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The Future of Placebo Control in Acupuncture Research

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Once thought to be the indomitable tower of truth, the double-blinded, placebo-controlled randomized clinical trial (RCT) is now faltering from poor architecture. A recent study, presented in the prestigious *New England Journal of Medicine* (*NEJM*), has turned a critical spotlight on what has been held as the "gold standard" of medicine, the double-blind RCT.

This meticulous meta-analysis, co-authored by Asbjorn Hrobjartsson, MD and Peter Gotzsche, MD of the Department of Medical Philosophy and Clinical Theory at the University of Copenhagen in Denmark, has received much media attention and has renewed interest within the medical community over the nature of the placebo control.

That the elite *NEJM* has published this article may be cause for celebration among this nation's acupuncturists. One of the most daunting juggernauts in the evolution of acupuncture as a profession and medical option in the United States is the expectation that acupuncture's assumed efficacy will be rigorously tested in placebo-controlled RCTs. Hrobjartsson and Gotzsche's article[1] calls into question the notion that the placebo effect exists at all. Their systematic review of 114 placebo controlled RCTs measured outcomes of placebo arms versus the natural recovery rate of the illnesses being studied. Of the 114 studies involved in the meta-analysis, 32 had binary outcomes (in which the subject is either better or not better) and 82 had continuous outcomes (which measure the continuum between cured and not cured). Some studies measured subjective outcomes (subject's perception of benefit); others employed objective outcomes (measured by specific tests). Twenty-seven trials involved the treatment of pain. The results suggest that the placebo effect did have an efficacious value above and beyond the natural progression of healing in the 27 pain studies. In addition, the placebo may have had a possible, but small, benefit in the continuous subjective category. Otherwise, the meta-analysis overwhelmingly revealed what its authors suspected: that in comparison with no treatment, subjects randomized to placebo arms generally do not have better outcomes.

According to Ted Kaptchuk, OMD, the placebo effect can be attributed to several variabilities. "Under the rhetorical label of powerful placebo lies many rich contributions to health care. These include: nature taking its course; regression to the mean; routine medical and nursing care; regimens such as rest, diet, exercise and relaxation; easing of anxiety by diagnosis and treatment; the patient-doctor relationship; classic conditioning and learnt behaviors; the expectation of relief and the imagination; and the will and belief of both patient and practitioner."[2]

In a series of articles, Katpchuk calls into question the validity of RCTs. He states, "In a self-authenticating manner, the double-blind RCT became the instrument to prove its own self-created value system."[3] There are several problems inherent in the randomized-controlled design. For instance, he suggests that there may be an equivalent to the Heisenberg principle in clinical experiments, in that the mere process of being enrolled in an experiment might alter its outcome.[3]

Furthermore, aspects of the RCT such as informed consent and blinding alter the effects of placebo and drug. Knowledge that one has a chance of receiving placebo, in particular, has the ability to change outcomes by diminishing a subject's belief in the treatment. It may also be that participation in clinical experiments increases sensitivity and vigilance to drug effects. Clearly, participation can alter the outcomes of verum or placebo bilaterally.

Although they decisively debunk the belief that the RCT is capable of revealing core truths about drug effects, Kaptchuk's articles do not call into question the randomization process per se. Since the placebo factors listed above would presumably be split equally among both arms, it is still possible to conclusively show that a drug has effect beyond the placebo, within the experimental milieu. One exception to this rule would be if subjects knew what to expect of a medication prior to enrolling in a study. For instance, if a subject has already taken a medication, the subject may notice its physiological interaction, or lack thereof. This would undoubtedly skewer outcomes in favor of the verum. Many studies unfortunately do not screen for prior use.

The essence of Kaptchuk's theory is that studying the effects of drugs within the framework of the RCT is quite different than the effect a drug might have when taken on an individual basis, or in a different context; in other words, that enrolling in a clinical experiment immediately alters the healing experience. This, depending on a variety of biases, is capable of generating either erroneous data or half-truths. "Any method of evidence production has it's own potential for distortions," he says. "... It may be that in some circumstances even the best instruments of detection effect the phenomena being measured and that medical "facts" may not exist independent of the apparatus of their production."[3]

An example of the bias generated by the experimental milieu lies in a study authored by Kaptchuk, et al., "Are Randomized Controlled Trail Outcomes Influenced by the Inclusion of a Placebo Group? A Systematic Review of Nonsteroidal Antiinflammatory Drug Trials for Arthritis Treatment."[4] By comparing a group of 25 treatment arms randomized in placebo controlled trials versus 33 treatment arms randomized in comparative drug trials, this study demonstrates that efficacy of NSAID treatment was substantially less effective in the placebo-controlled studies. This is yet another example of bias due to the effect of knowledge.

When boiled down, Kaptchuk's studies seem to clearly indicate that belief in treatment has a significant effect on outcome. To the extent that the placebo-controlled RCT casts doubt, one's assurance of being treated often increases one's ability to believe in the treatment they are receiving and thus lowers the probability of healing.

The development of RCTs came at a point when clinicians began realizing that outcomes decreased proportionally to the amount of controls built into a study. This supported the view that trials based on clinical observation alone tended to report optimistic results, and therefore could not be trusted. Method became more important than results. Another way of looking at it is that results could only be produced by proper method. In either case, in the middle of the last century the RCT replaced the observational study as the gold standard in medical research. Interestingly, two recent meta-analyses contradict this supposition by showing that observational studies and RCTs produce similar results.[5,6] This topic is still hotly debated and might affect the future of acupuncture research.

Another side of the placebo debate involves a similar transformation in medicine that has occurred in the past one hundred years. As Mark Sullivan, MD points out, "Orthodox medicine, in perfecting its method for the testing of pharmacological interventions, will come to acknowledge placebo-associated healing, and then exclude it as illegitimate. Where healing initially validated method,

now method will validate healing."[7] At the core of pharmacological medicine is the ambition to define healing as a purely direct biochemical mechanism, which yields the "drug versus disease" mentality. This reductionist model discounts non-specific healing, including the placebo effect, faith-based healing and any form of healing that does not reveal a direct biochemical mechanism. "Knowledge can not have direct therapeutic action within this framework ... Knowledge that is intrinsic to the clinical encounter (e.g., beliefs, expectations, and fears of patient and physician) is excluded through the double-blinded technique."[7] The physician-patient relationship has been given secondary status to the drug-patient relationship as remedy for illness. In an ideal world, basic and clinical research would pursue a balance between non-specific healing and mechanistic healing that maximizes the clinical effects both. And to the extent that knowledge can itself have real therapeutic action, diagnosis is treatment.

Research into the meaning and value of the placebo has produced many interpretations and gone in many directions. The Hrobjartsson/Gotzsche study[1] essentially shows that the placebo effect does not exist. The natural progression of illness is roughly equivalent to the progression of illness under the effects of placebo control. Although they are equivalent in magnitude, the healing processes occurring in these dimensions are different (although, if 35% of people get better regardless of the clinical or non-clinical backdrop, it could be argued that psychological state plays no role in health and healing whatsoever). The fact that patients that chose to "go it alone" do just as well as those engaged in the proverbial doctor-patient relationship implies this. Therefore, there is no special effect associated with receiving a placebo while in the care of a physician.

On the other hand, the studies presented by Kaptchuk reveal quite a different view of this topic. Taken together, the variety of studies presented here suggest that health and healing are far more complex than previously suspected and that, to a great degree, research objectives have the ability to produce an array of clinical effects. More specifically, people react differently according to the healing environment. There is not a uniform reaction between populations in diverse research and non-research setting but rather a panoply of responses. The more we can learn about these responses, the more we will come to understand the mind-body relationship and when and how belief can be effectively used as a medical treatment.

Another result of the relationship between basic clinical research, basic research and biochemical models of human functioning is an infrastructure overwrought with bias. In the domain of clinical academic research, the questions that are asked are those that will make money. This model is conducive to RCT design and success but ultimately creates a fallacious understanding of the human body. This canon of knowledge denies the reality of the human body which lies outside its chemistry. By defining the body, biochemists create the body. Clinicians from all medical paradigms operate within a particular world-view. So, it is not fair to portray Western medical minds as being the sole proprietors of this process. However, the balance of medical care in the United States currently disproportionately favors Western medicine.

The implications of the varied commentaries on the placebo effect and RCT are significant for the acupuncture profession. As researchers begin to unravel the mysteries of acupuncture through the lens of placebo-controlled studies, many obstacles have become apparent. First, creating placebo controls in double-blind acupuncture studies via sham acupuncture has been exceedingly difficult. Secondly, acupuncture treatments are sculpted for each individual, so the notion of control is not in line with traditional thinking. The core of the RCT is to eliminate the quirks of individuality with controls and the randomization process.

In general, the biomedical model tries to find pharmacological medicines that treat specific pathologies and focuses on lesions or biochemical pathways. Medicine has therefore moved away

from being able to recognize the secondary features of the individual, and the degree to which these secondary features are involved in illness determines, at least in part, the ability of the Western model to diagnose and treat. So the benefit of studying the phenomenology of the RCT is cultivation of research tools better equipped to handle a variety of medical paradigms.

The articles presented above clearly indicate that data gleaned from observational studies, comparison trials, natural history studies and outcome studies is useful. They also weaken belief in the RCT. From this weakness, the acupuncture community will have a viable platform to introduce novel research models better suited to examine the efficacy of Chinese medicine when they arise. Although acupuncture will always be under the scrutiny of rigorous biostatistics, the call is on to determine exactly in what manner.

Finally, the importance of the placebo effect in acupuncture goes beyond the desire to produce meaningful results in acupuncture research. If one thing is certain, it is that the secondary aspects of illness and healing, the phenomenon of reduction in the RCT, comprise a powerful healing force. It should be important for all healers and physicians to consider what aspects of their practice boost these forces and what aspects diminish them. And perhaps medicine will someday evolve in the direction of results, not method.

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Other recommended articles:

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