosophy [15], and the experience of an invasive technique (needling). Invasive techniques (e.g., surgical procedures) are based on compelling rational explanations and therefore experienced as profoundly meaningful, which may contribute to symptom reduction through a particularly strong 'meaning response' [16–19]. In contrast, drug treatments are often not perceived to be as meaningful. Non-specific effects also include a good doctor-patient relationship which can further enhance patient improvement, and negative patient expectations about 'conventional medicine' which may already have been experienced as inadequate. Interviews with acupuncture patients have shown that the holistic view of patient illness represented by acupuncture is also an essential factor in the healing process [20].

Because of the variety of conceivable non-specific effects, it stands to reason that their magnitudes also greatly differ. Although it is still frequently assumed that all placebo effects are of the same magnitude, this is erroneous. In fact, the size of placebo effects can widely vary depending on the therapeutic measure under investigation, the study design, the care and attitude of the therapist, the therapeutic premises – briefly, the nature of the non-specific effects that come into play [21, 22]. Non-specific effects must not be confused with the concept of natural history, which refers to the natural course of a disease over an extended observation period, nor with regression to the mean, which describes the fact that very severe pain cannot worsen but only improve. Regression of extreme values toward the mean is thus not merely a statistical artifact, as is sometimes claimed.

A waiting-list control group is not the best means of observing the natural course of a disease. Unfortunately, the sum of specific plus non-specific treatment effects cannot simply be assessed by use of a waiting list, as this does not take into account the disappointment of patients on the waiting list. Patients who must put up with remaining on a waiting list may well emphasize the negative aspects of their condition, and therefore report a disease course that is even less favorable than the 'natural course'. Thus, testing an active treatment

against a waiting list always tends to produce a significant outcome in favor of the active treatment. Authors in the field of psychology in particular have found that waiting-list controls are essentially meaningless, since any treatment is better than none [23].

The idea of separating out specific from non-specific effects is also reflected in intention to treat (ITT) analyses. At first glance, it seems unreasonable that, for the purpose of statistical analysis, patients that have changed treatment groups should be included in the group to which they had been initially randomized. It is unreasonable if we assume that a study is able to assess the pure biological effects of a treatment, in other words its specific effect under ideal conditions (efficacy). Yet, the idea behind ITT analyses is that the effect of a treatment under actual conditions (effectiveness) can only be assessed as the sum of specific and non-specific effects. Non-specific effects, e.g. critical patient attitudes or negative patient expectations, will play a major role in the change of treatment group and hence, for the purpose of ITT analysis, these are assigned to the original treatment.

A secondary analysis of 141 long-term trials [24] showed that non-specific effects also play a major role in randomized controlled double-blind drug trials, and may account for nearly 60% of variance of all treatment effects. The special situation of a clinical trial evidently created the perception of a healing ritual with the attendant strong non-specific effects. Even unblinding the investigators did not affect the magnitude of the placebo response (non-specific effects) in that analysis.

In recent decades, many plausible models of specific analgesic effects of acupuncture have been developed, e.g. the endorphin hypothesis, Melzack's gate control theory, and the principle of counter-irritation, or diffuse noxious inhibitory control (DNIC), which some authors consider as a possible candidate for explaining central pain modulation through acupuncture [25–27]. Yet these standard neurophysiological models fail to explain the long-term effects of acupuncture over periods of more than 4 months [28]. According to these models, the activation of pain-inhibiting mechanisms by stimulation of nerve fibers should not persist for more than a few hours, and the initial worsening of symptoms that is often observed in acupuncture treatment should not occur at all.

As pain perception results from a balance between afferent nociceptive mechanisms and efferent antinociceptive mechanisms, the nociceptive input might be regulated by unconscious and conscious mechanisms, for example by positive expectations about therapy (expectation-induced placebo analgesia) or by negative anticipatory anxiety related to pain [11, 13, 14, 29, 30]. Numerous functional MRI (fMRI) and PET studies have identified structures in the central nervous system that form a neuronal network to control pain perception. These structures include the prefrontal cortex (PFC), the rostral anterior cingulate cortex (rACC) and the brainstem. Placebo-induced increases in activity have been identified in all these studies [11, 29–31].

The most obvious explanation of why sham acupuncture is as effective as verum acupuncture, and this explanation is in line with results of fMRI measurements and PET studies, is that acupuncture activates regions of the PFC (expectations for pain relief) that modulate activity in pain-responsive regions (including the thalamus) and activate the descending antinociceptive system. Stronger activation correlates with greater placebo-induced pain relief (high placebo responders). The close functional-anatomic connection between opioid analgesia and placebo-induced analgesia ('shared neuronal network') leads to an interesting correlation between how effectively opioids activate the rACC and how well test subjects respond to a placebo for analgesia. Maybe high placebo responders are characterized by a more efficient opioid system [31]. This establishes a biochemical correlate for placebo-induced analgesia. One wonders, however, whether such biological mechanisms that explain placebo-induced acupuncture should not properly be classified as specific effects.

The perceived significance of an event can trigger substantial physiological action – perhaps even variations in mortality from lymphatic cancer in different generations of Chinese Americans can be explained in terms of rootedness in traditional Chinese mythology [16]. It is worth considering that differences in positive outcomes between acupuncture studies in China and in the Western world could be due not solely to poorer study design or to publication bias [32], but also to the fact that acupuncture holds a much deeper significance for the Chinese than it does for patients rooted in critically rational patterns of Western thought.

Perhaps it is not even crucial to conclusively answer the question whether acupuncture helps patients through specific or non-specific effects for even non-specific effects can trigger substantial physiological action. That we cannot yet describe these effects in detail does not mean that they do not exist.

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