Reconsidering the placebo response

Acupuncture studies provide new insights into how treatment context affects outcomes.

In scientific studies, the term placebo usually refers to an inert pill or procedure that serves as a comparison to an active intervention (typically a drug or psychotherapy). Now a handful of acupuncture studies not only provides additional evidence that a placebo itself can have dramatic impact on illness, but also suggest that the context in which an intervention takes place can bolster the placebo response.

The nature of the placebo response—and whether it even exists—has been the subject of scientific discussion for decades. In a 1955 paper, pioneering anesthesiologist Dr. Henry K. Beecher famously described the placebo response as powerful. Nearly a half-century later, a review published by the prestigious Cochrane Collaboration concluded instead that the placebo might be powerless. More recently, the Cochrane reviewers conducted another analysis and reached a middle ground, concluding that for some clinical conditions—particularly pain and nausea—placebos may confer symptom alleviation, while in other situations they do not.

This raises the obvious question: why would placebos work in some cases but not in others? The latest research has been aimed at better understanding the placebo response by studying it on its own rather than just as a comparison to a drug or psychotherapy.

Multiple mechanisms

Research suggests there is not one placebo effect, but many. Studies over the years have identified multiple components that underlie response to a placebo intervention. Probably the best-known mechanism is biological: the experience of taking inert pills activates endogenous opioids (known as endorphins) in the brain to relieve pain.

Other evidence suggests that psychological mechanisms may contribute to the placebo response. Two of the best-studied psychological processes are conditioning and expectation, which no doubt also have a basis in neurobiology. The first is a learning process in which repeated exposures pairing a neutral stimulus (such as a pill or needle) with an active intervention (such as a drug) become so linked in a person's brain that the very sight of a pill or needle is sometimes enough to provide pain relief. A related psychological process is expectation, which can be manipulated through words, symbols, and actions.

In clinical situations, these two processes may be two ways of understanding the same mechanism or mechanisms. One study found that when investigators described a topical cream as a "powerful painkiller," participants receiving it reported that it provided more pain relief than when the same cream was described as inert. Other investigators recruited participants and subjected them to brief electrical shocks. They then randomly assigned half of participants to take pain relievers they said cost $2.50 each, while the others received pills they said cost 10 cents a piece. (In reality, all the pills were the same and made of sugar.) The investigators found that 85% of participants receiving pre-shock treatment with the "high-cost" pills reported muting of pain from shocks, compared with 61% of those who thought they were receiving "low-cost" pills.

Now several acupuncture studies suggest that one of the most powerful psychological mediators of the placebo response is the patient-clinician interaction. This may work by enhancing both conditioning and the expectation of relief.

Out of failure, questions

Four randomized controlled studies in Germany dismissed by some observers as "failures" prompted others to re-examine the placebo response. The studies found that fake acupuncture was as effective as real acupuncture. To skeptics of acupuncture, this provided evidence that the intervention is useless. But the German studies suggested otherwise: all four also found that both types of acupuncture (real and fake) were significantly better at alleviating various types of pain than both a waiting list control (in three of the studies) and physical therapy and as-needed pain relievers (in one).

One interpretation of these results is that acupuncture may work not by stimulating the flow of *qi* through the body's meridians—as is believed in traditional Chinese medicine—but by efficiently eliciting the placebo response. Indeed, this is what one German team concluded after conducting a subsequent analysis that divided study participants into believers and skeptics about acupuncture. The researchers found that participants who had high expectations that acupuncture would help them were roughly twice as likely to respond to acupuncture—whether the legitimate or fake variety—than were the skeptics. Thus, the studies add to other evidence that expectation of relief is a powerful mediator of the placebo response.

A limitation of this view is that even the shallow and minimal needling that occurred during the sham acupuncture used in the German studies might stimulate acupuncture points enough to release endorphins. To control for this possibility, researchers at the Center for Health Studies in Seattle conducted what is now known as the "toothpick study." They created an acupuncture device in which toothpicks pressed the skin and then retracted, and compared this with actual acupuncture needles that penetrated the skin. Because the study involved participants with lower back pain, people in the study could not see what type of treatment they were receiving. The investigators randomly

assigned 638 patients with chronic low back pain to one of four treatment arms: standardized acupuncture for back pain, individualized acupuncture tailored to the patient's particular symptoms, sham acupuncture with toothpicks, and usual medical care (pain relievers or physical therapy as needed). The investigators found not only that all three types of acupuncture were more effective at relieving lower back pain than usual medical care, but also that the three were equally effective. In other words, toothpicks were just as good at relieving back pain as acupuncture needles.

Critics point out that the investigators used toothpicks to stimulate valid acupuncture points, so it's possible that this may have released *qi* or endorphins. But other observers believe that this study strengthened the evidence that acupuncture may work by eliciting the placebo response. As such, the toothpick study inspired a new set of trials designed to more carefully understand how that response works.

Enhancing the placebo

Two of the most recent acupuncture studies have been designed to evaluate the context in which acupuncture takes place, as well as the intervention itself.

In one trial, researchers at Harvard Medical School recruited 262 patients with irritable bowel syndrome (IBS) and randomly assigned them to three interventions, each designed to provide a specific placebo component. Those assigned to a waiting list were assessed and observed at baseline and at the end of the study, to control for clinical attention and the natural fluctuations of symptoms. The second group received sham acupuncture delivered in a neutral businesslike manner by clinicians using a retractable needle that did not pierce the skin, to invoke the expectation of symptom relief. A third group received the same type of sham acupuncture augmented by an "optimal" medical encounter, provided by a warm and understanding clinician.

The differences between the neutral and augmented clinical encounters were marked. In the neutral acupuncture group, the patient and clinician met initially for five minutes or less. Clinicians told the patients that because this was a scientific study, they were not supposed to converse during treatment. In the augmented acupuncture group, clinicians initially met with patients for 45 minutes, during which they used a structured interview that prompted them to ask patients about their symptoms, solicit the patient's own views about how they interpreted or experienced symptoms, use active listening techniques, and show empathy.

After three weeks, 62% of participants assigned to the augmented sham acupuncture group reported adequate relief of IBS symptoms, significantly more than the 44% reporting adequate relief in the neutral sham acupuncture group, which in turn was significantly greater than the 28% reporting adequate relief in the group that received only attention. The results suggested that it was possible to boost the placebo response in dose-escalation fashion.

In a more recent randomized controlled study, investigators at the M.D. Anderson Cancer Center compared traditional Chinese acupuncture with sham acupuncture for knee osteoarthritis, and further compared a neutral clinical style with a positive clinical style. They randomized 560 patients to one of three groups: 238 to a positive communication–style acupuncture group, characterized by optimistic clinicians (who said things like "I think this will work for you"), 242 to a neutral communication–style acupuncture group (who said outcome "really depends on the patient"), and 80 to a waiting list control group. Participants in each acupuncture group were further randomized to receive either Chinese acupuncture or sham acupuncture.

On the basis of three clinical scales, the investigators found that sham acupuncture performed just as well as traditional Chinese acupuncture at relieving pain—and (like the IBS study) that both were significantly more effective than staying on a waiting list. When the researchers divided results not by modality (sham versus real acupuncture) but by clinician communication style (high expectations versus neutral), they found that participants assigned to the high expectations group had significantly better pain relief scores on two of three scales than those assigned to the neutral group.

The knee pain study had several limitations. Notably, the sham acupuncture used needles that penetrated the skin slightly, possibly enough to stimulate endorphin release. And while the investigators attempted to "blind" the study by disguising the type of acupuncture participants were receiving, some of them might have been able to guess.

A healing context

The most recent acupuncture studies suggest that therapeutic context and warm, positive clinician-patient interactions may enhance the placebo response. This may come as little surprise to mental health clinicians, who understand the value of building a therapeutic alliance with patients (see *Harvard Mental Health Letter*, September 2004). But at a time when office visits are often reduced to 15-minute encounters, the acupuncture research provides a reminder that—although insurance companies may not want to reimburse for it—a caring encounter may be more likely than a rushed one to benefit the patient.

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For more references, please see www.health.harvard.edu/mentalextra.