AN AUDIENCE WITH…

Ted Kaptchuk

Associate Professor of Medicine, Harvard Medical School, Boston, USA. Ted Kaptchuk investigates placebo effects and has published over 100 articles — including clinical trials, neuroimaging studies, historical investigations, methodological reviews and ethical analyses. He is currently serving on the National Advisory Counsel of the National Institutes of Health's National Center for Complementary and Alternative Medicine, and has recently completed a 4-year term as an expert panelist at the FDA.

What is the placebo effect and what is the importance of understanding it?
The simplest answer is that the placebo effect is the changes we detect in the placebo arm of a randomized controlled trial (RCT). That definition is historically accurate because we did not have a placebo effect until we had an RCT and were then able to see that people who were given inert substances improved. However, what is happening in the placebo arm of an RCT is complex and involves all kinds of non-placebo phenomena such as spontaneous remission, regression to the mean, bias, measurement artifacts and natural fluctuations of the illness. So, it may be more precise to describe the placebo effect as the response patients have to the ritual of medicine. That is, the patient response to the appearance of a therapy, to the patient–doctor relationship, to the entire apparatus of an RCT or a clinical encounter. It is everything that isn't the pharmacological effect of a drug for a procedure. Importantly, it is a threat for drug development and continues to pose a problem for how we accurately measure a drug effect. Many good pharmaceutical interventions are not succeeding to demonstrate their efficacy because of a high placebo effect.

Please could you explain the current 'state of the art' of research in this area?
There have been major advances in the science of the placebo effect. Well-controlled laboratory studies demonstrate that the placebo effect elicits quantifiable changes in neurotransmitters, hormones, immune regulators and regionally specific brain activity that could influence peripheral disease processes through plausible physiological mechanisms. Depending on the environmental cues, placebo effects seem to involve primarily expectation and, at other times, classical conditioning — sometimes both mechanisms. We are beginning to see that there is no such thing as 'a' placebo response but a spectrum of responses. However, what the placebo effect is exactly in clinical or RCT populations compared to what we find in laboratory experiments is still unclear, and has not been tackled sufficiently.

How might the placebo effect impact on the interpretation of clinical trial results?
Researchers in general are aware, particularly for subjective illnesses such as irritable bowel syndrome (IBS), depression or chronic pain, that the assay sensitivity of such trials is threatened by high placebo responses. For example, with the selective serotonin reuptake inhibitors (SSRIs) many trials have not shown superiority compared with placebo. We do not understand why this is happening, but we do know that there is a phenomenon called placebo drift, which, for clinical trials to treat depression, seems to be getting higher over time. For obsessive–compulsive disorder trials, the drift used to be lower than 5% in placebo arms but is now over 20%. This could be related to the environment — patient selection, the way researchers conduct the trials or the nature of the illnesses themselves. For RCTs to gain in efficiency, much more needs to be known.

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How can understanding the placebo effect help investigators design clinical trials for new drugs that aim to treat illnesses associated with high placebo effect?
In RCTs we assume that the pharmacological effect is added on to a placebo effect but in fact that may not be true for all illnesses, particularly those that are defined by patient complaint. For example, with the SSRIs it may be that we are getting a ceiling effect. If the placebo effect is independently high and does not use the same biological mechanism as the SSRI — and both effects seem to have similar magnitude — then, if there is a ceiling effect you can't go much higher anyway. There are some fundamental assumptions about how we statistically interpret the placebo response in an RCT that need to be investigated.

Is it possible, with what we know about the placebo effect, to ensure that the trial can show whether a treatment has a true benefit?
We are still at the hypothesis stage. I don't think that for any particular illness we understand the placebo response well enough to know whether what we are dealing with is primarily the patient, the practitioner, the imprecision of the outcome measures, or the variability of the illness itself. There are a lot of hypotheses to decrease the placebo effect: improve the outcome measures, decrease the patient contact or empathy communicated by the researcher, or reduce the number of visits. At the moment there is no evidence that these work. Reducing the placebo effect is an active concern of my research team. In our recent study in IBS (*BMJ* 336, 967–968; 2008) we really reduced the placebo effect by removing the doctor–patient interaction. But if you cut that down too much in an RCT you are going to have dropouts, so controlling it at one point might introduce problems elsewhere. We are badly in need of systematic research efforts to understand what we are trying to control and how we minimize the placebo effect during drug development to detect a signal between the pharmacological intervention and the placebo control.