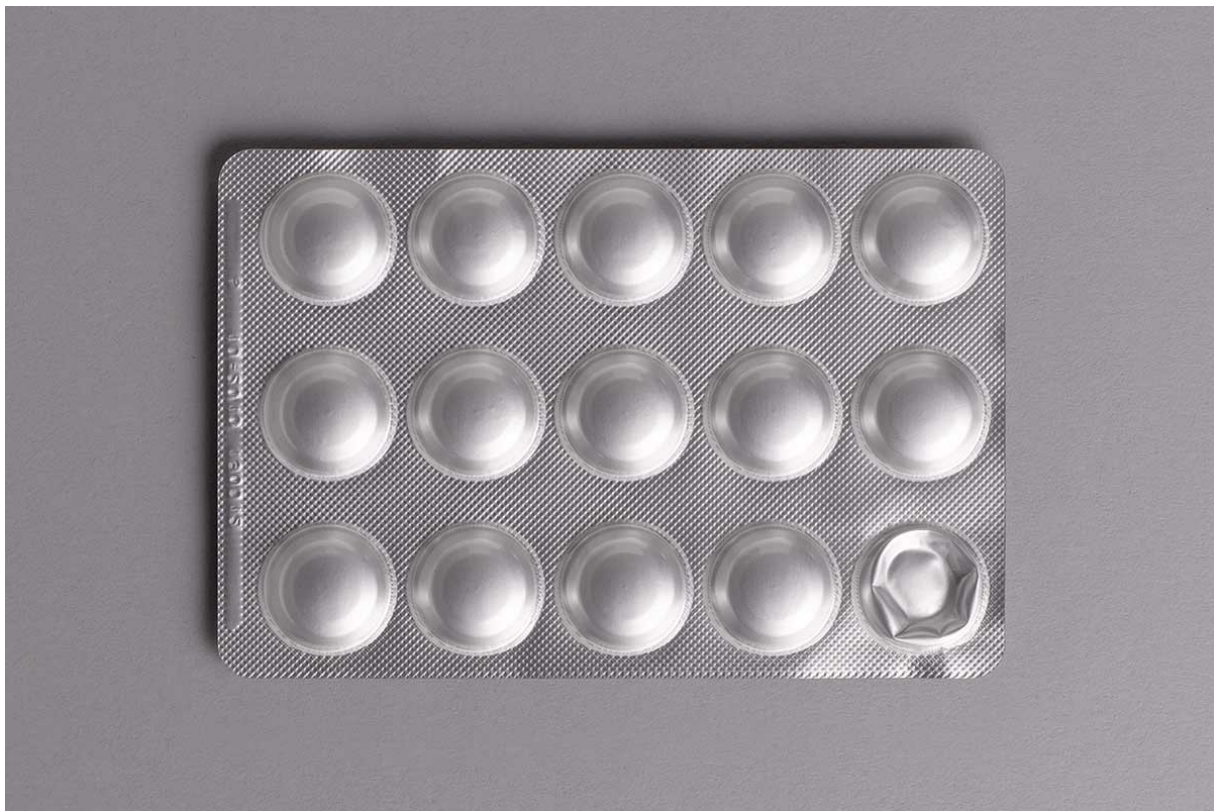


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Tap the placebo effect to unlock your body's healing powers

No side effects, non-addictive and makes you feel better. From IBS to insomnia, could the honest placebo be the treatment we've been looking for?



It's time for your placebo

Marcel Stive/Plainpicture

LINDA BUONANNO had been sick with irritable bowel syndrome for 15 years when she saw a TV advertisement recruiting participants for a new study. Desperate for help, she signed on, even after learning that the potential treatments she would be offered consisted of either nothing – or pills filled with nothing.

When the experiment ended, she begged the researchers to let her keep the pills. “I felt fantastic,” Buonanno says. “I felt almost like I was before I got sick with IBS. It was the

best three weeks of my life.”

She has been trying to get her hands on more ever since. A replication study will start later this spring, and Buonanno is desperately hoping she gets in.

This is the placebo effect in action, and it may come as a surprise to learn that it works even when people know they are being given a sham treatment. That finding has brought with it the possibility of using placebos as therapy. The vision is of a future in which clinicians cajole the mind into healing itself and the body – without the drugs that can be nearly as much of a problem as those they purport to solve.

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But before your doctor can prescribe you one of Buonanno's pills, a lot of slippery questions must be tackled: what conditions respond to the placebo effect? Where are the boundaries of this nascent science? More importantly, can we harness it with predictable effects?

The placebo effect has been on a considerable journey: once just a thorn in medicine's side, it is now the latest promising way to manipulate the mind into healing the body. Placebo controls are the gold standard of clinical trials, used to figure out whether a drug works better than nothing – but instead of obeying the rules and feeling no different when given a placebo, people often report beneficial effects.

“In drug trials, the placebo effect is the background noise they have to separate out,” says Ted Kaptchuk, the lead researcher behind Buonanno's trial at Beth Israel Deaconess Medical Center in Boston. “But we're saying, this noise is really important. We want to get that noise in the equation too.”

We now know that when a person is given a pill they're told is a real medication, or any of a wide range of medical interventions, including surgery, their body creates a real physiological effect. In pain studies, placebos have been shown to dampen activity in the brain's pain-processing areas and increase the production of the body's own analgesic chemicals (see "Your brain on placebo").

It may not be so surprising that pain should succumb to the power of suggestion, but the placebo effect also works on conditions that would not be considered to have a psychological component. People being treated for Parkinson's disease with apomorphine, were only told they might receive a dose of the drug. They showed more dopamine activity in parts of their brain normally affected by the real drug. Not even the immune system is immune: in one experiment, healthy participants spent three days taking pills containing immunosuppressant cyclosporin A – a drug used to help stop the body rejecting an organ transplant – with a fruit-flavoured drink. Five days later, they took placebo pills with the same drink. Blood tests showed that immune compounds suppressed by the actual drug also dropped with just the placebo and drink. Even faked surgical interventions have been shown to create real improvement.

Great expectations

One key to unlocking the body's self-healing mechanisms seems to be the setting up of an expectation of improvement. And it works the other way too: if you think your drug has been replaced with a placebo, even a strong painkiller's effects will be dulled. So how can we harness this effect, given that we know very little about how it works? In pursuit of that goal, Kaptchuk founded the Program in Placebo Studies, while groups in Germany, the UK, Italy and Australia are also studying how to integrate placebo insights into patient care.

There's just one problem: using placebo in this way requires deceit, which falls foul of several major pillars of medical ethics, including patient autonomy and informed consent. That was why Kaptchuk decided to try being honest with patients, and how Buonanno found herself taking pills packed with inert filler from a bottle marked "placebo".

IBS is one of those conditions, like depression and chronic pain, that is heavy with symptoms but has neither clear biological cause nor easy cure. Buonanno had spent years in pain; and no doctor or drug seemed to help.

The staff at the medical centre had explained to her that though the brightly coloured pills contained no medication, evidence from previous studies suggested that placebos could exert real effects in IBS by provoking a response from patients' own bodies. If she wanted to maximise the placebo's chance of working, they told her, it was important she take the pills exactly as instructed, twice a day. On the fourth day, she realised that her symptoms were gone.

Why does the honest placebo work? One theory concerns the expectations set by the intervention itself. "It's not just the drug, it's everything that surrounds the drug," says Kaptchuk. Placebos are not inert substances: they are made of verbal suggestion, classical conditioning, and a lifetime's associations learned about the cues of the medical ritual: the

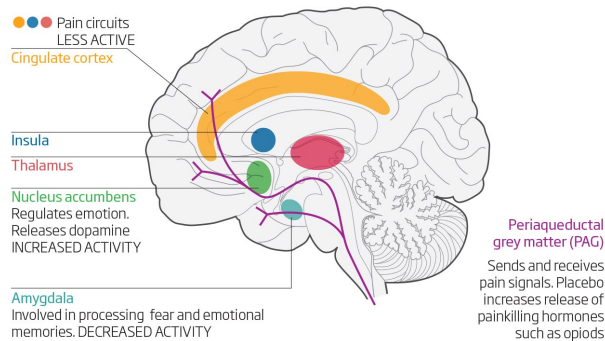
white coat, the office, the doctor's manner. (*Nature Reviews Neuroscience*, vol 16, p 403). Any and all of these may cue the body's healing powers.

The key word is "may": the placebo can be difficult to use. It doesn't work for everyone, and when it does, its effects can be unpredictable. In one pain study, for instance, some people reported feeling more pain, not less, and activity in their brain's painkilling opioid and dopamine systems decreased, instead of increasing like everyone else's. Another study flummoxed researchers by creating almost the opposite effect of what they intended: verbal suggestions intended to reduce nausea in one group and promote it in the other muddled the effects, not only subjectively but also physiologically.

Even when the results go your way, it's hard to understand why. In the small trial Buonanno participated in, 59 per cent of the honest-placebo group felt better. It wasn't much better than... placebo?

Your brain on placebo

Brain imaging studies have revealed specific areas of the brain are involved in the placebo effect



Much research is now under way to pin down what exactly makes any individual susceptible to the placebo response. Some studies implicate personality traits like optimism and a belief that you control your own destiny. Or is it suggestibility? "He's such a good doctor," Buonanno says of the study gastroenterologist. "So I said OK, I'll do anything to make anything work." Would her symptoms have still improved if she'd been more sceptical?

Other work is investigating whether any genetic links underlie the placebo response. One of Kaptchuk's collaborators, Kathryn Hall, has found a link between placebo responses in IBS and variations of a gene that breaks down neurotransmitters including dopamine and adrenaline.

And some are even looking into doctors' brains. Vitaly Napadow, a neuroscientist at Massachusetts General Hospital, plans to look at the brains of physicians and patients simultaneously while he approximates a doctor-patient encounter – albeit half both parties in separate fMRI machines. If it works, this could begin to tease out what brain areas are involved when the doctor gets the placebo right.

In the meantime, there are already a few things doctors can do to exploit the placebo effect

in clinical settings. In Germany, the Placebo Competence Team publishes suggestions for physicians. For example, giving a patient sufficient medical information helps, along with instructing them not to Google their symptoms. It's also important to tell a patient which medications they're taking and why. "It sounds trivial," says Ulrike Bingel, one of the placebo team, at the University of Duisburg-Essen, Germany. But in post-operative wards, people are often hooked up to multiple IVs. "Is this a painkiller, is it a steroid, an antibiotic? If the patient doesn't know, you might lose 50 per cent of the effect."

One form of placebo conditioning has recently had promising results, and could form part of a programme to wean people off opiate painkiller addiction (see "Sleeping it off"). Buonanno's experience hints at the power of these associations: after the study ended, she tried to continue the effect with substitute placebos from health food stores. But they didn't look the same, and they hadn't been prescribed to her. "Nothing" failed.

So why had it worked in the initial trial? Was it the form of the pills? The empathetic staff? The medical environment?

This spring, the new study aims to find out. Kaptchuk's group will repeat the IBS trial, but this time it will include genetic testing, along with in-depth psychological interviews to unravel exactly which expectations and beliefs make the difference. Every word uttered by the staff will be carefully scripted to minimise the wrong impression.

While expectations come in many forms, one might be the biggest of all. "If we're ever going to use placebos in clinical practice, they can't be the booby prize," Kaptchuk says. "We have to change the culture and meaning of the word placebo."

Linda Buonanno is a good start.

Discover more about harnessing the power of your mind

Sleeping it off

The US is in the grip of a major opiate addiction crisis. Prescriptions for these painkillers have shot up nearly three-fold in two decades.

Placebos may help people ramp down use of such habit-forming drugs. In a 2015 study at the University of Pennsylvania, sleep researcher Michael Perlis asked people with insomnia to take a high nightly dose of the hypnotic drug Ambien. Then for one group he replaced the active pills with an identical-looking placebo, every other night. For the next 12 weeks, these insomniacs slept just as well as the group who took Ambien every night – with half the dose.

It was a small study, but Perlis think it could work just as well to reduce opiate painkiller use. "This should work anywhere," he says.

This article appeared in print under the headline "The right kind of nothing"