PLACEBOS

Honest fakery

Armed with a clearer understanding of how placebos work, researchers are suggesting that inactive substances might be used to mitigate chronic pain.

BY JO MARCHANT

In April, Ted Kaptchuk addressed hundreds of physicians and scientists at the Behind and Beyond the Brain symposium in Porto, Portugal. Within minutes, ripples of laughter were spreading around the conference hall.

Kaptchuk, a researcher at Harvard Medical School in Boston, Massachusetts, was showing the audience a cartoon in which a doctor hands over a prescription note. "I want you to take this placebo," says the white-coated medic to her bemused patient. "If your condition doesn't improve, I'll give you a stronger one." The chuckles were a response to the absurdity of openly treating a patient with fake pills. By definition, placebos have no active ingredient, so the idea that someone might benefit from knowingly taking one — let alone that different placebos could have different effects — seems nonsensical. But Kaptchuk invited his audience to take the scene seriously. Honest placebos can work, he insisted. And some placebos really are stronger than others.

Kaptchuk's trials are overturning many assumptions about the best way to care for patients, particularly those in pain. After four decades of probing the mechanisms of placebo responses, researchers are advancing the argument that inert pills are more than just negative controls in clinical trials: they can be a treatment in their own right.

PLEASING MEDICINE

The modern idea of the placebo effect stems from 1955, when US physician Henry Beecher analysed the results of 15 studies and concluded that, regardless of a patient's complaint, around one-third showed a significant response to a placebo[1]. The effect is now well-established, particularly for conditions that rely on subjective reports, such as pain.

There are lots of reasons why someone in a clinical trial might feel better. Symptoms often ease with time, or trial participants might report an improvement to please the experimenters. Because of this, placebo responses are commonly viewed as illusory — a baseline against which to compare the action of new drugs. But there is now a large body of research showing that the effects of placebos can be very real.

Fabrizio Benedetti, a placebo researcher at the University of Turin, Italy, points to a 1978 study[2] by neuroscientist Jon Levine that, he says, represents the moment that "the biology of placebo was born". Levine and his colleagues administered intravenous infusions of saline to patients who were recovering from surgery, telling them that it might be morphine. One-third of them reported a significant reduction in pain. Then, the researchers secretly added naloxone, which blocks the action of painkillers such as morphine by binding to opioid receptors in the brain, to the infusions and the patients' pain returned. Levine had shown that a placebo response could be biochemically blocked.

Levine's study was revolutionary because it suggested that patients don't simply imagine or pretend that their pain is eased with placebos. Their analgesia reflects a measurable, physical change — mediated by the release in the brain of endogenous opioids called endorphins[2]. This finding has since been confirmed by dozens of brain-imaging studies, which show increased binding of endorphins to opioid receptors in response to placebo painkillers, as well as reduced activity in areas of the brain involved in processing pain[3].

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Endorphins aren't the only neurotransmitters involved. Placebos can activate endocannabinoids (which bind to the same receptors as the psychoactive constituents of cannabis) or dopamine, or they can reduce the levels of prostaglandins (which dilate blood vessels and increase sensitivity to pain). In general, Benedetti says, "placebos can modulate the same biochemical pathways that are modulated by drugs".

Inert substances cannot, of course, create biological changes. A placebo's active ingredient, says Kaptchuk, is a person's psychological response to being treated. Tor Wager, a neuroscientist at the University of Colorado Boulder, agrees. His functional magnetic resonance imaging (fMRI) studies were among the first to show that placebos reduce activity in relevant brain areas when people are subjected to pain. But before the onset of pain, his fMRI scans show something different: receiving a placebo increases activity in the two parts of the brain involved in emotion and valuation, the prefrontal cortex and the ventral striatum[3]. "We think the placebo is causing a re-evaluation of the pain," concludes Wager. "It doesn't mean the same thing to you."

LEARNING NOTHING

Placebos influence expectation: how good or bad we think our pain is going to be. This expectation is influenced by what we're told about a treatment and also its nature — invasive treatments (such as surgery or acupuncture) often elicit larger placebo responses than interventions that seem more modest (such as pills). Social factors including the attitude of the practitioner can also influence patients' symptoms[4,5]. What's now coming to light, however, is that placebo responses can also be learned. Just as Russian physiologist Ivan Pavlov discovered that dogs salivate in response to a buzzer associated with food, similar mechanisms are thought to drive placebo responses previously assumed to rely purely on conscious expectation.

For example, giving volunteers several doses of a real painkiller — or surreptitiously reducing the strength of experimental pain — makes subsequent placebo responses to the same stimulus stronger and more consistent. Benedetti calls this process "pre-conditioning". When he and neuroscientist Luana Colloca, now at the University of Maryland in Baltimore, subjected volunteers to electric shocks, pre-conditioning resulted in a five-fold boost to the average pain relief conferred by a placebo[6].

In some circumstances, such learned responses can override conscious expectations. Wager and his colleagues reported that after four episodes of pre-conditioning, an inert cream reduced pain in volunteers even when they knew it was a placebo[7]. "Eventually, it doesn't matter what you think, because your brain has learned," says Wager.

Different drug memories can trigger different neurochemical pathways. Benedetti demonstrated this effect by pre-conditioning some volunteers with morphine and others with the non-opioid painkiller ketorolac[8]. The subsequent placebo response of those in the morphine group involved endorphin release, whereas in the ketorolac group it was mediated by endocannabinoids. "It shows that not all placebos are equal," says Benedetti.

The key question is whether these drug-like placebo responses can be harnessed in medical care. Patients could benefit from measures such as using language designed to boost expectations or to strengthen the social bond between doctor and patient[4]. But researchers are now suggesting something previously unthinkable — a role for placebos themselves.

Colloca suggests that, by taking advantage of learning mechanisms, doctors could give placebos honestly and reduce the amount of medication. For example, a doctor might prescribe a blister pack of painkillers, and tell the patient that it contains both drugs and placebos — but not which pills are which. Earlier this year, Colloca and her colleagues reviewed 22 studies that used similar techniques, covering conditions such as insomnia, autoimmune diseases and pain[9]. They concluded that these approaches have the potential to reduce side effects (although some of these may be conditioned responses, too), limit problems with drug dependency and toxicity, and reduce costs.

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Benedetti loves the idea. "This is one of best applications of placebos in clinical practice," he says. In a trial published in February, he showed that in people with Parkinson's disease, pre-conditioning with the drug apomorphine made patients respond to a placebo just as strongly as they did to the active drug[10]. Alternating drugs and placebos might delay the development of tolerance, he suggests.

Kaptchuk is going one step further. For conditions such as chronic pain, for which placebo effects are large, drugs aren't very effective and taking them can have downsides (see page S4), he suggests sometimes ditching medication altogether and openly giving placebos. He made headlines in 2010 with a placebo study for irritable bowel syndrome (IBS) in which patients were told that they were receiving a sugar pill[11]. "Historically, the assumption has been that deception or concealment is necessary for placebos to work," Kaptchuk says. "My logic was that maybe we could tell patients upfront that placebos may work and tell them to give it a try." The results were startling: 59% of patients who knowingly took sugar pills reported adequate relief from their symptoms, compared with 35% in the no-treatment group — better than most IBS drugs, he adds. "I was very surprised by the results," says Kaptchuk, "even though I hoped it would work."

And it wasn't a fluke. At the symposium in Porto, Kaptchuk followed the cartoon with the results of a new test of an open-label placebo. The trial included 97 patients with chronic lower back pain who had not responded to previous therapies. All continued their usual treatment, but those randomized to the open-label placebo group were also given twice-daily sugar pills, along with an explanation of the research behind why these might help them.

Over three weeks, patients in the placebo group reported a marked drop in pain, whereas the pain of the treatment-as-usual group didn't significantly change. The open-label placebo triggered "sometimes modest, sometimes dramatic, improvements in pain and disability that had major impacts on people's lives", says lead researcher Cláudia Carvalho, a psychologist at the ISPA-University Institute in Lisbon.

Carvalho and her co-authors are still not sure why placebos seem to help patients who haven't responded to treatments in the past. Carvalho suspects that for some, knowingly taking placebos may have made them more aware of the role of the mind in controlling pain. "It empowered them and changed their relationship with their pain," she says.

More studies of honest placebos are in the pipeline — other teams are conducting trials in cancer-related fatigue and depression, and Kaptchuk is recruiting for a trial that aims to replicate and extend his original findings in IBS. If the results continue to be positive, Kaptchuk suggests that for appropriate conditions, placebos — honestly prescribed by clinicians — could become a routine part of medical care. "Placebos have always been a negative for medicine," he says, "but for many patients, trying open-label placebos could be a first line of treatment before any drugs are prescribed." ■

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