The power of belief

When **Michael Brooks** went in search of the truth about the placebo effect, he was shocked by what he found

IT SEEMED like a good idea until I saw the electrodes. Dr Luana Colloca's white coat offered scant reassurance. "Do you mind receiving a series of electric shocks?" she asked.

I could hardly say no – after all, this was why I was here. Colloca's colleague, Fabrizio Benedetti of the University of Turin in Italy, had invited me to come and experience their placebo research first hand. Colloca strapped an electrode to my forearm and sat me in a reclining chair in front of a computer screen. "Try to relax," she said.

First, we established my pain scale by determining the mildest current I could feel, and the maximum amount I could bear. Then Colloca told me that, before I got another shock, a red or a green light would appear on the computer screen.

A green light meant I would receive a mild shock. A red light meant the shock would be more severe, like the jolt you get from an electric fence. All I had to do was rate the pain on a scale of 1 to 10, mild to severe.

After 15 minutes – and what seemed like hundreds of shocks – the experiment ended with a series of mild shocks. Or so I thought, until Colloca told me that the last series of shocks were all severe.

I had felt the electric fence jolts as a series of gentle taps on the arm because my brain had been conditioned to anticipate low pain whenever it saw a green light – an example of the placebo effect.

Benedetti watched the procedure with a smile on his face. He was not sure his team could induce a placebo response in me if I knew I was about to be deceived. As it turns out, I succumbed, hook, line and sinker.

Such is the power of placebo. This was once thought to be a simple affair, involving little more than the power of positive thinking. Make people believe they are receiving good medical care – with anything from a sugar pill to a kindly manner – and in many cases they begin to feel better without any further medical intervention.

However, Benedetti and others are now claiming that the true nature of placebo is far more complex. The placebo effect, it turns out, can lead us on a merry dance. Drug trials, Benedetti says, are particularly problematic. "An ineffective drug can be better than a placebo in a standard trial," says Benedetti.

The opposite can also be true, as Ted Kaptchuk of Harvard Medical School in Boston points out. "Often, an active drug is not better than placebo in a standard trial, even when we can be confident that the active drug does work," he says.

Some researchers are so taken aback by the results of their studies that they are calling for the very term "placebo" to be scrapped. Others suggest the latest findings undermine the very foundations of evidence-based medicine. "Placebo is ruining the credibility of medicine," Benedetti says.

How did it come to this? After all, the foundation of evidence-based medicine, the clinical trial, is meant to rule out the placebo effect.

If you're testing a drug such as a new painkiller, it's supposed to work like this. First, you recruit the test subjects. Then you randomly assign each person to one of two groups to ensure both groups are alike. One group gets the painkiller, the other gets a dummy treatment. Then, you might think, all you have to do is compare the two groups.

It's not that simple, though, because this is where the placebo problem kicks in. If people getting an experimental painkiller expect it to work, it will work to some extent – just as seeing a green light reduced the pain I felt when shocked. If the control group know they're getting a dummy pill whereas the other group know they're getting the "real" drug, the experimental painkiller might appear to work better than the dummy when in fact the difference between the groups is entirely due to the placebo effect.

So it's crucial not to tell the subjects what they are getting. Those running the trial should not know either, so they cannot give anything away, creating the gold standard of clinical trials, the double-blind randomised controlled trial. This does not eliminate the placebo effect, but should make it equal in both groups. According to conventional wisdom, in a double-blind trial any "extra" effect in the group given the real drug must be entirely down to the drug's physical effect.

Mind boggling

Benedetti, however, has shown this is not necessarily true. His early work in this area involved an existing painkiller called a CCK-antagonist. First, he performed a standard double-blind randomised controlled trial. As you would expect, the CCK-antagonist performed better than the placebo. Standard interpretation: the CCK-antagonist is an effective painkiller.

Now comes the mind-boggling part. When Benedetti gave the same drug to volunteers without telling them what he was doing, it had no effect. "If it were a real painkiller, we should expect no difference compared to the routine overt administration," he says. "What we found is that the covert CCK-antagonist was completely ineffective in relieving pain."

Benedetti's team has since shown that the combination of a patient's expectation and the administration of the CCK-antagonist stimulates the production of natural painkilling endorphins. It has been known since 1978 that the placebo effect alone can relieve pain in this way. What Benedetti has uncovered, however, is a far more complex interaction between a drug and the placebo effect. His work suggests the ▶

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"If you don't know you have been given the painkiller, it has no effect"

CCK-antagonist is not actually a painkiller in the conventional sense, more of a "placebo amplifier" – and the same might be true of many other drugs.

"We can never be sure about the real action of a drug," says Benedetti. "The very act of administering a drug activates a complex cascade of biochemical events in the patient's brain." A drug may interact with these expectation-activated molecules, confounding the interpretation of results.

This could be true of some rather famous – and profitable – substances. Benedetti has found that diazepam, for instance, doesn't reduce anxiety in patients after an operation unless they know they are taking it. The placebo effect is required in order for it to be effective. It's not yet clear if this is also true of diazepam's other effects.

Even with drugs that do have direct effects independently of patients' expectations, the strength of these effects can be influenced by expectation. If you don't tell people that they are getting an injection of morphine, you have to inject at least 12 milligrams to get a painkilling effect, whereas if you tell them, far lower doses can make a difference.

Such findings prove that we need to change the way trials are done, Benedetti says. He thinks this is true of all placebo-controlled trials, not just those involving conditions in which placebos can have a strong effect, such as on pain.

The alternatives include Benedetti's hidden treatment approach, where participants are not always told when they are getting a drug, and the "balanced placebo design", in which you tell some people they got the drug when they actually got the placebo and vice versa.

These approaches are a great way of teasing apart true drug effects from placebo, says Franklin Miller of the US National Institutes of Health. The problem is the degree of deception involved. "There is no way we're going to be able to do clinical trials that involve deceiving patients about what they are getting. I don't see that as a useable method," he says.

Colloca disagrees. With hidden treatments, a patient might not know when the drug infusion starts and ends, but they know that a drug will be given. Therefore, she argues, there is full informed consent.

For Kaptchuk, the issue is not just teasing apart drug effects from placebo; it's the very notion that only treatments that are better than placebo have any value. "It's never enough to just test against placebo," he says.

In a study published in April, his team compared three "treatments" for irritable bowel syndrome. One group got sham acupuncture and lots of attention. The second group also got sham acupuncture, but no attention. A third group of patients just got left on a "waiting list".

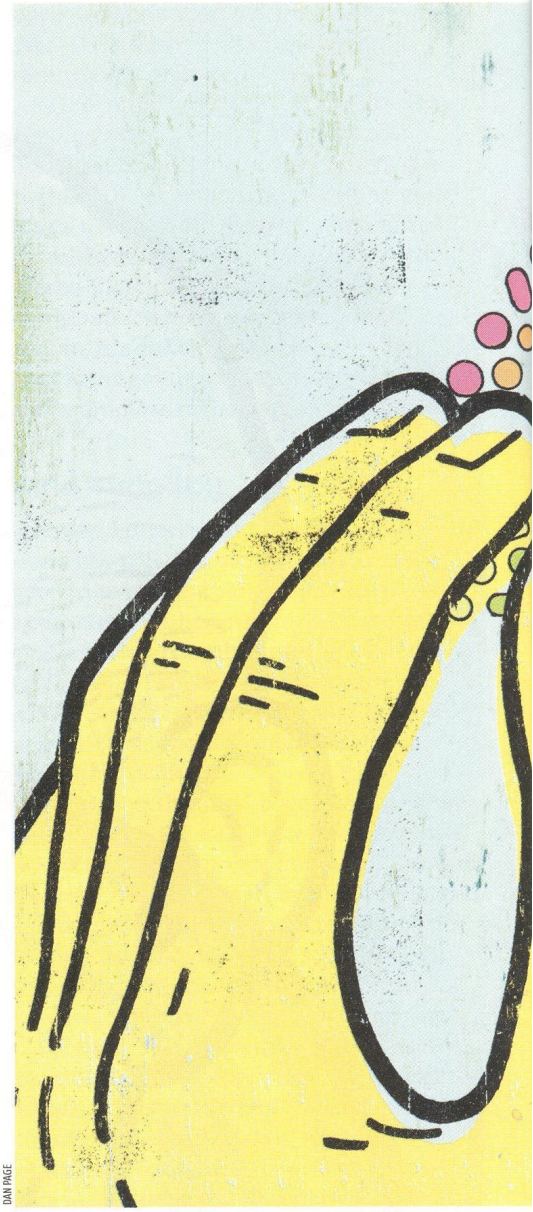
Patients in both sham acupuncture groups did better than those kept on the fake waiting list. However, the group who had felt listened to and consulted about their symptoms, feelings and treatments reported an improvement that was equivalent to the "positive" trial results for drugs commonly used to treat irritable bowel syndrome – drugs that are supposed to have been proved better than placebo. Does this finding mean the drugs should not have been approved, even though patients are better off with either drugs or placebo than no treatment at all?

This study shows how a placebo can be boosted by combining factors that contribute to its effect. And all sorts of factors can be involved. Even word of mouth can help, Colloca says, such as learning that a treatment has worked for others.

Conditioning through repetition, as in the process I went through, is another important factor. "Many trials use the repeated administration of drugs, thus triggering learning mechanisms that lead to increased placebo responsiveness," Benedetti says.

This is yet another reason to change clinical trials, he argues. It could explain, for instance, why the placebo effect appears to be growing stronger in clinical trials, causing problems for drug companies attempting to prove their products are better than placebo.

The issue isn't just about disentangling the effect of a placebo from that of a drug. It's also about harnessing its power. For instance, Colloca thinks the conditioning effect could be exploited to reduce doses of painkilling drugs with potentially dangerous side effects.



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The problem with trying to exploit the placebo effect, says Miller, is that the term means very different things to different people. Many doctors don't believe placebo has any effect other than to placate those demanding some kind of treatment. "People say it's noise, or nothing, or something just to please the patient," Miller says.

Those involved with clinical trials, by contrast, tend to overestimate the power of placebo. Consider the way trials are carried

"The findings threaten the very credibility of modern medicine"

out. If the people in the control group – the ones who get the placebo – get better, it's almost always attributed to the placebo effect. But in fact, there are many other reasons why those in the control group can improve. Many conditions get better all by themselves given enough time, for instance. To distinguish between the apparent effect of a placebo and its actual effect, you have to compare a placebo treatment with no treatment at all, as in the irritable bowel study.

Contextual healing

In an article published earlier this year, Miller and Kaptchuk argue that the very notion of placebo has became so laden with baggage that it should be ditched. Instead, they suggest that doctors and researchers should think in terms of "contextual healing" – the aspect of healing that is produced, activated or enhanced by the context of the clinical encounter, rather than by the specific treatment given.

Whatever you call it, trying to harness the placebo effect raises tricky ethical issues: can doctors exploit it without lying to patients? Maybe. If my shocking experience is anything to go by, knowing you are getting a placebo does not necessarily stop it working.

"It's a complicated issue, but one that deserves a lot more attention," Miller says. "Finding ethically appropriate ways to tap the use of placebo in clinical practice is where the field needs to be moving."

Doctors, however, are not hanging around waiting for the results of rigorous studies that show whether or not placebos can be used effectively and ethically for specific conditions. Surveys suggest around half of doctors regularly prescribe a placebo and that a substantial minority do so not just to get patients out of the consulting room but because they believe placebos produce objective benefits.

Are they doing their patients a disservice? In 2001 Asbjorn Hróbjartsson of the Nordic Cochrane Institute in Stockholm, Sweden, did a meta-analysis of 130 clinical trials that compared the placebo group with a no-treatment group, to reveal the "true" placebo effect. The studies involved around 7500 patients suffering from about 40 different conditions ranging from alcohol dependence to Parkinson's disease. The meta-analysis concluded that, overall, placebos have no significant effects. Two years later the team published a follow-up study with data from 11,737 patients, and Hróbjartsson will publish another in the next few months. "The results are similar again," he says. Placebos are overrated and largely ineffective, Hróbjartsson concludes, and doctors should stop using them.

However, if you consider only studies whose outcomes are measured by patients' reports, such as how much pain they feel, placebos do appear to have a small but significant effect, he says. In other words, the placebo effect can make you feel better – even if you aren't actually better.

Does this mean it's not a real effect? Was I deluded when I reported feeling severe shocks as mild ones? "What does 'real' mean in this situation?" responds Hróbjartsson. "My concern is not so much whether effects of placebo are real or not, but whether there is evidence for clinically relevant effects."

Giving patients plenty of TLC is where placebo intervention should end, he thinks. "Most of us working in the field think that's just another way of saying 'be a good doctor'."

Colloca and Benedetti think there is scope for doing much better than that. "We already know that placebos don't work everywhere, therefore the small magnitude of the placebo effect in that meta-analysis is not surprising at all," Benedetti says. "It is as if you wanted to test the effects of morphine in gut disorders, pain, heart diseases, marital discord, depression and such like. If you average the effects of morphine across all these conditions, the outcome would be that overall morphine is ineffective."

The other reason not to take the meta-analyses too seriously is the evidence that placebo can have measurable biochemical effects. The release of painkilling endorphins, for instance, has been confirmed by showing that drugs which block endorphins also block the placebo effect on pain, and by brain scans that "light up" endorphins. Placebos have also been shown to trigger the release of dopamine in people with Parkinson's disease. In 2004, Benedetti demonstrated that, after conditioning, individual neurons in the brains of Parkinson's patients respond to a salt solution in the same way as they do to a genuine drug designed to relieve tremors.

When it comes to the placebo effect, it seems, nothing is simple. We still have a lot to learn about this elusive phenomenon. ●

Michael Brooks's latest book is *13 Things That Don't Make Sense* (Doubleday)