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in practice...

The Placebo Effect Has Come of Age

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In 1969, William McGuire described the three stages of what he called the life history of an artifact (McGuire, 1969). The first stage is ignorance. With respect to the placebo effect, this characterizes the history of medicine up to the middle of the 20th century. Before then, placebos might be used to mollify persistent patients, but the idea that they might produce actual benefits was rarely considered. In the 1950s and 1960s, a spate of studies reported beneficial effects of placebos, not only on subjective well-being, but also on concomitant physiological function. This signaled the transition from the ignorance stage to what McGuire called the coping stage in the life history of an artifact. The coping stage is the period in which the existence of an artifact is recognized and research methods are developed to control for it. In the last half of the 20th century, the use of placebo-controlled randomized clinical trials (RTCs) became the norm.

The papers in this theme issue of Mind Body Regulation indicate that the concept of placebo is maturing from the coping stage into the final stage in the life history of an artifact: the exploitation stage. It is here that interest in a concept evolves from the view of it as an artifact that needs to be controlled to a phenomenon that is interesting in its own right. The focus shifts toward understanding the placebo effect. The questions being asked include: What are the psychological and physiological mechanisms by which placebo effects are produced? What are the conditions that placebo effects can or cannot be affected by placebo? What factors maximize or minimize the placebo effect? How reliable is it? Can placebo responders be identified and, if so, who are they? And finally, the sixty four thousand dollar question: how can placebo effects be harnessed ethically in clinical practice?

This latter question is particularly important in light of the following observations. There are conditions (e.g., depression) for which placebos can be as effective—or almost as effective—as approved medications (Kirsch, 2009; Kirsch et al., 2008). Placebos differ from these medications, however, in at least one important way: they are virtually free of dangerous side effects. I say virtually free because placebos can cause side effects. This is one type of the negative effects of placebos that has given rise to the concept of the nocebo effect, which is an undesirable effect produced by placebos or placebo-like stimuli (e.g., verbal information and conditioning). The best example of placebo-induced side effects is a study reported in The Lancet in 1981, in which telling people that headaches are a side effect of lumbar puncture resulted in significantly more self-reported headaches following the procedure (Daniels & Sallie, 1981). Still, the incidence of adverse events following placebo treatment is substantially less than their incidence following administration of active drugs (e.g., Philipp, Kohnen, & Hiller, 1999).

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The ethics of placebo in clinical practice

The biggest barrier to the use of placebos in clinical practice is the almost universal perception that for a placebo to be effective it must be administered deceptively. Since expectancies

appear to play a major role in placebo responding, informing people accurately that they are being given a placebo should prevent it from being effective. There is a way around this, however. If a convincing rationale can be presented, perhaps placebos can be prescribed openly without deception. Recently, my colleagues and I developed and tested such a rationale (Kaptchuk et al., 2010). We told patients suffering from irritable bowel syndrome (IBS) that placebos have been shown to be effective for their condition, that their effects are induced at least in part by a well-known mechanism (that of classical conditioning), and that for that reason, the act of taking a placebo pill could work as a new mind–body treatment that could reduce IBS symptoms. We found that the patients in our study accepted this rationale, took their placebo pills as prescribed (two pills twice a day), and got better in comparison to patients in a control group that were not given the placebo pills.

In the current issue, Foddy (2011) challenges "the view that the deceptive nature of placebo treatments creates an insurmountable ethical barrier to their use." He acknowledges that our study (Kaptchuk, et al., 2010) has shown that open label administration of placebo can produce clinically meaningful benefits, but questions whether those benefits could be a strong as those of a deceptive placebo. We think they can in fact be that strong. The effect we obtained was similar to that obtained by active medication in treatment of irritable bowel syndrome (IBS). A meta-analysis of clinical trials of alosetron as a treatment for IBS showed that 51% of patients treated with the drug obtained adequate relief, compared to 38% of patients treated with placebo (Rahimi, Nikfar, & Abdollahi, 2008). In our study, the non-deceptive, open label placebo produced a response rate of 59%, higher than that of alosetron, and significantly higher than that of a conventional double-blind placebo.

Nevertheless, the argument that deceptive administration of placebo is ethical cannot easily be dismissed. Although open administration may provide an alternative for some patients with some disorders, it needs to be assessed for a broader range of conditions, and there may be patients for whom the rationale we used would not be convincing and who would therefore not experience much benefit. Nevertheless, treatment with placebo—whether deceptive or non-deceptive—is not the only viable alternative. When placebo works, it does so by means of its psychological characteristics, that is, because of the meaning that it has for the patient (Moerman, this issue: 2011). That means that other psychological treatments are likely to work. These are treatments that intend to work by examining the meanings that events have for people, and they can thus be understood as non-deceptive placebos. It is interesting to note that hypnosis is an efficacious treatments for IBS, according to a review of outcome studies (Tan, Hammond, & Gurralam Joseph, 2005), and the clinical use of hypnosis has been interpreted as a non-deceptive placebo (Kirsch, 1994).

Antidepressants and the placebo effect

Abi-Jaoude (this issue: 2011) has provided a very thoughtful and useful commentary on my studies of the placebo effect in antidepressant medication (Kirsch, 2010; Kirsch, et al., 2008; Kirsch, Moore, Scoboria, & Nicholls, 2002). In so doing, he has raised some very important questions. In particular, he notes that the apparent magnitude of the drug-placebo difference is influenced by the metric that is chosen. My colleagues and I have reported a difference of less than two points on the Hamilton Rating Scale for Depression (HRSD) (Kirsch, et al., 2008; Kirsch, et al., 2002). Using an overlapping data set, Swedish regulators found a 16% difference in response rates (Melander, Tomas Salmonson a, Abadie, & van Zwieten-Boot, 2008), which they claimed was clinically meaningful. How can these two sets of data be reconciled?

The key to this lies in understanding response rates and the illusions that they can create (Altman & Royston, 2006; Kirsch & Moncrieff, 2007). The criterion conventionally used to define a response to antidepressant treatment is a 50% reduction in treatment. Those

showing this reduction are categorized as treatment responders, whereas those not showing it are considered non-responders. Once the words 'responder' and 'non-responder' terms are applied we think that these are the percentages of people who improved substantially versus the percentages who did not improve at all, but this is an illusion. Actually, difference in improvement between a responder and a non-responder can be as little as one point on whatever scale is used to measure depression. The people who improve on drug but not placebo are most likely to be those who would have a 50% or 49% reduction of symptoms on the drug and a 48% or 49% reduction on placebo.

Certainly people know this, but when they interpret data, they often seem to forget it. Their conclusions about what is clinically significant seem to assume that non-responders have shown little improvement and that responders have shown much more improvement. They neglect to notice that the 10–15% difference between the real drug and placebo might very well reflect the proportion of patients whose improvement on placebo is so great that even a tiny boost in efficacy will push them over the threshold that distinguishes response from non-response.

To make matters worse, it turns out that the 50% criterion that has been consensually adopted as the definition of a clinical response is very close to the median and the mean of improvement distributions for antidepressants. This makes it even more likely that the shift from response to non-response is attributable to small differences that cross the 50% threshold for responding.

A second issue raised by Abi-Jaoude (2011) concerns the effects of knowing that one might receive a placebo. He cites meta-analyses showing that the response to antidepressants is lower when patients know that they getting an active treatment than when they know that they might be given placebo, and that the greater the likelihood of getting a placebo, the lower the therapeutic response (Papakostas & Fava; Sinyor et al., 2010; Sneed et al., 2008). Abi-Jaoude interprets this as indicating that placebo-controlled trial designs may underestimate drug and overestimate placebo effects. I interpret these data differently. When people are given a drug, part of their response will be due to the chemical composition of the drug and part to the placebo effect. In other words, the placebo effect and the drug effect are components of the drug response. When one manipulates the expectancy of getting the real drug (e.g., there is a 0% vs. 33% vs. 50% chance of getting a placebo in this trial), one is altering the placebo component of the response to the drug. That cannot change the drug effect, which is the chemical effect of the drug over and above the placebo component of the drug response. So what these studies demonstrate is that 1) the size of the placebo effect can be altered, 2) drug and placebo effects are additive, and 3) for that reason, altering the placebo component of the drug response changes the overall response to the drug. But the size of the drug effect remains the same.

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