

THE Placebo Phenomenon

An ingenious researcher
finds the real ingredients of
“fake” medicine.

by CARA FEINBERG

TWO WEEKS INTO Ted Kaptchuk's first randomized clinical drug trial, nearly a third of his 270 subjects complained of awful side effects. All the patients had joined the study hoping to alleviate severe arm pain: carpal tunnel, tendinitis, chronic pain in the elbow, shoul-

der, wrist. In one part of the study, half the subjects received pain-reducing pills; the others were offered acupuncture treatments. And in both cases, people began to call in, saying they couldn't get out of bed. The pills were making them sluggish, the needles caused swelling and redness; some patients' pain ballooned to nightmarish levels. “The side effects were simply amazing,” Kaptchuk explains; curiously, they were exactly what patients had been warned their treatment might produce. But even more astounding, most of the other patients reported real relief, and those who received acupuncture felt even better than those on the anti-pain pill. These were exceptional findings: no one had ever proven that acupuncture worked better than painkillers. But Kaptchuk's study didn't prove it, either. The pills his team had given patients were actually made of cornstarch; the “acupuncture” needles were retractable shams that never pierced the skin. The study wasn't aimed at comparing two treatments. It was designed to compare two fakes.

Although Kaptchuk, an associate professor of medicine, has spent his career studying these mysterious human reactions, he doesn't argue that you can simply “think yourself better.” “Sham treatment won't shrink tumors or cure viruses,” he says.

But researchers *have* found that placebo treatments—interventions with no active drug ingredients—can stimulate real physiological responses, from changes in heart rate and blood pressure to chemical activity in the brain, in cases involving pain, depression, anxiety, fatigue, and even some symptoms of Parkinson's.

The challenge now, says Kaptchuk, is to uncover the mechanisms behind these physiological responses—what is happening in our bodies, in our brains, in the method of placebo delivery (pill or needle, for example), even in the room where placebo treatments are administered (are the physical surroundings calm-

ing? is the doctor caring or curt?). The placebo effect is actually many effects woven together—some stronger than others—and that's what Kaptchuk hopes his “pill versus needle” study shows. The experiment, among the first to tease apart the components of placebo response, shows that the *methods* of placebo administration are as important as the administration itself, he explains. It's valuable insight for any caregiver: patients' perceptions matter, and the ways physicians frame perceptions can have significant effects on their patients' health.

For the last 15 years, Kaptchuk and fellow researchers have been dissecting placebo interventions—treatments that, prior to the 1990s, had been studied largely as foils to “real” drugs. To prove a medicine is effective, pharmaceutical companies must show not only that their drug has the desired effects, but that the effects are significantly greater than those of a placebo control group. Both groups often show healing results, Kaptchuk explains, yet for years, “We were struggling to increase drug effects while no one was trying to increase the *placebo* effect.”

Last year, he and colleagues from several Harvard-affiliated hospitals created the Program in Placebo Studies and the Therapeutic Encounter (PiPS), headquartered at Beth Israel Deaconess Medical Center—the only multidisciplinary institute dedicated solely to placebo study. It's a nod to changing attitudes in Western medicine, and a direct result of the small but growing group of researchers like Kaptchuk who study not *if*, but *how*, placebo effects work. Explanations for the phenomenon come from fields across the scientific map—clinical science, psychology, anthropology, biology, social economics, neuroscience. Disregarding the knowledge that placebo treatments can affect certain ailments, Kaptchuk says, “is like ignoring a huge chunk of healthcare.” As caregivers, “we should be using every tool in the box.”



Ted Kaptchuk in his home office in Cambridge

WESTERN MEDICINE, however, has been slow to agree with him—partly because of his message, and in his case, often because of the messenger. An acupuncturist by training, he is an unlikely leader in the halls of academia. With a degree in Chinese medicine from an institute in Macao, Kaptchuk is one of the few faculty members at Harvard Medical School (HMS) with neither a Ph.D. nor M.D.—“a debit, not a credit at most medical schools,” says Finland professor of clinical pharmacology emeritus Peter Goldman, one of his early Harvard advisers. (Kaptchuk’s diploma is recognized as a doctorate in many states, but not in Massachusetts.) When Kaptchuk came to Harvard in 1995, “he knew about Chinese herbs and healing needles, and he’d written a very fine book on Chinese medicine [*The Web That Has No Weaver* (1983)],” says Goldman, “but he didn’t know the first thing about how to conduct clinical studies.”

Kaptchuk joined the faculty as an instructor in medicine and apprenticed himself to several seasoned clinicians and investigators. Within a few years, he was winning National Institutes of Health grants and publishing in medicine’s top journals. “What his colleagues saw was a fierce intellect and curiosity,” said Goldman. “He was asking questions no one was asking.”

Ironically, says Kaptchuk, it was his success as an acupunctur-

ist that made him leave the profession for academia. “Patients who came to me got better,” he says, but sometimes their relief began even before he’d started his treatments. He didn’t doubt the value of acupuncture, but he suspected something else was at work. His hunch was that it was his engagement with patients—and perhaps even the act of caring itself.

For his ideas to gain traction with Western doctors, however, Kaptchuk knew he needed scientific proof. His chance would come in the early 2000s in a collaboration with gastroenterologists studying irritable bowel syndrome (IBS), a chronic gastrointestinal disorder accompanied by pain and constipation. The experiment split 262 adults with IBS into three groups: a no-treatment control group, told they were on a waiting list for treatment; a second group who received sham acupuncture without much interaction with the practitioner; and a third group who received sham acupuncture with great attention lavished upon them—at least 20 minutes of what Kaptchuk describes as “very schmaltzy” care (“I’m so glad to meet you”; “I know how difficult this is for you”; “This treatment has excellent results”). Practitioners were also required to touch the hands or shoulders of members of the third group and spend at least 20 seconds lost in thoughtful silence.

The results were not surprising: the patients who experienced

the greatest relief were those who received the most care. But in an age of rushed doctor's visits and packed waiting rooms, it was the first study to show a "dose-dependent response" for a placebo: the more care people got—even if it was fake—the better they tended to fare.

Kaptchuk's innovative studies were among the first to separate components of the placebo effect, explains Applebaum professor of medicine Russell Phillips, director of the Center for Primary Care at HMS. For years, doctor-patient interactions were lumped into a generic "placebo response": a sum of such variables as patients' reporting bias (a conscious or unconscious desire to please the researchers); patients simply responding to doctors' attention; the different methods of placebo delivery; and symptoms subsiding without treatment—the inevitable trajectory of most chronic ailments. "There was simply no way to quantify the ritual of medicine," says Phillips of the doctor-patient interaction. And the ritual, he adds, is the one finding from placebo research that doctors can apply to their practice immediately.

But other placebo treatments (sham acupuncture, pills, or other fake interventions) are nowhere near ready for clinical application—and Kaptchuk is not recommending that they should be. Such treatments all require deception on the part of doctors, an aspect of placebo medicine that raises serious ethical questions for practitioners.

This was disturbing for Kaptchuk, too; deception played no role in his own success as a healer. But years of considering the question led him to his next clinical experiment: What if he simply *told* people they were taking placebos? The question ultimately inspired a pilot study, published by the peer-reviewed science and medicine journal *PLOS ONE* in 2010, that yielded his most famous findings to date. His team again compared two groups of IBS sufferers. One group received no treatment. The other patients were told they'd be taking fake, inert drugs (delivered in bottles labeled "placebo pills") and told also that placebos often have healing effects.

The study's results shocked the investigators themselves: even patients who *knew* they were taking placebos described real improvement, reporting twice as much symptom relief as the no-treatment group. That's a difference so significant, says Kaptchuk, it's comparable to the improvement seen in trials for the best *real* IBS drugs.

ALTHOUGH this IBS "open-label" study was small and has yet to be replicated, fellow placebo researcher Frank Miller of the department of bioethics at the National Institutes of Health considers it a significant step toward legitimizing placebo studies. But to really change minds in mainstream medicine, Miller says, researchers have to show biological evidence that minds actually *change*—a feat achieved only in the last decade through imaging technology such as positron emission tomography (PET) scans and functional magnetic resonance imaging (fMRI).

The first evidence of a physiological basis for the placebo effect appeared in the late 1970s, when researchers studying dental patients found that by chemically blocking the release of endorphins—the brain's natural pain relievers—scientists could also block the placebo effect. This suggested that placebo treat-

ments spurred chemical responses in the brain that are similar to those of active drugs, a theory borne out two decades later by brain-scan technology. Researchers like neuroscientist Fabrizio Benedetti at the University of Turin have since shown that many neurotransmitters are at work—including chemicals that use the same pathways as opium and marijuana. Studies by other researchers have shown that placebos increase dopamine (a chemical that affects emotions and sensations of pleasure and reward) in the brains of Parkinson's patients, and patients suffering from

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depression who've been given placebos reveal changes in electrical and metabolic activity in several different regions of the brain.

Kaptchuk's team has investigated the neural mechanisms of placebos in collaboration with the Martinos Center for Biomedical Imaging at Massachusetts General Hospital. In two fMRI studies published in the *Journal of Neuroscience* in 2006 and 2008, they showed that placebo treatments affect the areas of the brain that modulate pain reception, as do *negative* side effects from placebo treatment—"nocebo effects." (*Nocebo* is Latin for "I shall harm"; *placebo* means "I shall please.") But nocebo effects also activate the hippocampus, a different area associated with memory and anxiety. As happened with Kaptchuk's patients in the "pill versus needle" study, the headaches, nausea, insomnia, and fatigue that result from fake treatments can be painfully real, afflicting about a quarter of those assigned to placebo treatment in drug trials (see "The Nocebo Effect," May-June 2005, page 13). "What we 'placebo neuroscientists'...have learned [is] that therapeutic rituals move a lot of molecules in the patients' brain, and these molecules are the very same as those activated by the drugs we give in routine clinical practice," Benedetti wrote in an e-mail. "In other words, rituals and drugs use the very same biochemical pathways to influence the patient's brain." It's those advances in "hard science," he added, that have given placebo research a legitimacy it never enjoyed before.

This new visibility has encouraged not only research funds but also interest from healthcare organizations and pharmaceutical companies. As healthcare companies increasingly reward doctors for maintaining patients' health (rather than for the number of procedures they perform), "research like Ted's becomes increasingly relevant," says Minot professor of medicine and HMS dean for graduate education David Golan, a professor of biological chemistry and molecular pharmacology.

This year, the Robert Wood Johnson Foundation, the nation's largest philanthropy focused on health and healthcare, awarded Kaptchuk's PiPS program a \$250,000 grant to support a series of seminars at Harvard designed to connect placebo experts with researchers in related fields. And the latest findings to emerge from PiPS—a 2012 study showing that genetic variations may explain why only certain people respond to placebo effects—has caught the attention of the Food and Drug Administration.

That study, published last October in *PLOS ONE*, showed that

patients with a certain variation of a gene linked to the release of dopamine were more likely to respond to sham acupuncture than patients with a different variation—findings that could change the way pharmaceutical companies conduct drug trials, says Gunther Winkler, principal of ASPB Consulting, LLC, which advises biotech and pharmaceutical firms. Companies spend millions of dollars and often decades testing drugs; every drug must outperform placebos if it is to be marketed. “If we can identify people who have a low predisposition for placebo response, drug companies can preselect for them,” says Winkler. “This could seriously reduce the size, cost, and duration of clinical trials...bringing cheaper drugs to the market years earlier than before.”

NOT ALL OF Kaptchuk’s studies have been so warmly received. Though few academics quarrel with the quality of his research, he’s remained a prime target for such watchdog groups as Quackwatch and The Skeptics’ Society, organizations that question nonconventional medical approaches. (Other well-known targets include Deepak Chopra, Andrew Weil ’63, M.D. ’68, and the late Nobel Prize winner Linus Pauling.) In 2011, he and a team of researchers published a paper in *The New England Journal of Medicine* (*NEJM*) that raised the hackles of some of his fiercest critics.

That paper (praised by scholars as one of the most carefully controlled and definitive placebo studies ever done) described a study of 40 asthma patients given four different interventions: active treatments with real albuterol inhalers; placebo treatments with fake inhalers that delivered no medication; sham acupuncture treatments; and intervals with no treatment at all. The patients returned for 12 sequential visits, receiving each type of treatment three times—a novel approach in placebo study that created a large amount of data (480 treatments in total) and turned subjects into their own controls (if patients are compared to themselves from one treatment to the next, researchers can eliminate subjects’ individual differences as a variable). The researchers had hoped to find improved lung function with both the real and sham treatments; what they found instead was that only the real treatment yielded results—the others showed no significant improvement. Yet when Kaptchuk’s team measured patients’ own assessments of improvement, the researchers found no difference reported between the real and sham treatments: the patients’ *subjective* responses directly contradicted their own *objective* physical measures.

To Dr. Harriet Hall, a retired family physician who writes critically about alternative and complementary medicine for such publications as *Skeptic Magazine* and *Skeptical Inquirer*, this discrepancy between objective and subjective results is precisely where the danger lies. As she told a reporter for *The Atlantic* in December 2011, following the publication of Kaptchuk’s *NEJM* study, “Asthma can be fatal. If the patient’s lung function is getting worse but a placebo makes them feel better, they might delay treatment until it is too late.”

To Kaptchuk’s team, on the other hand, the conflicting results not only reveal important lessons for researchers and clinicians, but illuminate a gap that is central to placebo research. “Placebos have limitations, and we need to know what they are,” Kaptchuk says. “We’d hoped for measurable objective changes in breathing; what we got instead was a more precise diagram of placebo effects and how clearly the ritual of medicine makes people more comfortable.” That in itself is important information, he says. “Our job is to make people feel better,” and though this study

was small, “what we’ve really done here is open up a new set of questions.” No one has yet studied how long-term experience with the ritual of medicine might ultimately affect the course of chronic afflictions, he says. “We hope we’ve opened up that path.”

Kaptchuk and his team have begun to take steps in that direction, continuing to ask new questions and push the boundaries of placebo research. A study published online this past year in the *Proceedings of the National Academy of Sciences* demonstrated that the placebo response can occur even at the unconscious level. The team showed that images flashed on a screen for a fraction of a second—too quickly for conscious recognition—could trigger the response, but *only* if patients had learned earlier to associate those specific images with healing. Thus, when patients enter a room containing medical equipment they associate with the possibility of feeling better, “the mind may automatically make associations that lead to actual positive health outcomes,” says psychiatry research fellow Karin Jensen, the study’s lead author.

Those findings led to the team’s most recent work: imaging the brains of physicians while they treat patients—a side of the treatment equation that no one had previously examined. (The researchers constructed an elaborate set-up in which the doctors lay in fMRI machines specially equipped to enable them both to see their patients outside the machine and administer what they thought was a nerve-stimulating treatment.) “Doctors give subtle cues to their patients that neither may be aware of,” Kaptchuk explains. “They are a key ingredient in the ritual of medicine.” The hope is that the new brain scans will reveal how doctors’ unconscious thought figures into the treatment recipe.

WITHIN ACADEMIA, Kaptchuk and his fellow researchers have not escaped criticism, but the voices have been few and far between. The most notable appeared in 2001 in the *NEJM*—the same publication that included Kaptchuk’s asthma study a decade later. In a paper titled, “Is the Placebo Powerless?” two Danish researchers reviewed 114 published studies involving 7,500 patients and questioned both the research methods and the short duration of most placebo studies. Many of the trials reviewed lacked “no-treatment” groups—an important control group missing even in Kaptchuk’s first “pill versus needle” study.

But Kaptchuk’s response to such criticism is perhaps as rare in academia as his pedigree. “If I remember correctly,” said Asbjorn Hrobjartsson, the lead author of that 2001 paper during a recent phone conversation, “Ted was already thinking along the same lines as we were and realized [our paper] pointed out real methodological problems.” When Hrobjartsson came to speak at Harvard a year later, he stayed at Kaptchuk’s home, and in 2011, the two coauthored a paper (with the NIH’s Frank Miller) on biases and best practices in placebo study.

When Kaptchuk talks about Hrobjartsson’s 2001 paper now, he winces, then nods with acceptance. “At first when I read it, I worried I’d be out of a job,” he says. “But frankly, [Hrobjartsson] was absolutely right.” In order to legitimize his findings to mainstream practitioners, the results must be expertly quantified, he acknowledges. “We have to transform the art of medicine into the science of care.” ▽

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