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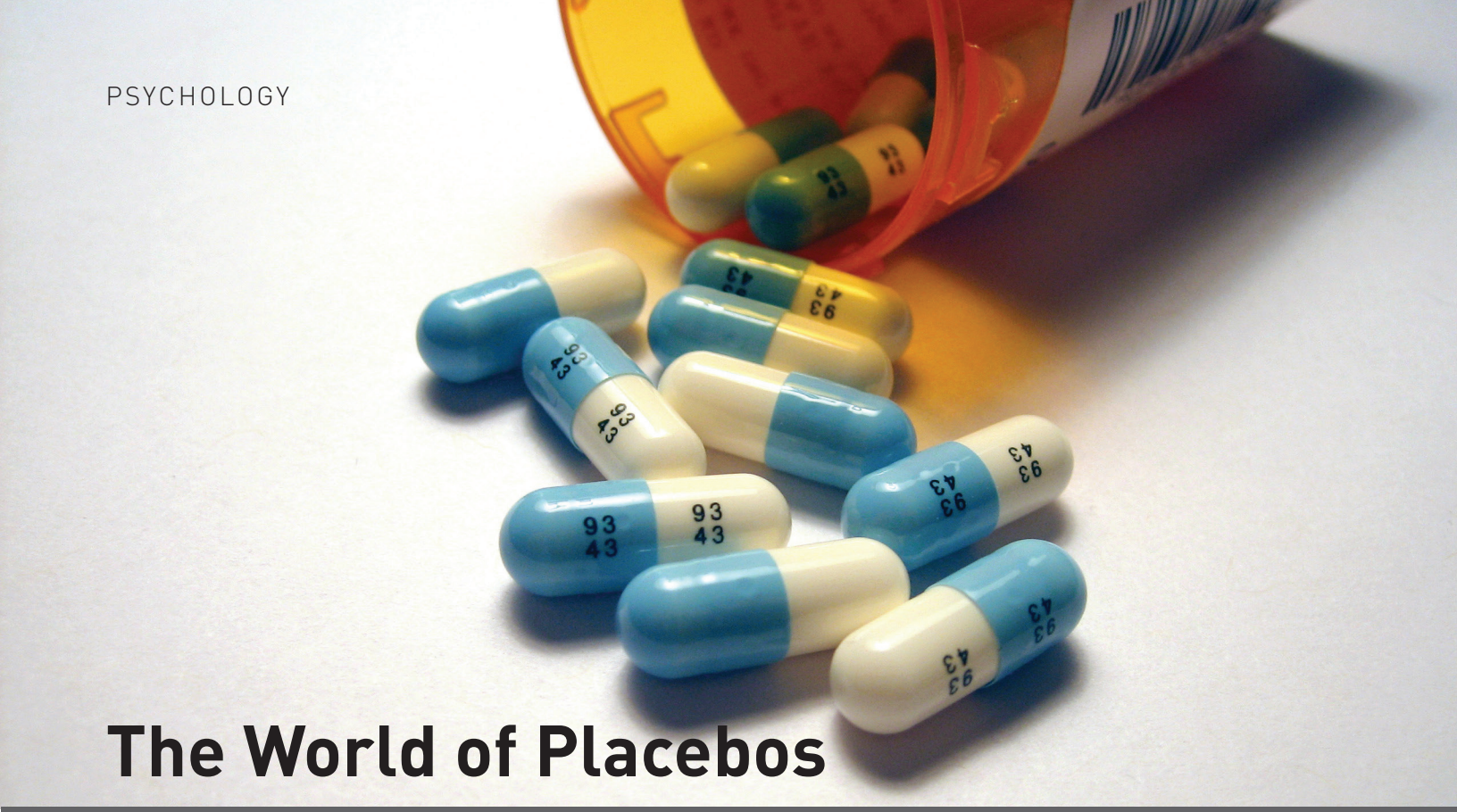

The World of Placebos

BY ZACHARY WANG '20

Introduction

The Placebo Effect is a fascinating but poorly understood mystery of medicine and human biology. Its workings continue to surprise scientists and patients everywhere. This is a brief introduction to the placebo effect from its early roots to current issues and new discoveries in the field.

Then...

The First "Placebo"

In the 16th century, religious authorities conceived of a unique way to test whether or not someone was actually possessed (Lemoine, 2015). When individuals showed questionable signs of diabolical possession, they would be given false relics. If the "possessed" acted as if they were real, the healer would be able to deduce that the seizures or other symptoms were either fake, or the result of an overactive imagination. In this manner, one of the earliest documented instances of using an ineffectual replica of a real treatment was conceived.

The First "Actual" Placebo

In 1752, James Lind, a doctor in the Royal Navy, published "A Treatise of the Scurvy" in which he unknowingly performed the first recorded use of placebo groups (Lemoine, 2015). The inventor of what would one day be called a "controlled trial," Lind selected 12 sailors suffering from scurvy and divided them into groups of two, assigning each group one of six different treatments. The groups received either cider, an elixir of vitriol (sulfuric acid), vinegar, seawater, lemons and oranges, and, lastly, a mixture of garlic, mustard, and horseradish root, respectively. The sailors in the lemons and oranges group healed in days as well as those in the cider group, though not as quickly. The other four groups were the placebo groups, and their treatment proved to be fatal. Ethically, one would hope that Dr. Lind did not intend to kill the other four groups, given the substances administered were considered therapeutic at the time, though not for the treatment of scurvy.

Medicine Embraces the Placebo

It took until 1785 for the term "placebo" to first show up in the Motherby's New Medical Dictionary, where it is defined as "a commonplace medication or method" (Lemoine, 2015). The word "commonplace" should probably be taken to mean "overused and unimportant." The first time the word appeared in its modern form was 1958, after the advent of double-blind controlled trials with randomized assignment. From this point on, placebos gained scientific respectability in contrast to the earlier connotation of pseudoscience.

The Discovery of the Placebo Effect

Figure 1: Drugs earlier approved by the FDA (such as Prozac) are now failing further tests due to the placebo effect.

Source: Wikimedia Commons (Credit: Tom Varco)

Figure 2: Pharmaceutical companies like Merck are facing the consequences of the increasingly powerful placebo effect, as well as their customers.

Source: Wikimedia Commons (Credit: Merck KgaA)

In a famous article published in the *Journal of the American Medical Association* in 1955, using data from 15 studies encompassing 1082 patients with varied types and degrees of pain, Henry K. Beecher showed that a placebo analgesic is effective, on average, in 35.2% of cases, though individual studies ranged from 4% to 86% efficacy (Beecher, 2015). Pain that was least natural in origin, i.e. experimental pain triggered in a laboratory on healthy subjects, was least responsive to placebos whereas natural pain, like chest pain, was most sensitive to placebos. Since then, countless publications have quantified the effectiveness of placebos and the existence and importance of the placebo effect, varying with the patient's and physician's awareness of the placebo. Thus, the placebo effect gained fame as an impressive feat of human biology and legitimacy in the eyes of the medical community.

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...and Now

The Ailing Pharmaceutical Industry

The Problem:

Merck was in trouble. In 2002, the pharmaceutical giant was rapidly falling behind its competitors in sales (Silberman, 2009). To make matters worse, patents on five best-selling drugs were about to expire, allowing cheaper generics to flood the market. The company had not introduced a truly new product in three years, and its stock was plummeting. In an interview, Edward Scolnick, Merck's research director at the time, described his plan to bring Merck back to the top. Fundamental to this strategy was a new focus on antidepressants, a field where Merck had previously lagged behind its competitors who were making some of the most profitable drugs such as Zoloft, Prozac, and Xanax in the world (Grohol, 2016). This plan hinged on an experimental antidepressant codenamed MK-869. And though still in clinical trials, it was shaping up to be a blessing to Merck and its leadership. The drug exploited human brain chemistry in brilliant and innovative ways with little to no side effects. It tested brilliantly early on, and Merck representatives showed off its amazing potential at a meeting of 300 securities analysts (Silberman, 2009).

Though doing well on the surface, MK-869 was starting to falter (Drugs in R & D, 2002). Although many test subjects felt that the drug lifted their sense of hopelessness and anxiety, nearly the same number of subjects did so as well with a placebo. Thus, Merck's foray into antidepressants failed. In further testing, MK-869 proved to be no more effective than placebos.

Merck's MK-869 wasn't the only highly anticipated medical breakthrough undone by the placebo effect (McGoey, 2010). From 2001 to 2006, the percentage of new products pulled from development after Phase II trials, where they are first tested against placebos, shot up 20%. Failure in the more extensive Phase III trials rose by 11%. So despite unprecedented amounts of investment in research and development, the FDA only approved 19 original remedies in 2007—the fewest since 1983—and 24 in 2008. Half of all medications that fail in late-stage trials are undone due to their inability to beat out a simple sugar pill.

The Consequences:

What's the fallout of this phenomenon? Fewer new medicines are becoming available to suffering patients and further financial woes troubling the pharmaceutical industry (Silberman, 2009). In November of 2009, a new type of gene therapy for Parkinson's disease, championed by the Michael J. Fox Foundation, was abruptly withdrawn from Phase II trials after unexpectedly tanking against placebo. A stem-cell startup called Osiris Therapeutics got a drubbing on Wall Street that March, when it suspended trials of its pill for Crohn's disease, an intestinal ailment, citing an "unusually high" response to placebo. Two days later, Eli Lilly broke off testing of a much-touted new drug for schizophrenia when volunteers showed double the expected level of placebo response.

And it's not just new drugs that are failing against placebos. Products that have been available for decades, like Prozac, are now failing in more recent follow-up testing (McGoey, 2010). If these same drugs were being developed now, they may not pass FDA approval.

According to drug developers, it's not that the old medications are getting weaker, but that the placebo effect, a beneficial effect produced by an inert placebo drug or treatment, is getting stronger (Spiegel, 2010). And it appears that the placebo effect is not just becoming stronger, but also increasing in breadth.

Effectiveness of Open Label Placebos

Linda Buonanno had suffered 15 years of

intense cramps, bloating, diarrhea and pain she describes as "worse than labor" (Fleming, 2017). She was willing to try anything to get relief from her irritable bowel syndrome (IBS) and leapt at the chance to take part in a trial of an experimental new therapy. Her hope turned to disappointment, however, when the researcher handed her a bottle of capsules he described as placebos containing no active ingredients. Nonetheless, she took the pills twice daily. Four days later, her symptoms all but vanished. "I know it sounds crazy," says Buonanno, of Methuen, Massachusetts. "I felt fantastic. I knew they were just sugar pills, but I was able to go out dancing and see my friends again." Placebos have a reputation problem. It is widely believed they are only effective when those taking them are deceived into thinking they are taking real drugs. However, prescribing dummy or fake treatments is unethical. Yet in Buonanno's case there was no deception and she experienced substantial relief. And she is not alone.

On the 27th of April 2017, clinical epidemiologist Dr. Jeremy Howick and a group of other scientists working out of the University of Oxford, Harvard Medical School, and multiple psychology departments published the *Effects of placebos without deception compared with no treatment* (Charlesworth, 2017). A meta-analysis and review of five research studies covering 260 patients, showing the effectiveness of "open-label" placebos for a number of health issues. "Open-label" placebos are normal placebos, except that patients know that they're placebos. Howick writes "[normally] we have to believe they are "real" treatments, which means the doctor would have to lie to us and say that the placebo was actually a real treatment. Or, in the case of a clinical trial, that it might be a real treatment. After all, if a doctor handed you a pill and said, 'this is just a sugar pill', you'd probably assume it wouldn't work. But sometimes our assumptions are mistaken" (2017). Previously, the belief was that the placebo effect only worked when patients believed they were taking real medicine. With this study, this is no longer necessarily the case.

According to Howick, "the history of open-label placebos can be traced back to at least 1965 when Baltimore doctors, Lee Park and Uno Covi, gave open placebos to 15 neurotic patients. They told the patients: 'Many people with your kind of condition have been helped by what are sometimes called sugar pills and we feel that a so-called sugar pill may help you too'" (2017). Many of the patients got better. Paradoxically, since these were neurotic patients, they thought that the doctors had lied to them and given them real drugs.

The first study reviewed was led by Professor Ted Kaptchuk, of Harvard Medical School, who gave 80 IBS patients, including Buonanno (Fleming, 2017), either no treatment or open-label placebo pills (Charlesworth, 2017). He found those who took placebos for three weeks experienced greater improvements in symptoms, including less severe pain. In another of the studies in Howick's review,

"Previously, the belief was that the placebo effect only worked when patients believed they were taking real medicine. With this study, this is no longer necessarily the case."

Figure 3: Pavlov's dogs and their keepers. Ivan Pavlov demonstrated classical conditioning by training dogs to salivate by association.

Source: Wikimedia Commons (Credit: Wellcome Images)

chronic lower back pain patients openly given dummy pills to add to their existing treatments reported an average 30% pain reduction. In the three other review studies, people given open-label pills reported reduced symptoms for depression, lower back pain, and attention deficit hyperactivity disorder.

"Open-label placebos probably work in two ways," writes Howick. "The first is expectation. Open-label are usually given with a positive suggestion: the doctor will tell the patient the pill is just a placebo but adds that it 'produces significant improvement for patients like you'. This positive suggestion creates a positive expectation, which can activate the reward mechanisms in the brain and help the body produce its own pain-reducing substances, such as endorphins" (2017).

The second possible explanation is conditioning. Pavlov was a Russian physiologist who accidently discovered the phenomenon of classical conditioning while studying dogs' gastric systems (Specter, 2014). He found that dogs would salivate when they heard or smelled food in anticipation of feeding. This is an expected response given the role of saliva in digestion. However, the dogs also began to salivate when events occurred which would otherwise be unrelated to feeding. By playing sounds to the dogs prior to feeding them, Pavlov showed that they could be conditioned to associate neutral, unrelated events with being fed. Just as Pavlov's dogs learned to associate the sound of a bell with food and began salivating whenever they heard the bell, most of us have been conditioned to expect a positive outcome when a trusted doctor gives a treatment. "So even though we know a pill is a placebo," Howick writes, "our bodies may react in a way that helps us heal. There have been several studies, including one in humans, showing that the immune system can be activated much in the same way that Pavlov's dogs salivated at the mere sound of a bell" (2017).

"Fortunately, the review of open-label placebos demonstrates something more general: placebo effects are real for many common conditions and people can use the placebo effect without placebo pills."

Since open-label placebos have been shown to improve symptoms, should they be made available? After all, they seem to help people with nowhere else to go, like Buonanno, and have no side effects being made from sugar or other harmless substances. According to Howick, no (2017). "That may be unwise because it would support a pill-popping, overmedicalized culture." Fortunately, the review of open-label placebos demonstrates something more general: placebo effects are real for many common conditions and people can use the placebo effect without placebo pills. Doctors who give positive messages and take time to communicate with enhanced empathy to patients can bring about positive benefits with or without pills. "Far from being unethical," Howick says, "since placebo effects can benefit many patients it is probably unethical not to exploit them."

The placebo effect, though already poorly understood and mysterious, seems to be evolving in strength and breadth right before our very eyes. A few months ago, most were confident that placebo effects only occurred when patients were unaware they were taking a placebo. And yet recently we learned that wasn't the case. The consequences of the placebo effect's "new abilities" are far-reaching and represent a double-edged sword. On the one hand, people who find no succor from presently available pharmaceuticals may now find relief. On the other hand, many people who need new, upcoming treatments may have their hopes dashed by a sudden discontinuity of research into a treatment. Just as our understanding of the placebo effect seems to be evolving, so is its future role in medicine. Will we find it to be an enemy, stealing hope away from anxious patients? Or will we find in it a novel and previously-untapped base for treatment, helping doctors assist suffering patients without harsh side-effects? D

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