

Health

PLACEBO'S NEW POWER

What the emergence of the “honest placebo”
says about healing in America

BY ALEXANDRA SIFFERLIN



FOR OVER 20 YEARS, LINDA BUONANNO lived in fear that her irritable bowel syndrome (IBS) would suddenly interrupt her daily routine with frequent trips to the bathroom and unbearable cramping. Buonanno, now a 71-year-old medical assistant and hairdresser from Methuen, Mass., tried everything from drugs to dairy-free diets. Nothing worked. She remembers a particularly tough period over 10 years ago, when she was working on the factory floor of a medical-device company for up to 10 hours a day, six days a week. When an IBS episode would strike, her co-workers would cover for her as she huddled in a corner, keeled over in pain. If she wanted to go dancing with friends at the local club on Sunday, Buonanno would stop eating on

PHOTOGRAPHS BY ZACHARY ZAVISLAK FOR TIME



Health

Friday so there wouldn't be anything in her system to interrupt her plans. "It was a horrible way to live," she says.

One day in 2009, she saw a TV ad looking for people with IBS to enroll in a study. She signed up and was thrilled when she was among about 80 people selected to take part in a first-of-its-kind clinical trial. But when she found out what kind of treatment she'd be receiving, Buonanno felt deflated: a placebo pill. The doctors told her there were no active ingredients in the pills, and the word PLACEBO was labeled clearly on the bottle. She felt she'd gotten her hopes up for nothing.

Three weeks later, after taking the pill twice daily, Buonanno was symptom-free. She had never gone so long without an attack. "I didn't have a clue what was going on," she says. "I still don't."

The medical community has been aware of the placebo effect—the phenomenon in which a nontherapeutic treatment (like a sham pill) improves a patient's physical condition—for centuries. But Ted Kaptchuk, a professor of medicine at Harvard Medical School and one of the leading researchers on the placebo effect, wanted to take his research further. He was tired of letting the people in his studies think they were taking a real therapy and then watching what happened. Instead, he wondered, what if he was honest? His Harvard colleagues told Kaptchuk he was crazy, that letting people in a clinical trial know they were taking a placebo would defeat the purpose. Nevertheless, in 2009 the university's teaching hospital, Beth Israel Deaconess Medical Center, launched the first open-label placebo, or so-called honest placebo, trial to date, starting with people who had IBS, including Buonanno.

The findings were surprising. Nearly twice as many people in the trial who knowingly received placebo pills reported experiencing adequate symptom relief, compared with the people who received no treatment. Not only that but the men and women taking the placebo also doubled their rates of improvement to a point that was about equal to the effects of two IBS medications that were commonly used at the time. "I was entirely confused," says Kaptchuk. "I had hoped it would happen, but it still defies common wisdom."

Now Kaptchuk and his team at the Program in Placebo Studies and Therapeutic Encounter at Beth Israel Deaconess Medical Center have secured a \$2.5 million grant from the National Institutes of Health to replicate that first IBS trial. So far the researchers have treated 270 patients; they are hoping to treat a total of 340 people with IBS via their ongoing clinical trial.

It's unclear what underlies the placebo effect. Some experts argue that the human body subconsciously responds physically and physiologically to the ritual of treatment, like Pavlov's dogs, while others argue it's the power of positive thinking. For better or worse, entrepreneurs are beginning to pay attention, and you can now buy placebo pills on Amazon for \$8 to \$15 a bottle. Not everyone agrees that honest placebos work. It shouldn't make sense. And yet in today's medical environment, where the sense of being cared for can be lost behind ever higher medical bills and less and less face time with doctors, it can make all the sense in the world.

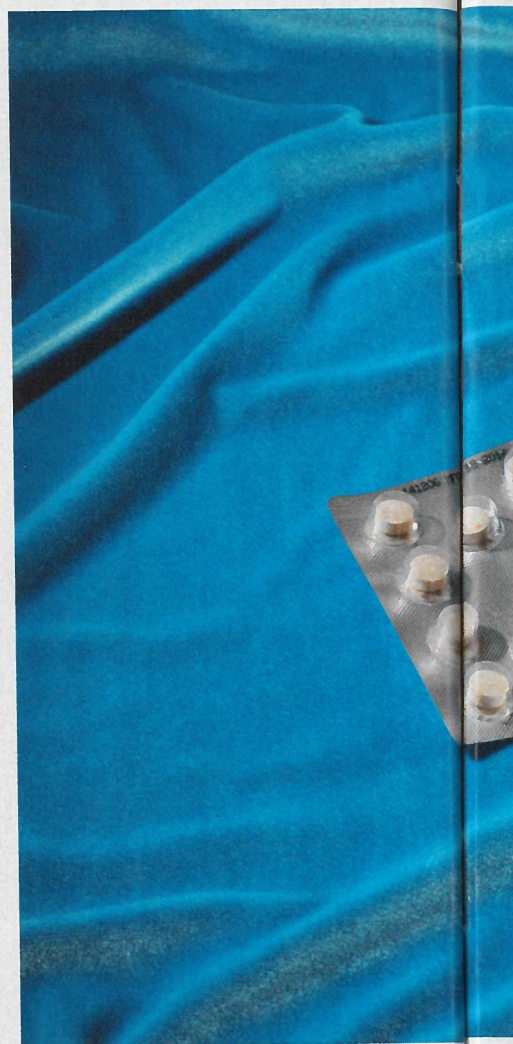
THE PLACEBO EFFECT has a long medical history. In 1807, President Thomas Jefferson wrote to a friend, "One of the most successful physicians I have ever known has assured me that he used more bread pills, drops of coloured water, and powders of hickory ashes, than of all other medicines put together." During World War II, an anesthesiologist named Henry K. Beecher observed that many wounded soldiers declined morphine to treat their pain, despite the fact that civilians with similar injuries would demand it. To Beecher, this suggested that living through trauma affected soldiers' perceptions of their pain and circumstances, and that a portion of people's ability to heal must come from their own psychological expectations. Following Beecher's insights, the placebo became an instrument in mainstream clinical practice in the advent of double-blind and randomized clinical trials, in which researchers began comparing their drugs with fake medications to assess just how effective a given treatment truly was.

Today placebo is well recognized in modern medicine. Doctors at the Houston Veterans Affairs Medical Center have shown that sham surgeries—slicing

people's knees open and sewing them back up without any treatment—provide the same improvements for people with osteoarthritis of the knee as real knee surgery. There's even a phenomenon known as the nocebo effect, in which people's negative expectations about something make them feel worse. Some experts believe the nocebo effect accounts for at least part of the growth in people reporting food sensitivities to gluten and dairy.

Researchers are learning that placebo has nuance too. For instance, the effect appears to be stronger if people are told a medication is hard to get or expensive, and color may also matter, with people responding better to blue pills as sedatives and white pills for pain. Still, a lot remains unknown. Some people have strong responses to placebos—including honest placebos—while others experience no impact at all, the same as happens with any treatment.

Since that first IBS study, Kaptchuk and his co-authors have shown in other research that people taking honest placebos





experienced more migraine relief than people not taking any treatment. Other researchers have found that patients who are aware they are taking placebos still see improvements in symptoms like cancer fatigue and seasonal allergies.

In a 2016 study published in the journal *Pain*, researchers including Kaptchuk randomly assigned 83 people with chronic low back pain at a hospital in Lisbon to either continue taking their pain medication as usual or start taking honest placebo pills with their typical treatment. Before the start of the study, the men and women filled out questionnaires about the intensity of their pain and how much disability it was causing them. After that, people treating their pain as usual continued to take their nonsteroidal anti-inflammatory drugs, while the people taking placebos were given bottles labeled PLACEBO PILLS with instructions to take the pills twice a day. After three weeks, the people in the study rated their pain and disability levels again. The researchers found that, on average, the group taking

painkillers reported a 9% reduction in usual pain, a 16% reduction in maximum pain and no reduction in disability. But the people knowingly taking placebos experienced a 30% reduction in both usual and maximum pain and a 29% drop in disability.

Kaptchuk doesn't fully understand what's going on, but he has some ideas. "Sometimes the body knows more than the mind," he says. He struggles to find adequate analogies, but likens it to watching *Romeo and Juliet* when you know what's going to happen. If the performance is evocative enough, even though you know it's fake, "your body

reacts in ways that go beyond the mind," he says. You might get a lump in your throat or tear up.

More important to Kaptchuk than understanding why honest placebos work is figuring out how the gain in scientific knowledge could translate into clinical practice. "Placebo has generally been denigrated in medicine, but I always wanted to figure out ways to ethically harness it," he says.

Scientists already know that the very act of being treated is enough to improve some conditions. Placebo effect may account for anywhere from 30% to 45% of response to antidepressants, for example, and a 2015 study found that the same people who respond well to placebo pills are also more likely to have better results when they take real antidepressants. But even if placebo or honest placebo can provide relief, placebos themselves rarely cure. It's unclear if the effects of a placebo can change the physiological processes that underlie a disease, even if they can ease a disorder's symptoms. A placebo cannot shrink a cancerous tumor, for example. Still, placebo treatments do appear to activate neurotransmitters in the brain that could play a role in symptom relief.

In Buonanno's case, after the initial three-week study ended in 2010, her IBS symptoms came back in full force for several years. Since she had already participated in the first Harvard honest placebo trial, she wasn't eligible to take part in one that's ongoing. Instead, Kaptchuk continues to treat her as a case study. Now, every six weeks, Buonanno drives 45 minutes for a checkup with Kaptchuk at his home clinic, where they discuss her condition and Kaptchuk gives her the antidote she's been taking for the past year: a bottle of sugar pills. "All I know is that it works," she says. "That's all I care about."

The question remains of how exactly the lessons learned from placebo trials should be embraced, and there's plenty of disagreement. Some critics argue that the concept of giving people placebo pills could eventually create a crutch, that people will assume they need a pill for every ailment. Other scientists are skeptical of the honest-placebo findings themselves, arguing that the results are exaggerated or prove only

34%

Percentage of Americans
who have great confidence in the
country's medical-industry leaders



the power of suggestion. Some critics claim the doctors must imply to people in trials that what they are taking will work, though Kaptchuk and his team insist they do not. He says his team picks conditions that have responded to blind placebo trials in the past, like back pain and migraines. They tell the participants that placebos have been shown to affect those conditions in studies in which people don't know they are taking them. They say they don't know if a placebo treatment can work if people know about it, but that's what they're testing.

"Placebo is not magic," says Alia Crum, principal investigator at the Stanford Mind & Body Lab, who is also studying placebo. "We view placebo effect as the product of your body's ability to heal, which is activated by our mind-sets and expectations to heal, and shaped by medical ritual, branding of drugs and the words doctors say."

Crum says honest-placebo research is fascinating and important, but she doesn't see doctors prescribing placebo pills anytime soon. Instead, she's interested in how doctors can get their patients into the right mind-set for medical care. "We've been pumping billions of dollars into developing new drugs and treatments without making much headway on the chronic-disease crisis," she says. "What if we spent that same time, money and effort on achieving a greater understanding of the patients' natural abilities to heal?"

In her research, Crum studies how adjusting factors in a patient's environment affects treatment. She has found that how warm and competent a doctor is when interacting with a patient can affect how that person responds to therapy.

In a March 2017 study, Crum followed 164 people who participated in an experiment in which a doctor induced a small allergic reaction on their arms through a histamine skin-prick test. All of the people developed a red swollen mark from the prick, but the size was much smaller among the people who thought their physician was highly competent and "warm"—because of behaviors like making eye contact and calling the patient by name—and who received affirmation from the doctor that a cream for the reaction would lessen the symptoms, even though there was nothing in it. What the competent

doctor said about the cream—either that it would make the rash worse or better—actually affected the physical appearance of the rash too.

On the other hand, people in the study had the largest bumps when they received the same treatment but felt their doctor was cold in personality and didn't offer any assurances that the cream would help their reaction. Not only that, but what the less competent doctor said about how the cream would react with the rash made no difference at all on its appearance.

"Doctors think it's good to have patients like you to get high rating scores," says Crum. "But it's actually important in making the treatment more effective."

Kaptchuk is less inclined to view placebo effect as mind-set alone and foresees a future in which a practitioner might send a person home with a bottle of placebo pills. Like Crum, he thinks doctor oversight is a crucial part of the puzzle. But before placebo researchers have had time to figure out the balance, entrepreneurs are already on the move.

JENI DANTO, a therapist and mother of five children ages 11 to 17, created a parenting hack called Magic Feel Good, which you can buy on Amazon for \$8.99. When her children were younger, it seemed that every week one child or another was suffering from phantom pain or a suspicious tummy ache before school. If she and her husband Akiva determined that the complaints weren't serious or even real, Akiva would slip into the kitchen and stir up a mixture of orange juice, grape juice and honey and then bring it to their child in a medicine cup, calling it "Magic Feel Good." "I think sometimes parents just give Tylenol," Jeni says. "It's not a judgment. It's a fact. We've all been there."

Danto realized that other parents

could benefit from their strategy and in 2014 created her product: a blister pack of vitamin C-enriched sugar pills for kids' mysterious aches and pains. The pills come inside a package designed to look like a fantasy book, with labeling that says the pills should be used only for nonmedical ailments. Magic Feel Good hasn't exactly taken off yet, but Danto thinks there could be growing interest in the future.

"I think people feel better when they are validated," she says. "When someone says they don't feel good, you're validating them by giving them something."

She may be right about a missing piece in medicine. There's a reason that research in the past decade has focused on the impact of empathy in medical care, showing it can improve patient satisfaction and outcomes while also easing doctor burnout. Most Americans feel that their providers are effective, but studies show that when patients have less empathetic doctors, they're less likely to say they are satisfied with their care or follow medical advice. It's about trust too. Survey results show that only 34% of Americans say they have great confidence in the country's medical-industry leaders, down from nearly 73% in 1966. Other research shows that Americans have less confidence in the health care system than people living in other developed countries.

Uwe Heiss, a self-described placebo activist and health care transformer, also sells placebo pills online, but catering to adults. His blue and white pills are called Zeebo and contain no active ingredients. Heiss has been selling them since 2015 and says the company has sold "thousands" of bottles to consumers, health care providers and clinical trials studying open-label placebo. Still, Heiss is keeping the company going with his own funds and is looking for sponsors to continue production. He takes his own pills daily, for things like pain and stress relief. Each time he takes a placebo pill, he says, he tries to focus on an intention and describe it out loud. For example, if he's taking a pill for back pain, he might say, "I am taking this pill to relieve my mind of the suffering from back pain." He's convinced it works and has written a book on the subject.

Dr. Jesse Hoover, a doctor of Eastern

**'I AM TAKING THIS PILL
TO RELIEVE MY MIND
OF THE SUFFERING
FROM BACK PAIN.'**

UWE HEISS, A SELF-DESCRIBED
PLACEBO ACTIVIST

medicine in Sante Fe, N.M., is a Zeebo customer and recently began offering the pills to some of his patients. Many of his clients feel they've exhausted other treatment options and come to him for therapies like acupuncture or Chinese herbal medicine. Hoover says that so far, his patients are skeptical of placebo pills, but he thinks the pills could be another option in his tool kit.

"In modern medicine, we discount the patient," says Hoover. "Many people have the experience of talking to the doctor for five minutes, and then the doctor turns to lab work. If a patient says they don't get night sweats, a doctor will write, 'Patient denies night sweats,' as if we can't trust that the patient realizes what they are experiencing. All of this sets us up to embrace something like placebos."

The American Medical Association is wary of placebos. In its Code of Medical Ethics, the group says doctors can use placebos for diagnosis or treatment only if they have patients' cooperation, obtain patients' consent to receive a placebo (even if they don't know when they are receiving it) and if they avoid using placebo simply to "mollify a difficult patient."

"Giving a placebo for such reasons places the convenience of the physician above the welfare of the patient," the association writes. "Physicians can produce a placebo-like effect through the skillful use of reassurance and encouragement, thereby building respect and trust, promoting the patient-physician relationship and improving health outcomes."

DESPERATION IS COMMON among the people participating in the honest-placebo trials, and the simple feeling of being taken seriously seems to go a long way. Buonanno says her IBS symptoms started soon after she got divorced 47 years ago, and she thinks her disorder is partly stress-related. She says her doctors, including Kaptchuk, tell her she can probably stop taking the placebo pills and that it's unlikely she would have any problems, but after several recurrences, she is too scared to do so.

"I am the kind of person that listens to professionals, and if they tell me to take this pill and that it's going to work, I believe them," Buonanno says. "It's the

PLACEBO HEALING

The rituals of medical care—even without drugs—may be powerful for healing, according to some studies



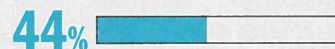
Doctor engagement

PATIENTS WITH IRRITABLE BOWEL SYNDROME WHO FELT RELIEF AFTER HAVING ...

No treatment



Fake acupuncture



Fake acupuncture and a warm, empathetic doctor



Positive expectations

PATIENTS GIVEN AN ALLERGY SKIN PRICK WHO WERE TOLD THAT A PLACEBO CREAM WOULD ...

SIZE OF RAISED BUMP

Decrease the reaction 4.7 mm

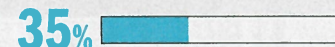
Increase the reaction 5.1 mm



Pill-taking rituals

PATIENTS WITH IRRITABLE BOWEL SYNDROME WHO FELT RELIEF AFTER RECEIVING ...

No pills



Honest placebos*



*DESCRIBED TO THE PATIENT AS INACTIVE MEDICINE, LIKE SUGAR PILLS

SOURCES: STUDIES BY TED KAPTCHUK (TABLE 1: BMJ, MAY 2008; TABLE 2: PLOS ONE, DECEMBER 2010) AND ALIA CRUM (TABLE 2: HEALTH PSYCHOLOGY, MARCH 2017)

combination of the mind over matter and the doctor's care. Something switches in your mind when you're desperate."

Response to any treatment is complex. Some people may be more responsive to the intention of treatment, and may do even better if therapies tap into their natural resiliency through quality doctor-patient relationships or better treatments.

"I've had patients tell me that if I told them to put on a pink tutu and dance because I thought it would help, they would do it," says Kaptchuk. "They know they are doing something totally ludicrous, but if they didn't have hope, they wouldn't get out of bed."

Kaptchuk and Crum agree that there are ways doctor-patient relationships could evolve to take advantage of some of the lessons from honest placebo trials, but that it is easier said than done in our current health care system. Time-crunched doctors don't necessarily have incentives to go the extra mile. "It's easy to bill for a medication or surgery," says Crum. "It's harder to quantify and give someone credit for the time and effort and attention and skill it takes to create relationships that are healing."

Crum and a colleague are working with Stanford Primary Care to roll out a curriculum called Medicine Plus, in which medical teams, including everyone from receptionists to physicians, learn how to create an environment that is most conducive for healing. The strategies focus on leveraging patients' mind-sets but build on the power of the placebo with the ultimate goal of helping medical practitioners harness the same forces that contribute to placebo effects alongside active medications and treatments, says Crum. Ideally, she says, one day these types of lessons should be incorporated into care much earlier, when health providers are in medical school.

Even a doctor's best bedside manner is not enough to cure someone of disease, but the new science of placebo begs the powers that be to pay attention to the small nuances of caregiving that matter. Placebo is complex, but it's not wizardry. Taking it seriously, even if it's unexplainable, may be worth the effort.

"It shouldn't come as a shock to us anymore that our minds affect our body," says Crum. "Why are we not asking what we're going to do about it?" □