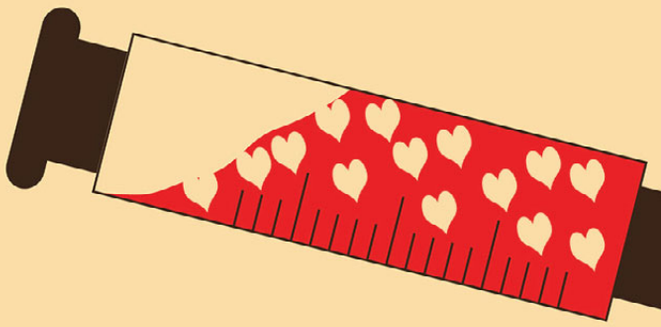
Louis Goss talks to Harvard Medical School placebo expert Dr Ted Kaptchuk, to ask: what does the 'placebo effect' mean for doctors, patients and pharmaceutical companies in clinical trials?



How I learned to stop worrying and love the placebo effect

On 14 February 2019, Danish firm Lundbeck and its Japanese partner Otsuka announced the results of two Phase 3 trials looking into the effectiveness of their previously successful antipsychotic, Rexulti (brexpiprazole), as a treatment for manic episodes associated with bipolar I disorder.

From the perspective of a pharmaceutical company, the trials were a complete disaster. The two multicentre, randomised, double-blind studies (in which Rexulti was tested on 650 individuals with bipolar I disorder) did not meet their primary endpoints of statistical separation from placebo.

In explaining the failure, Lundbeck and Otsuka claimed that: "In both studies, the placebo effect on the rating scales was substantially higher than anticipated."

The Rexulti case is not unprecedented. In fact, the number of drugs falling short of placebos in late-stage clinical trials has risen dramatically in recent years. Pharmaceutical companies claim that the flops are not simply a result of ineffective drugs – many of which have been through years of research and development processes and numerous early-stage trials – but instead a phenomenon called the placebo drift – a trend towards stronger acting placebos.

According to some, placebos (inert substances used as controls in clinical trials) have, over the past 25 years, become increasingly effective in treating certain conditions such as pain and mental illness.

What *is* a placebo?

Dr Ted Kaptchuk, Professor of Medicine at Harvard Medical School, explained: "A placebo is an inert substance, usually something like microcrystalline cellulose – sometimes sugar – that has no effect on human beings. It's inert. The placebo effect is not the effect of that pill. The placebo effect is everything that surrounds that pill in a therapeutic encounter. That includes symbols, rituals, behaviours, and even charged emotions like hope and uncertainty."

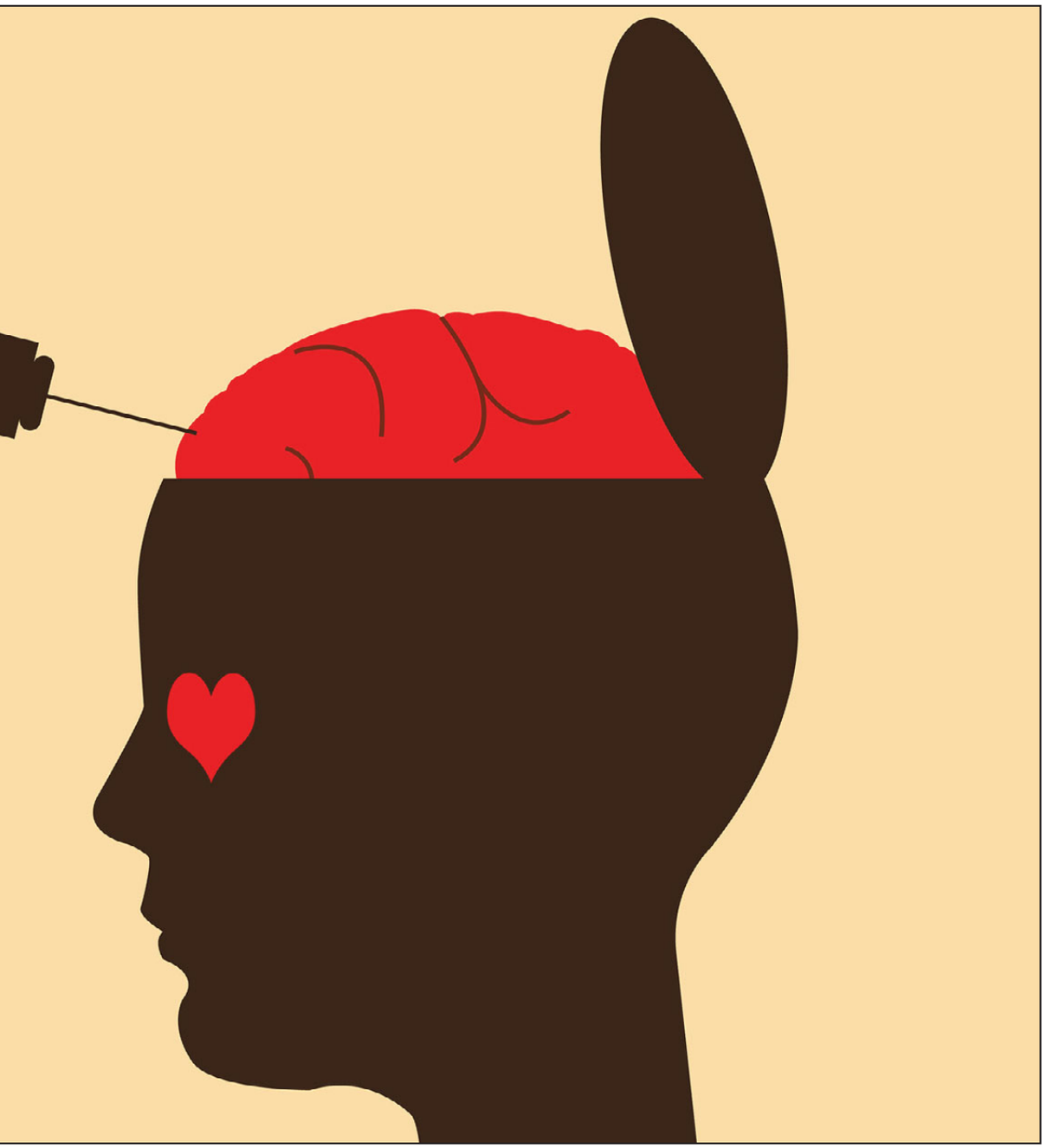
"In terms of neurobiology we do know a lot about the placebo effect… We know that when people respond to placebos, they release chemicals – neurotransmitters, like endorphins, cannabinoids, dopamine, sometimes we think serotonin – which actually modulate symptoms. We also know that when people respond to placebo in neuroimaging experiments we can see that placebo activates quantifiable, relevant and distinct areas in the brain that have to do with pain modulation or whatever the symptoms we're treating. So there's a neurobiology underlying it. We're now beginning to think there may be genetic signatures that suggest who's more likely or less likely to respond to the placebo effect," Kaptchuk said.

However, when asked what factors influence the placebo effect, Dr Kaptchuk was clear in stating that we still don't really know: "I would say that there are lots of claims, and I don't think we know what makes a placebo effect. I mean, my colleagues have people research the expectation conditioning, patient doctor relationship, empathy – and I'm not sure we have any data that has been replicated clearly on those kinds of questions."

The issue is further complicated by the fact that placebos even seem to work when a patient is aware that the medicine they are taking is a placebo. 'Open-label placebos' (placebos given to patients in situations in which they are aware that they are receiving an inert substance) have proved effective in improving symptoms associated with conditions such as allergies, irritable bowel syndrome (IBS), depression, chronic lower back pain, migraines and cancer-related fatigue.

Furthermore, research shows that the placebo, and countervailing nocebo effects, can be triggered by nonconscious cues. In one study, led by Harvard Medical School Professor Karin Jensen from 2012, participants were shown two different faces while being exposed to either low or high temperatures.

Participants were then all exposed to moderate heat while being shown either Face A (associated with high heat), Face B (associated with low heat) or a control face which they had not seen before, for periods of 12 and 100 milliseconds. Those who were shown Face A reported higher pain responses in both the 12 milliseconds and 100 milliseconds experiments. "To the best of our knowledge, our study presents



> **Our study presents unique evidence that conditioned placebo responses can be activated by cues outside of conscious awareness**

unique evidence that conditioned placebo responses can be activated by cues outside of conscious awareness," the study says.

"The evidence is pretty positive there. The research agenda is that the placebo effect is not a conscious expectation and it probably involves non-conscious activation of regions in the brain," Kaptchuk said. "It's demonstrated. Whether that happens consistently… so far it's been consistent, but you shouldn't count things too early," he added.

A short of history of the placebo effect

As far as we can tell, Benjamin Franklin offered the first recorded instance of the placebo effect in writing about placebo-controlled trials of mesmerism in 1784. In a blinded trial, Franklin, one of the Founding Fathers of the United States, tested the effectiveness of the methods developed by Franz Mesmer, a German doctor who believed in the healing effects of an invisible natural force called Lebensmagnetismus. Franklin came to the conclusion that any effects were the result of illusions created by the human mind.

English physician John Haygarth applied similar methods to the assessments of 'Perkins' tractors' – metal rods invented by US doctor Elisha Perkins, which the Connecticut physician claimed could relieve aches and pains. The three-inch rods, which were sold at the high price of five guineas, were marketed on the claim that they could "draw off the noxious electrical fluid that lay at the root of suffering."

In trialling the therapeutic rods, Haygarth tested Perkins' tractors against sham wooden versions of the medical device. Surprisingly, both the 'real' and fake rods worked. As said by Haygarth himself, the experiment showed "to a degree which has never been suspected, what powerful influence upon diseases is produced by mere imagination."

As noted by Dr Kaptchuk in a paper from 1998: "Blind assessment began in the late 18th century as a tool for detecting fraud in a campaign mounted by elite mainstream scientists and physicians to challenge the suspected delusions or charlatanism of unconventional medicine. It demarcated orthodox medicine from what was considered deviant healing."

In the latter half of the 19th and the first half of the 20th century, pharmacologists and physicians came to realise the benefits of placebo-controlled trials, as the scepticism towards outsiders was turned inwards, towards the medical establishment itself. Blind assessment and placebo-controlled trials offered a means of achieving objectivity amidst increasing interest in the power of suggestion and the 'therapeutic nihilism' movement of the mid- to late-19th century. This belief in the necessity for blind assessments was subsequently enshrined into law.

As expanded upon by Dr Kaptchuk: "The whole question of placebo effect is really post-1950s. It really becomes a major issue with the 'Pure Food and Drug Act 1962' where the law states you have to do placebo-controlled trials. So it's not part of any traditional knowledge. It's to demarcate what's legitimate and non-legitimate in biomedicine.

"The whole purpose of the randomised control trial is to take out the effects of the imagination, rituals, and symbols and only test the pharmacological effect. In doing that they actually showed that there's an effect of the rituals and imagination. It's kind of strange. The scientific method set out to squash this kind of stuff but it actually created the problem and it's been ignored for 70 years. But labs like my lab and other labs in the world are saying this is not a problem. This is an opportunity!"

From TCM to the placebo effect

Born in Brooklyn in 1947, Dr Kaptchuk pioneered the study of traditional Chinese medicine (TCM) in Europe and the United States. It was through his work in TCM that Dr Kaptchuk – who in 2011 was made director of Harvard's Program in Placebo Studies and the Therapeutic Encounter (PiPS) – became interested in the placebo effect: "I was hired by Harvard Medical School to do research into Asian medicine and they told me my

job is to find out whether anything in the area of Asian medicine was more than just a placebo effect. And when I asked them 'what's the placebo effect?' they told me it was the effect of an inert substance. And I thought 'that's an oxymoron, probably I could do more good by studying this than studying Asian medicine' so I switched," Kaptchuk said.

"I think my interest was in the methodology of randomised control trials. I don't think Chinese medicine has anything special to say about placebo effect. In fact it doesn't have the word placebo effect."

The placebo drift

Medicines, particularly for conditions such as pain and mental illness, have in recent years become increasingly hard to distinguish from placebos in clinical trials. In essence, the gap has been closed. The effects of real drugs have, over time, become more and more similar to sham treatments in randomised clinical trials (RCTs).

Some studies, such as one 2015 paper from researchers at Canada's McGill University, argue that the placebo effect is getting stronger, particularly in the United States. "Placebo responses in RCTs of chronic neuropathic pain have increased over time and treatment advantage over placebo has decreased over the period 1990 to 2013, a trend wholly specific to trials conducted in the United States," the study says.

The paper suggests that a trend towards "larger and longer" clinical trials in the United States is responsible for the so-called 'placebo drift'.

"Over the period analysed, neuropathic pain RCTs have become bigger, longer, and conducted at more sites in the United States, but not elsewhere in the world.

Furthermore, our multivariate analysis suggests that it is this increase in trial size and duration that is most associated with increasing placebo response magnitudes in the United States. Whether or not these associations indicate a causal effect is unknown. The positive relationship between trial duration and the magnitude of the placebo response might be explained by a positive feedback mechanism by which initially perceived pain reduction leads to increasing analgesia over the course of the trial… Longer trials may also feature more nonspecific therapeutic effects, for example, more opportunities for, and ultimately richer, social support, attention from trial staff, and education.

Larger trials may feature relaxed eligibility criteria, resulting in different patient characteristics," the study says.

Another study from 2002, a meta-analysis of 75 trials of medication for major depressive disorder (MDD), found: "The response to placebo in published trials of antidepressant medication for MDD… has increased significantly in recent years, as has the response to medication."

However Dr Kaptchuk was sceptical: "I'm not sure I believe that data," he said. "The numbers are real small, and actually, the newspapers have been reporting the data that shows that the placebo effect in depression is higher now than in 1980 or 1990, but I'm not sure I believe it, because there's other data, even in depression, showing that it's not true."

As noted in one such study from 2010, a meta-analysis of 198 randomised trials of antiepileptic drugs, conducted by researchers at the Russian State Medical University in Moscow: "In the epilepsy studies reviewed here, we did not find a 'placebo drift' (a strong correlation between placebo rate and year of publication)." Despite demonstrating "the existence of a marked placebo effect in most RCTs… 'Placebo drift' was not found to be statistically significant in these epilepsy studies," the study said.

"The patients that come into trials in 1980 may be different than people coming in 2018." Dr Kaptchuk said. "So I'm not convinced yet, about what's called placebo drift, the drift towards a stronger placebo. I'm not convinced. I think it's just not clear. I don't buy it yet."

In explaining the narrowing gap, Dr Kaptchuk suggested: "We need better drugs. People are blaming the placebo effect. Maybe that's it. Maybe the drugs aren't that good. They're all second generation, third generation. It's clear that it's costing the pharmaceutical industry much more money – and failed studies are just a major, major problem of being able to show a difference – but is that because the placebo effect is bigger, or is it because the drugs are not so good?"

"I think people are really blaming the placebo because it's easier to blame than the fact that maybe the drugs aren't as good as they're touted to be… what the statements say is the 'placebo effect beat out the drug' but they always say 'it's the placebo effect', they never say 'well maybe the drug isn't so good.' It's kind of 'the other kid started the fight,'" Dr Kaptchuk said.

Placebos in the clinic

As noted by Dr Kaptchuk, the placebo effect is "in some situations, very strong." Thus, despite causing problems for pharmaceutical companies, the placebo effect could be useful for patients, doctors and physicians.

Dr Kaptchuk commented on the moral use of placebos in a clinical setting: "I think there's a possibility that the doctor-patient relationship increases the placebo effect. But I think a really good drug doesn't need a placebo effect to increase its effect. I think the evidence is weak drugs could use a better doctor-patient relationship – drugs that really are just marginally better than placebo. A better doctor-relationship is probably helpful for the patient."

However, the ethics of placebos prevents their use in clinical settings: "My line is any deception, misinformation or manipulation of patients is considered unethical. So you can't deceive patients and say 'this is a powerful drug' when it's really a placebo," Dr Kaptchuk said.

Nevertheless, one survey from 2007 found that nearly half (45%) of physicians use placebos in clinical settings. Meanwhile, a meta-analysis of 16 studies involving 2,981 GPs found that: "The percentage of GPs having used any form of placebo at least once in their career ranged from 29% to 97%, in the last year at least once from 46% to 95%, at least monthly from 15% to 89%, and at least weekly from 1% to 75%."

The power of placebo

Overall, Dr Kaptchuk was clear in stating the potential the placebo effect holds for both doctors and patients: "I think the first thing is people have self-healing capacities, especially in situations and conditions where what they're experiencing is their own self-perceptions, their own self-awareness. Pain, nausea, dizziness, insomnia, fatigue, that's one thing. Be aware that this is not a bad thing, that's a good thing. For the pharmaceutical industry it's really a neutral thing – and that's an understatement. But for patients it's really good, and clinicians it's not so bad, as long as you're ethical – and also, given that there's some evidence that a good doctor-patient relationship is helpful, make sure you like your doctor."

However Dr Kaptchuk concluded in stating: "I think it's really hard on doctors. They're trained to treat the placebo effect as a bogeyman. I teach medical students, and we read a clinical trial and the conclusion is 'oh it's better than placebo therefore it's good' or 'oh it's not the same as a placebo therefore it's not good'. There's a whole bogeyman-ness and that's actually an ethical statement which masquerades as a scientific statement. There's nothing bogeyman about a placebo effect. Actually it's a real phenomenon and medical school education needs to take that into account."

> **"People have self-healing capacities, especially in situations and conditions where what they're experiencing is their own self-perceptions, their own self-awareness"**