

Placebo Effects in Acupuncture

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ABSTRACT

This article is a summary of a talk presented in February 2019 at a conference on acupuncture sponsored by the National Institutes of Cancer (NCI) and the National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH). The article touches on the history of placebos in biomedicine and its absence in traditional East Asian Medicine. It then examines some of the predicaments of evaluating acupuncture's efficacy in relationship to placebo controls. Although acupuncture in randomized controlled trials (RCTs) generally demonstrate equivalence or even superiority to medical interventions or other nonpharmacologic therapies, acupuncture's ability to show superiority to placebo controls has been inconclusive, contradictory and, at best, modest. This article highlights the efforts of the German health insurance funds to evaluate acupuncture. Using a large meta-analysis, the article summarizes acupuncture's effectiveness and efficacy. Subsequently, RCTs and meta-analyses testing the hypothesis that sham acupuncture, and other device placebos, have augmented placebo responses are described. It seems that acupuncture, and devices in general, have enhanced placebo responses. These findings may be relevant to designing and evaluating placebo-control acupuncture RCTs. Research into placebo acupuncture may also be helpful for other conditions where detection of intervention-placebo differences can be problematic. Further research is warranted.

Keywords: acupuncture, genetics, placebo effect, randomized clinical trials

INTRODUCTION

AFTER WORLD WAR II, placebo controls, together with randomization and statistical inference, became indispensable methodologic tools.^{1,2} Placebo controls act as a clear line in the sand: if a novel therapy does not surpass the placebo response, the new therapy is bogus and illegitimate. The placebo itself needs to mimic the experimental intervention in all manners except its "active" component. Furthermore, based on interpretations of the 1962 Kefauver Amendments to the Pure Food, Drug and Cosmetic Act, federal regulation generally requires pharmaceuticals and devices requesting Food and Drug Administration (FDA) approval to demonstrate superiority over placebo with least 2 randomized controlled trials (RCTs). According to contemporary biomedical understanding, therapies "work" because they elicit more than a placebo response. Legitimate agency is determined not by how the intervention affects

patients as much as whether the benefits have a proper methodologic pedigree.¹

To the author's knowledge, East Asian medicine traditionally has no description, concern, or knowledge of placebo controls or treatments. Efficacy is evaluated by observation of how patients respond to treatment. (This method was also the dominant model before World War II in Western medicine.) From a historical East Asian perspective, ideal evidence as to whether or not acupuncture "works" was observations of patients.

COMPREHENSIVE GERMAN INITIATIVE

In the early 2000's, German insurance companies launched the largest and most comprehensive investigation into acupuncture's utility. The single largest study was a unique

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large mega-observational study, in fact one of the largest interventional observation study ever published. In 2007, 10 German health insurance funds decided to provide free acupuncture to 454,920 patients with chronic low back pain, osteoarthritis, and headache. The only condition for the cost-free acupuncture was that researchers could use the outcomes as data for evaluating acupuncture's benefit and risks for these conditions. These patients received 3,840,000 acupuncture treatments and self-reported: 21.8% "marked improvement," 54% "moderate improvement" ("decided"), 16.1% "minimal," 3.9% no change or worsening, 4.2% "unable to judge," and 9.4% discontinued for various reasons.³ Minimal adverse effects were detected. Acupuncture "worked" for 75% of the patients. For biomedicine, this trial, and other such observation studies, are merely anecdotal. Even more so are observations of single practitioners or individual patients. Patients could have just gotten better because of natural history, a "tincture of time," regression to the mean or from placebo effects. For the acupuncture profession and the German insurance companies this was impressive data.

The German insurance companies also financed a series of large RCTs that directly compared acupuncture with standard or optimal medical care. In this study, acupuncture was generally equivalent or superior to standard or optimal biomedical care. When studies included sham acupuncture the results were less positive: acupuncture and sham acupuncture were generally indistinguishable or modest.⁴⁻⁷ Interestingly, cost-effective studies on this data, similar data, and the insurance companies' historical data found that acupuncture was significantly less expensive than biomedical care.⁸⁻¹³ The German companies not concerned about the providence of the benefit—whether it was better or not than placebo—decided to continue to pay for acupuncture in patient care. Despite the dismal results of the German trials in terms of "beyond placebo," the outcome for acupuncture utilization was positive in Germany.

META-ANALYTIC EVIDENCE

Looking from a wider perspective worldwide perspective beyond only the German trials, attempts to summarize whether acupuncture is more than placebo have been more positive. The largest meta-analysis examining acupuncture RCTs for pain was performed by the Acupuncture Trialists' Collaboration.¹⁴ Using 29 RCTs, individual data were taken from a total of 17,922 patients with 3 chronic pain conditions: back and neck pain, osteoarthritis, and chronic headache/migraine. Most patients ($n=14,597$) were in RCTs with acupuncture versus nonacupuncture controls (medical treatment, no-treatment, and other therapies), whereas many ($n=5,230$) were in RCTs with sham controls. Acupuncture compared with nonacupuncture controls measured as standardized mean difference was significant for all 3 illnesses

($P<0.001$) with an effect size of about 0.50 for all 3 conditions. Acupuncture compared with sham acupuncture was also significant for all these conditions ($P<0.001$), but the effect size was between 0.15 to 0.23. The meta-analysis showed that when acupuncture as compared with other treatments on average contributes meaningful benefits. Although acupuncture compared with sham acupuncture was found to be "more than a placebo," it provided only a modest effect size. An update meta-analysis from the same research team with an additional 13 RCTs and a total now of 20,827 patients had similar results.¹⁵ In general, the acupuncture profession, many hospitals and governmental agencies, such as the U.S. Veteran's Administration, consider this meta-analysis to be the most definitive study of acupuncture so far. Critics, however, continue to argue the effect size of between 0.15 and 0.23 is explainable by lack of double-blinding or is too small to be clinically meaningful. The question of whether acupuncture "is it more than placebo effects" still has room for interpretation.¹⁶

ACUPUNCTURISTS RESPOND

The debate concerning placebo effects poses a dilemma for the acupuncture profession. A published review of how acupuncturists have interpreted this body of evidence found 8 categories of responses.¹⁷ These included: (1) numerous methodologic weaknesses of acupuncture RCTs; (2) inappropriateness of placebo controls given that acupuncture includes multiple modalities; (3) sham controls are not inert; (4) rejection of evidence-based medicine epistemology; (5) discrepancy between acupuncture performed in RCTs with real-world acupuncture; (6) acupuncture theory needs to be re-evaluated, (7) emerging evidence that acupuncture and sham acupuncture can have the same clinical effect but have very different neural brain mechanism,^{18,19} or, more recently, that the different neural mechanism of genuine acupuncture produces clinically relevant physiologic changes that sham acupuncture cannot evoke,²⁰ and, finally, (8) enhanced placebo effects of acupuncture make it difficult to detect an acupuncture-placebo difference. I will not comment on the first 6 responses as, although important, they are supported by little hypothesis-driven empirical data. The seventh response concerning mechanism, however, is based on prospective research. Nonetheless, I will not comment on the seventh point because other scientists included in this special journal issue will discuss this perspective in great detail. Given that I have researched pointing extensively. I will focus on enhanced placebo effects.

ENHANCED PLACEBO EFFECTS

Twenty years ago, my team were one of the first groups to hypothesized that acupuncture and other medical devices

had enhanced placebo effects, that is, the notion that more elaborate medical rituals have augmented placebo effects.^{21,22} In our first study designed to test this hypothesis, our team prospectively investigated whether a validated sham acupuncture needle (Strietberger retractable needle) used over nonacupuncture points had a greater placebo effect than an inert pill in patients with persistent arm pain ($n=270$).²³ Published in *BMJ*, we found that the sham device had greater effects than the placebo pill on self-reported pain and severity of symptoms for the entire course of treatment. We concluded that placebo effects are malleable and can depend on the behaviors embedded in medical rituals.

Toward better elucidating an understanding of placebo acupuncture effects, my colleagues and I published in *BMJ* an RCT in patients with irritable bowel syndrome (IBS) patients ($n=260$) that sought to disentangle the acupuncture ritual into 2 components: (1) the effect of the fake needling and (2) the effects of the patient–acupuncturist interaction. Patients were randomized to 3 arms: (1) no-treatment, (2) sham acupuncture needles with a minimal business-like interaction over nonacupuncture points, and (3) sham acupuncture over nonacupuncture points with a patient-centered clinical interaction based on Chinese medicine

intakes. At 3 and 6 weeks, 27% of patients on no-treatment had “adequate relief” (a validated IBS measure), 43% of patients on sham acupuncture without clinical engagement had adequate relief, and 62% of patients on sham acupuncture with clinical engagement had adequate relief.²⁴ The study suggested that the ritual of acupuncture treatment alone is better than no treatment and the addition of clinical engagement significantly boosts the placebo acupuncture alone. We concluded that the effects of sham acupuncture were malleable and could be disentangled into components and incrementally added together in a way analogous to dose dependence. The augmented placebo produced clinical results similar to powerful IBS pharmaceuticals that are rarely used because of the risk of serious side-effects.

Subsequently, our team undertook a double-blind crossover RCT study with asthma patients to better understand the scope of placebo acupuncture on both objective and subjective outcomes. We also compared 2 fake devices: sham acupuncture (Streitberger needle) and placebo inhalator (identical to alburol devices without the alburol). Published in the *New England Journal of Medicine*, the study recruited 40 asthmatics who had their asthma medicine withdrawn on 12 different days.²⁵ In an elaborate crossover design, for the course of 12 treatment sessions,

TABLE 1. META-ANALYSES COMPARING DIFFERENT TYPES OF PLACEBOS AND PAIN RESPONSES

Condition	Author (year)	RCTs	n	Differential placebo response	Comments/conclusions
Knee osteoarthritis	Bannuru (2015) ²⁶	149	39,814	Pain reduction effect size (95% CI): Intra-articular placebos: 0.29 (0.09–0.49) Topical placebos: 0.20 (0.02–0.38) Oral placebos: 0.18 (0.05–0.30) Acetaminophen: 0.18 (0.05–0.30)	Network meta-analysis. Interarticular and topical statistically superior to oral and both reached prespecified clinical significance threshold. Oral placebo similar to acetaminophen. Sham acupuncture not included in analysis to reduce heterogeneity. Conclusion: “All placebos are not equal.”
Osteoarthritis (any joint)	Zou (2016) ²⁷	215	41,392	Placebo proportion of overall drug effect PR (95% CI): Invasive sham surgery (e.g., joint lavage): 0.91 (0.60–1.37) Injection placebo/acupuncture): 0.82 (0.75–0.90) Physical placebo (e.g., pulsed magnetic fields): 0.80 (0.64–0.99) Oral placebo 0.70 (0.65–0.75)	Placebo effect sizes: Sham surgery > acupuncture and injections > topical > oral placebos
Osteoarthritis (hand, knee, and hip)	Zhang (2008) ²⁸	198	16,354	Injection/needle placebos/acupuncture superior to oral pills (95% CI): $\beta=0.144$ (0.025–0.263); $P=0.020$	
Migraine prophylaxis	Meissner (2013) ²⁹	79	9,278	Outcome: Responders defined as attack frequency reduction of $\geq 50\%$ (95% CI). Sham surgery PR: 0.58 (0.37–0.77) Sham acupuncture PR: 0.38 (0.30–0.47) Oral PR: 0.22 (0.17–0.28)	Network meta-analysis. PR in sham acupuncture and sham surgery significantly greater than oral placebos ($P=0.004$, $P=0.03$, respectively)

Table based on Kaptchuk et al. 2020.³⁰

ES, effect size; standard mean difference baseline to endpoint. PR, proportion of responders; RCT, randomized controlled trial.

these patients were randomly treated on 3 different days each with either (1) bronchodilator, (2) placebo acupuncture, (3) placebo inhalator, or (4) no intervention for 2 hours each day. Thus, in total, patients were treated for 12 different episodes of induced breathing difficulty with 4 different kinds of interventions (i.e., 480 episodes of asthma exacerbation). Maximum forced expiratory volume in 1 second (FEV₁) (an objective outcome) was measured and patients' self-reported improvement ratings (a subjective measure) were recorded at each of the 12 treatment episodes. We found that albuterol, but not the 2 placebo interventions, improved FEV₁ in patients with asthma. Neither placebo treatment (sham acupuncture or fake albuterol inhalator) had any effect on objective measures, compared with no-treatment control. There was no placebo effect. Interestingly, the 2 placebo treatments (sham acupuncture and placebo inhalator) produced similar large benefits to genuine albuterol on subjective relief. Compared with either of the devices, albuterol was no different from placebo controls! Although there are debates about whether sham acupuncture is genuinely inert, as mentioned earlier, there is no such debate about fake albuterol inhalers. The effect of fake albuterol is uncontroversially about the ritual, symbols, and behaviors embedded in the therapeutic encounter. Noteworthy, from an acupuncture perspective, if subjective outcomes were the primary outcome of this RCT, genuine albuterol and placebo albuterol would show absolutely no difference. Drug-placebo difference disappeared when the placebo effect is unusually high. At least in this study, it seems that detecting efficacy can entirely depend on the magnitude of placebo response. All 3 of these RCT seem to confirm our original hypothesis that acupuncture has enhanced placebo responses.

Further confirmation of the existence of enhanced placebo acupuncture responses and other device placebos comes from a series of large meta-analyses examining placebo responses of different types of placebo (with the exception of one, all include sham acupuncture). These meta-analyses compared the impact of different types of placebos. The table clearly shows that sham acupuncture has superior effects, compared with other types of placebo except with the possibility of sham surgery. The final entry at the bottom of the table on knee osteoarthritis deliberately does not include sham acupuncture but shows clearly that the more elaborate the placebo treatment: the more elaborate the ritual, the higher the placebo effects. Table 1 summarizes these data.

CONCLUSIONS

In conclusion, our studies support the notion that sham acupuncture and other placebo interventions can powerfully shape patients' experiences and clinical outcomes. Such phenomenon need to be considered in an evaluation

of acupuncture's potential efficacy. Development of effective strategies to separate verum acupuncture and placebo remains an important challenge both in acupuncture and with interventions directed at subjective symptoms.³⁰ Research into placebo effects in acupuncture may be helpful. More research is warranted both for acupuncture and medicine in general on the question of detecting intervention and placebo controls.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

FUNDING INFORMATION

No funding was received for this article.

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