

When Pretending Is the Remedy

Scientists are dissecting the placebo effect in hopes of deploying its active ingredients as treatments | **By Trisha Gura**

Back in the 18th century, German physician Franz Mesmer peddled a concept called animal magnetism. Creatures contain a universal fluid, he asserted, that when blocked in flow, caused sickness. Mesmer used magnetized objects to redirect that flow in patients, initiating unusual body sensations, fainting, vomiting or violent convulsions that ended in profound salubrious effects.

Skeptical, Benjamin Franklin and French chemist Antoine-Laurent Lavoisier simulated one of Mesmer's typical sessions in 1784. They asked people suffering from ailments ranging from asthma to epilepsy to hug "magnetized" trees. The people swooned and shook, as expected. But then the researchers divulged that the trees were never magnetized. And everyone realized that something else was inducing the reactions to the trees. That something was later dubbed the placebo effect.

In the centuries since, the placebo response—that is, the beneficial result in a patient from an inert substance or bogus procedure—has emerged repeatedly in many forms. Researchers have shown that sugar pills reverse insomnia, fake injections relieve pain and sham surgeries treat Parkinson's disease.

Responses to such dummy treatments can be surprisingly powerful. Studies on placebos for depression show, for example, that they can reproduce more than 80 percent of the positive effects of antidepressants. That potential power has motivated a growing cadre of researchers to study the placebo, backed by an abundance of support from federal agencies, foundations, pharmaceutical companies and advocates for alternative health. "Right now we are overfunded," says Ted J. Kaptchuk, director of the newly launched Program in Placebo Studies at Beth Israel Deaconess Medical Center in Boston. "We have a lot of NIH projects. We are actively courting the pharmaceutical industry, and we have no problem getting entry."

One big challenge, however, is that placebo responses remain unpredictable. People given the same





The power of the placebo is most prominent in mental illness and other ailments in which improvement is subjective. In disorders such as asthma, placebos may make people feel better even if objective measures indicate they do not work.

pill or potion may show wildly different reactions. The effects can vary widely by illness. Pain, insomnia, fatigue, nausea, and disturbances to bowel, urinary or sexual function seem the most amenable to placebo treatments; broken limbs the least. Attempts to explain such variation have led scientists to delve deeper into the nature of the placebo effect. They have found that it shows up most prominently in illnesses that have a strong psychological component or when improvement is measured using subjective reports from patients.

With better neuroimaging tools and more sophisticated experimental designs, investigators are deconstructing placebo responses in the brain. They are finding that placebos can tap circuits governing expectation, attention and emotion. A placebo's power in these realms depends on social and environmental cues that act around the dummy pill, prick or potion. The doctor's behavior, for example, plays an essential role. "The placebo is

about the terrain of medicine," Kaptchuk observes. "What things are said; how the doctor behaves. It's the rituals and symbols—sitting in the waiting room, the patient exam, et cetera. And then, at the psychological level, it is the active ingredients of hope and trust and imagination, which are really antithetical to a scientific world."

Doctors hope to use this antithetical collection of findings to predict when and where a placebo will work and enhance its benefits in the clinic—ideally without deception. As the data reveal the biological mechanisms behind these "sham" remedies, placebos may become standard medical fare, used to augment and, in some cases, replace approved drugs and therapies. Incurable conditions, such as chronic pain, asthma and Alzheimer's disease, may one day yield to placebos, Kaptchuk suggests. Mesmer's idea of animal magnetism may have been bunk, but what he inadvertently tapped was not.

Subjective Salve

Placebos debuted in contemporary medical research, not as objects of study but as tools for clinical experiments. In 1955 Harvard Medical School physician Henry K. Beecher published a landmark report in which he estimated that 35 percent of any treatment group responded to a placebo. Entitled "The Powerful Placebo," the study offered evidence from 15 clinical trials of 1,082 patients to back up his claims of the existence of a placebo effect. He pushed for trials that compared patients taking drugs with those taking placebos. Only in 1968 did the Food and Drug Administration formally usher placebos into standard clinical trials as a way of ensuring that drugs worked as manufacturers claimed.

Meanwhile astute practitioners such as Kaptchuk were noticing something mysterious happening with their patients. Perhaps the most unusual associate professor at Harvard Medical School, Kaptchuk holds no Ph.D. or M.D. Instead, after graduating from Columbia University in 1968, he took off for Macao, China, earned a doctor of Oriental medicine (OMD) degree in 1975 and began to practice acupuncture a year later. Af-

FAST FACTS

Something behind Nothing

1» Dummy treatments can be surprisingly powerful. Placebos for depression can reproduce more than 80 percent of the positive effects of antidepressants.

2» In the brain, placebos tap circuits governing expectation, attention and emotion.

3» Doctors may someday routinely use placebos to augment and, in some cases, replace approved drugs and therapies.

ter 15 years, he realized that the needles themselves could not account for the curative effects of his practice. He quit and set out to explore what else was helping his patients feel better.

In studies conducted over two decades, Kaptchuk and others found that Beecher's initial estimates were flawed. For starters, Beecher had not separated patients' responses to the placebo from other phenomena, such as the fact that some patients simply got better with time. Even more curious, different placebos worked optimally for different ailments. Pills worked better for insomnia, for example, whereas shots provided the best pain relief. And placebo effects could occur by proxy. For instance, parents can help their child get better simply by feeling positive about their child's prescription.

Just as placebo studies seemed to be gathering force, in 2001 a Danish group dropped a bombshell. Epidemiologist Asbjørn Hróbjartsson of the Nordic Cochrane Center in Copenhagen and his colleagues conducted a meta-analysis in which they reviewed 114 trials that investigated 40 clinical conditions. In each, patients randomly received either a placebo or no treatment. Investigators found little evidence that placebos had significant clinical effects. Yet in that study, entitled "Is the Placebo Powerless?" and in two others published in 2004 and 2010, Hróbjartsson also found incredible variability in placebo responses. "We are seeing a dramatic effect in some laboratories and trials but lack of effect in others," he says.

One source of that variability was in how researchers tracked improvement. If doctors measured success by medical, objective measures such as blood pressure, placebos did not appear to work. But in certain settings, if researchers tracked recovery by how patients reported they felt, then placebos revealed their potency, especially in conditions such as pain and nausea.

Indeed, in 2002 Harvard psychologist Irving Kirsch found results consistent with the idea that the power of placebos is evident mostly when improvement is subjective, as it is in mental illness. In a meta-analysis of 47 trials of six of the most widely prescribed antidepressants, Kirsch and his colleagues discovered that 82 percent of the improvement in mood, as measured by a standard questionnaire, could be duplicated by giving patients a placebo pill instead of an antidepressant. In a similar study published in 2008, Kirsch and his colleagues found that the only people in whom antidepressants worked significantly better than placebo pills were patients with the


most severe cases. He reached a controversial conclusion: "Unless your patient is extremely depressed, you shouldn't be prescribing an antidepressant."

Placebos also seem to work on a subjective level in nonpsychiatric conditions, such as asthma. In a 2011 study Kaptchuk, Kirsch and their colleagues gave 46 volunteers with asthma either an inhaler with a drug (albuterol), an inhaler with saline, sham acupuncture or nothing. During each of 12 visits, researchers measured how much air the patients could inhale and exhale, both before and after treatment. The respiratory scores of those treated with albuterol rose by 20 percent, whereas all the others got just a 7 percent bump, suggesting the placebos had no effect.

But when the researchers asked the asthma sufferers to rank their respiratory discomfort on a scale of 0 to 10, everyone except those who got no treatment reported a 50 percent improvement. Even though the drug was causing a "robust" medical effect, as compared with the placebo, patients could not reliably detect the difference. Perhaps the placebo activates a mechanism that is distinct from the pharmaceutical's targeted pathway but, in some respects, is equally effective. "A medical treatment has two components: the actual pharmacological effect and the placebo component of the active treatment," Kirsch says.

The Brain against Pain

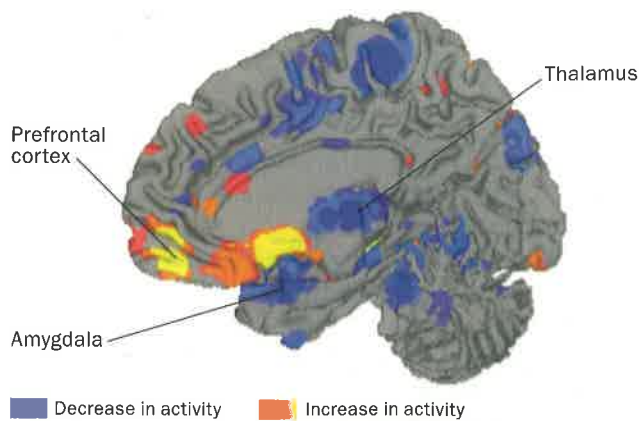
To further unravel that placebo component, neuroscientists have also been mapping the brain's response. In a pioneering 2002 study psychiatrist Predrag Petrovic of the Karolinska Institute in Sweden and his colleagues investigated the placebo's brain signature in pain relief, something scientists had previously linked to changes in the body's endorphin system. Petrovic and his colleagues told nine healthy volunteers that they would be receiving two potent painkillers, but only sometimes did the injection consist of the opioid remifentanyl; in other cases, it was saline. Forty seconds after an injection, the team stimulated a subject's left hand with an electrode that either heated to the point of pain, gave off benign warmth or provided no sensation at all. Meanwhile the researchers scanned subjects' brains using positron-emission tomography.



As data reveal the mechanisms behind these "sham" remedies, placebos may become standard medical fare. Incurable conditions such as chronic pain, asthma and Alzheimer's disease may one day yield to placebos.

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Belief can bring pain relief. When people thought they were getting a painkiller, the prefrontal cortex, which attaches meaning to pain, suppressed emotion areas such as the amygdala and pain perception hubs such as the thalamus, bringing respite.

Both the opioid and the saline activated a network of brain regions consisting of the brain stem, a seat of the opioid system that mediates pain relief, and the rostral anterior cingulate cortex, which is rich in opioid receptors and part of the body's reward system. Petrovic proposed that placebos, as with opioids, might be working by triggering cortical areas such as the anterior cingulate that, in turn, exert control over the analgesic systems of the brain stem.

In 2004 neuroscientist Tor D. Wager of the University of Colorado at Boulder and his colleagues further dissected the painkilling effect of a placebo using MRI and found that it involved additional brain regions. (The researchers also chose pain because it is easy to manipulate in a scanner.) The researchers administered a placebo cream while giving people painful shocks or putting intense heat on their forearms. In one experiment, they gave subjects a warning cue, a red "get ready" sign, just before those subjects received the painful stimulus. With that signal, participants expected pain, unless the cream was applied, in which case they expected relief. That expectation of relief first activated a cognitive "executive" center of the brain called the prefrontal cortex. After that, activity in the pain response areas of the brain declined, and subjects reported relief. This temporal pattern of brain activity suggested that placebo pain relief involves an expectation signal from the prefrontal cortex that tells the midbrain to release opioids to meet the expectation of reprieve. "There is a cognitive mechanism driving the opioid system," says Petrovic, who, in a reanalysis of his 2002 study, also pinpointed regions of the prefrontal cortex as drivers.

The placebo effect seems to involve emotions, too. Wager went on to reanalyze his 2004 data with a computer technique

that searches for patterns of brain activity that predict the best placebo responses. Wager and his colleagues reported in 2011 that a robust placebo effect was usually accompanied by changes in activity in regions of the brain that are charged with emotional appraisal, such as the insula, orbitofrontal cortex and amygdala.

This pattern is consistent with what Wager calls "endogenous regulation," the ability of humans to reinterpret their situation. In addition to boosting expectations of respite, placebos may somehow give people a better perspective on their predicament. Under the influence of a placebo, Wager speculates, people reevaluate what their pain means, reducing its emotional significance—say, deciding the pain will abate rather than cause persistent disability. During a placebo response, "our brain is likely doing a lot of the work without our real conscious input or even in spite of our conscious desires," he says. That is, people are unconsciously engaging brain mechanisms that serve to soothe.

Surprisingly, that self-soothing process may require focusing on the pain more than thinking about something else. Wager

and his colleagues conducted another study, published in 2012, in which they tried to distract individuals away from experimentally induced pain by giving them another task. But the distraction did not help the participants feel better. Instead when the researchers coaxed subjects to pay attention to the heat on their arm by asking them to rank its intensity, the subjects experienced greater relief. This outcome is consistent with "acceptance" or "relaxation response" therapies in which people surrender to their pain to better tolerate it.

Together these results suggest the placebo response consists of a particular pattern of brain activity that can be differentiated from that triggered by an active medication. Wager's team gathered backing for that idea in another study published in 2012. This time the investigators carefully separated expectation of pain relief from the effects of a medication (remifentanyl). The team found

that both the drug and expecting to get the drug (but actually receiving a saline placebo) reduced people's self-reported pain. More important, the expectation component worked via a separate mechanism, increasing activity in the prefrontal cortex and reducing it in emotion areas, whereas drugs influenced the pain-processing brain areas more directly and did so later, when levels of remifentanyl had a chance to reach their peak in the brain. Given these findings, placebo responses could add to the effective-

Distraction from the pain did not help participants feel better. On the contrary, they felt more relief when scientists made them pay attention to the heat on their arm by asking them to rank its intensity.

Attention from a doctor can be an effective placebo. In one study, the more care and concern for a patient a doctor expressed, the more likely the patient was to report relief from irritable bowel syndrome.

ness of a painkiller—or a drug for depression, nausea or rheumatoid arthritis.

Dosing the Doctor

If placebos offer a separate brand of therapy, doctors might like to explicitly add them to a treatment regimen or enhance their effects—ideally, without having to trick patients. “The ethical problem in practice is feeding your patients the presumption that in order for a placebo to be effective,” Kirsch says, “the person had to be deceived into thinking he was getting a real medication.”

One way to circumvent deception is to invoke the doctor-patient relationship. In a 2008 study of 262 patients with irritable bowel syndrome (IBS), Kaptchuk’s team assigned the patients to either placebo acupuncture or a waiting list. The researchers further subdivided the placebo group into those offered no conversation with the acupuncturist and those who received a heavy dose of attention, empathy and interaction from the practitioner. He or she actively listened to each patient’s problem, repeated his or her words, expressed confidence, touched the patient and lapsed into 20 seconds of thoughtful silence. “We laid it on,” Kaptchuk says.

The special care paid off. Researchers found a dose-response relation between the degree of doctoring and the proportion of patients who got better. Of the group sitting on a waiting list, 28 percent of people reported that their bowel symptoms improved. Of those receiving the bare-bones doctor-patient ritual, 44 percent reported significant relief. Among those who received a lot of attention from their doctor, 62 percent said they felt better. Thus, by simply manipulating a physician’s bedside manner, the placebo can be dosed.

In as yet unpublished results, Kaptchuk’s group discovered evidence that another aspect of this manner could be calibrated: empathy. The team gathered 12 physicians and put them in MRI scanners while the doctors thought they were offering a patient relief from the pain of a hot electrode strapped to his or her wrist. (The “patient” was really a confederate of the researchers.) In a doctor’s brain, the act of providing pain relief looked a lot like the response in a patient’s brain when he or she expected and perceived pain relief in previous experiments: an increase in activity in both the prefrontal cortex and the anterior insula, an



indicator of empathy for pain. Doctors also reported feeling relief. “You do sort of bond and feel some kind of responsibility to the patient,” says Michelle Dossett, a general practitioner in Boston who participated in the study. Finding ways to boost a doctor’s empathy and ability to transmit that feeling to patients might thus lead to an effective placebo.

Physicians might also be able to productively deliver fake pills and procedures without deception. In a 2010 study Kirsch, Kaptchuk and their colleagues gave 40 patients with irritable bowel syndrome pills they described truthfully as “placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes.” After taking these “open label” pla-

cebos twice daily for 21 days, patients reported feeling better overall and having less severe symptoms than the 40 patients who received no treatment.

Researchers are working to better understand and manipulate both the softer, environmental and harder, brain-based aspects of placebo responses. Perhaps one day physicians will be explicitly trained to express empathy or to use language that creates hope and expectation—with the placebo effect in mind. Someday, too, MRI scans might be used to predict placebo responses for individuals in advance. “It is really turning the art of medicine into a science of the art,” Kaptchuk says. “Can we really understand what is usually considered intangible, fringe or ignored and elevate it to a level of serious scientific inquiry?” Doing so, he says, would advance science and improve health. **M**

(Further Reading)

- ◆ **Placebos and Painkillers: Is Mind as Real as Matter?** Luana Colloca and Fabrizio Benedetti in *Nature Reviews Neuroscience*, Vol. 6, pages 545–552; July 2005.
- ◆ **The Emperor’s New Drugs: Exploding the Antidepressant Myth.** Irving Kirsch. Basic Books, 2010.
- ◆ **Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome.** Ted J. Kaptchuk et al. in *PLOS One*, Vol. 5, No. 12, Article No. e15591; December 2010.
- ◆ **How Placebos Change the Patient’s Brain.** Fabrizio Benedetti, Elisa Carlino and Antonella Pollo in *Neuropsychopharmacology Reviews*, Vol. 36, pages 339–354; 2011.
- ◆ **How Expectations Shape Pain.** Lauren Y. Atlas and Tor D. Wager in *Neuroscience Letters*, Vol. 520, Vol. 2, pages 140–148; June 29, 2012.

A LIFELINE FOR ADDICTS

Restoring the brain's flexibility may help addicts act on their desire to quit

BY MICHELE SOLIS

Reid had been drinking hard since 1994, when sickness, his father's death and business troubles had him reaching for more alcohol than usual. Eventually he was knocking back 10 or more drinks a day. In 2009 his family leveled an ultimatum. He had to give up alcohol or get out.

"That choice sounds real simple, but it's very, very hard," says the 58-year-old college-educated businessman, whose last name has been withheld. "I've got a wife to die for and two of the greatest kids in the world, and I'm sitting there looking in the mirror, asking myself, 'You're going to give all this up for that drink?'" he remembers. Still, he drank, secretly downing miniature bottles of vodka while walking the dog, hiding out in the bathroom or going through the car wash.

An alcoholic's sense of being trapped in old habits reflects an underlying resistance to learning that scientists are now documenting at the molecular level. Over the past five years researchers have turned up evidence that using drugs and alcohol causes a loss of flexibility in the brain, including in the regions needed for changing habits. Even brief periods of drug use damage the junctions between neurons, known as synapses. Their healthy operation is critical to translating will into action. The very structures needed to dig a person out of addiction are eroded by drug use.

Researchers are now looking for ways to replenish this flexibility with compounds that adjust how the neurotransmitter glutamate, a chemical messenger in the brain, operates at the synapses. "We're trying to restore the brain machinery that al-

lows a person to regain more control over their behavior," says Peter W. Kalivas, a professor at the Medical University of South Carolina, who studies the role of glutamate in addiction.

Returning the brain to a state where it is open to change, rather than resistant to it, could kick-start recovery. "This is not going to cure addiction, but it's definitely going to help," says Nora D. Volkow, director of the National Institute on Drug Abuse.

Drug-Induced Learning Problems

In the past scientists had focused primarily on how drugs take hold of the brain's reward regions. The new research on glutamate seeks to explain not how addiction sets in but why it is so hard to beat.

Even when addicts desperately want to stop, for fear of losing a job, a spouse or their life, they often still persist in taking drugs. Experts suspect this disconnect happens because drug use impairs a person's capacity to learn. Although scientists have long known that drug use induces a variety of cognitive shortcomings, during the past 10 years the learning deficit has emerged as a key reason why addicts stay addicted. In particular, addicts struggle to break old habits—even those not related to drug use.

This difficulty with developing a new routine can be measured in laboratory tests of "reversal learning" that ask a person to change how he or she responds to a familiar prompt. Addicts can learn an initial rule perfectly well, but they run into trouble when the rules change. In a 2006 study, for example,