

Assignment letter for the placebo story, written by editor Ted Greenwald with Silberman's input.

Assignment: Placebo effect

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The idea behind modern medicine is simple: put a chemical into someone's body and it will have a predictable effect. Sure, there are a few reasons why this might not happen – variable sensitivity to the compound, interference from other medications. By and large, though, we tend to accept that medicines work as intended. But there's one complication that's giving the medical industry fits: the placebo effect. To wit, 11 percent of balding men given a sugar pill start to re-grow hair (versus 26 percent using Rogaine). 60 percent of patients suffering from chronic pain who are told they're receiving morphine but get saline instead experience complete relief.

Although the phenomenon has been recognized since the days of the ancient Greeks who named it, the placebo effect remains little understood. In the past few years, research has established that it definitely exists, and it's neither bias ("all in your mind") nor natural history (normal fluctuation of symptoms). Placebos work through specific brain pathways and can have a profound impact on autonomic functions like endocrine activity and the immune system as well as cognitive functions like mood and memory. And the medical community is taking notice. The first over-the-counter placebo, Obecalp, for nonspecific childhood ailments, went on sale this summer. The new consensus around the placebo effect raises profound questions. If an inert substance like sugar or saline relieves pain in 20 percent of people and an analgesic helps 21 percent of recipients suffering from the same illness, did the medicine have much to do with it? Drug companies try to answer this question in two ways. First, they routinely start their trials with a placebo-only study and throw out all the candidates who showed a strong response, retaining the rest for testing. Second, they match their drug tests with control groups who receive only placebo. To gain FDA approval, the drug must outperform the placebo, if only marginally. There are problems with this system. For one, by rejecting people who respond to placebos, researchers make the placebo look less effective than it really is, skewing their results in favor of their drug. It also opens a loophole that pharma companies use to fudge results — say, by switching participants from the drug group to the placebo group so lingering side effects can be attributed to the placebo. Moreover, when a drug beats the placebo, it's likely that some percentage of recipients improved due not to the medication but to the placebo effect. Was it a small portion or the lion's share? There's no way to know. Sometimes the placebo outperforms the medicine it's pitted against. Ted Kaptchuk at Harvard found that placebo treatment tested better than any existing med in 270 patients with irritable bowel syndrome. Most mysterious, beneficial placebo effects are often accompanied by a negative "nocebo" effect that parallels harmful drug side effects.

These issues have become the elephant in the clinic, especially when it comes to the efficacy of the class of drugs known as SSRIs. Treatments like Prozac and Zoloft are the most frequently prescribed meds for depression - and the most profitable class of drugs on the market, accounting for \$10 billion annually in profit. Doctors report that they have undeniable positive, even life-saving effects in some patients. Yet in clinical trials, they rarely outperform placebos, and when they do, it's only slightly. Drug companies are desperate to demonstrate that SSRIs are effective. "The placebo effect is overwhelming the ability to make a distinction between the pharmacology of a drug and an inert imitation," Kaptchuk observes. All of which makes it a top scientific priority to understand the placebo effect. The NIH made a special call for proposals eight years ago, and research has exploded since then. Thanks to sophisticated brain imaging techniques and cleverly designed studies, researchers are closing in on the mechanisms that underlie the phenomenon and devising test procedures that can distinguish it from drug-induced effects. Jon-Kar Zubieta at University of Michigan is studying whether responsiveness to placebos is related to estrogen and testosterone levels. To minimize placebo effects in clinical trials, Fabrizio Benedetti at the University of Turin suggest supplementing overt drug tests, which presumably activate some degree of placebo effect, with a group of subjects on an IV drip so they can't tell whether or when they're getting dosed. A comparison would reveal the drug's own placebo nature.

We've made contact with a few pharma insiders about the havoc the placebo effect is bringing to their industry, and with researchers about what it means and how we might cope. Medicine will be changed by the current ferment. Let's capture the transitional moment and offer a glimpse into the future.