

Placebos Are Getting More Effective. Drugmakers Are Desperate to Know Why.

By Steve Silberman 08.24.09



Photo: Nick Veasey

Merck was in trouble. In 2002, the pharmaceutical giant was falling behind its rivals in sales. Even worse, patents on five blockbuster drugs were about to expire, which would allow cheaper generics to flood the market. The company hadn't introduced a truly new product in three years, and its stock price was plummeting.

In interviews with the press, Edward Scolnick, Merck's research director, laid out his battle plan to restore the firm to preeminence. Key to his strategy was expanding the company's reach into the antidepressant market, where Merck had lagged while competitors like Pfizer and GlaxoSmithKline created some of the best-selling drugs in the world. "To remain dominant in the future," he told *Forbes*, "we need to dominate the central nervous system."

His plan hinged on the success of an experimental antidepressant codenamed MK-869. Still in clinical trials, it looked like every pharma executive's dream: a new kind of medication that exploited brain chemistry in innovative ways to promote feelings of well-being. The drug tested brilliantly early on, with minimal side effects, and Merck touted its game-changing potential at a meeting of 300 securities analysts.

Behind the scenes, however, MK-869 was starting to unravel. True, many test subjects treated with the medication felt their hopelessness and anxiety lift. But so did nearly the same number who took a placebo, a look-alike pill made of milk sugar or another inert substance given to groups of volunteers in clinical trials to gauge how much more effective the real drug is by comparison. The fact that taking a faux drug can powerfully improve some people's health—the so-called placebo effect—has long been considered an embarrassment to the serious practice of pharmacology.

Ultimately, Merck's foray into the antidepressant market failed. In subsequent tests, MK-869 turned out to be no more effective than a placebo. In the jargon of the industry, the trials crossed the futility boundary.

MK-869 wasn't the only highly anticipated medical breakthrough to be undone in recent years by the placebo effect. From 2001 to 2006, the percentage of new products cut from development after Phase II clinical trials, when drugs are first tested against placebo, rose by 20 percent. The failure rate in more extensive Phase III trials increased by 11 percent, mainly due to surprisingly poor showings against placebo. Despite historic levels of industry investment in R&D, the US Food and Drug Administration approved only 19 first-of-their-kind remedies in 2007—the fewest since 1983—and just 24 in 2008. Half of all drugs that fail in late-stage trials drop out of the pipeline due to their inability to beat sugar pills.

The upshot is fewer new medicines available to ailing patients and more financial woes for the beleaguered pharmaceutical industry. Last November, 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 in 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.

It's not only trials of new drugs that are crossing the futility boundary. Some products that have been on the market for decades, like Prozac, are faltering in more recent follow-up tests. In many cases, these are the compounds that, in the late '90s, made Big Pharma more profitable than Big Oil. But if these same drugs were vetted now, the FDA might not approve some of them. Two comprehensive analyses of antidepressant trials have uncovered a dramatic increase in placebo response since the 1980s. One estimated that the so-called effect size (a measure of statistical significance) in placebo groups had nearly doubled over that time.

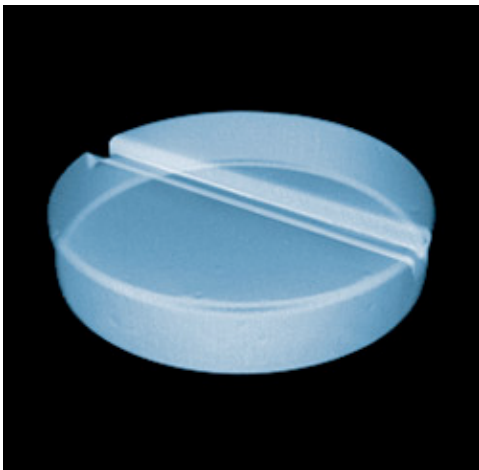
It's not that the old meds are getting weaker, drug developers say. It's as if the placebo effect is somehow getting stronger.

The fact that an increasing number of medications are unable to beat sugar pills has thrown the industry into crisis. The stakes could hardly be higher. In today's economy, the fate of a long-established company can hang on the outcome of a handful of tests.

Why are inert pills suddenly overwhelming promising new drugs and established medicines alike? The reasons are only just beginning to be understood. A network of independent researchers is doggedly uncovering the inner workings—and potential therapeutic applications—of the placebo effect. At the same time, drugmakers are realizing they need to fully understand the mechanisms behind it so they can design trials that differentiate more clearly between the beneficial effects of their products and the body's innate ability to heal itself. A special task force of the Foundation for the National Institutes of Health is seeking to stem the crisis by quietly undertaking one of the most ambitious data-sharing efforts in the history of the drug industry. After decades in the jungles of fringe science, the placebo effect has become the elephant in the boardroom.

The roots of the placebo problem can be traced to a lie told by an Army nurse during World War II as Allied forces stormed the beaches of southern Italy. The nurse was assisting an anesthetist named Henry Beecher, who was tending to US troops under heavy German bombardment. When the morphine supply ran low, the nurse assured a wounded soldier that he was getting a shot of potent painkiller, though her syringe contained only salt water. Amazingly, the bogus injection relieved the soldier's agony and prevented the onset of shock.

Returning to his post at Harvard after the war, Beecher became one of the nation's leading medical reformers. Inspired by the nurse's healing act of deception, he launched a crusade to promote a method of testing new medicines to find out whether they were truly effective. At the time, the process for vetting drugs was sloppy at best: Pharmaceutical companies would simply dose volunteers with an experimental agent until the side effects swamped the presumed benefits. Beecher proposed that if test subjects could be compared to a group that received a placebo, health officials would finally have an impartial way to determine whether a medicine was actually responsible for making a patient better.



In a 1955 paper titled "The Powerful Placebo," published in *The Journal of the American Medical Association*, Beecher described how the placebo effect had undermined the results of more than a dozen trials by causing improvement that was mistakenly attributed to the drugs being tested. He demonstrated that trial volunteers who got real medication were also subject to placebo effects; the act of taking a pill was itself somehow therapeutic, boosting the curative power of the medicine. Only by subtracting the improvement in a placebo control group could the actual value of the drug be calculated.

The article caused a sensation. By 1962, reeling from news of birth defects caused by a drug called thalidomide, Congress amended the Food, Drug, and Cosmetic Act, requiring trials to include enhanced safety testing and placebo control groups. Volunteers would be assigned randomly to receive either medicine or a sugar pill, and neither doctor nor patient would know the difference until the trial was over. Beecher's double-blind, placebo-controlled, randomized clinical trial—or RCT—was enshrined as the gold standard of the emerging pharmaceutical industry. Today, to win FDA approval, a new medication must beat placebo in at least two authenticated trials.

Beecher's prescription helped cure the medical establishment of outright quackery, but it had an insidious side effect. By casting placebo as the villain in RCTs, he ended up stigmatizing one of his most important discoveries. The fact that even dummy capsules can kick-start the body's recovery engine became a problem for drug developers to overcome, rather than a phenomenon that could guide doctors toward a better understanding of the healing process and how to drive it most effectively.

In his eagerness to promote his template for clinical trials, Beecher also overreached by seeing the placebo effect at work in curing ailments like the common cold, which wane with no intervention at all. But the triumph of Beecher's gold standard was a generation of safer medications that worked for nearly everyone. Anthracyclines don't require an oncologist with a genial bedside manner to slow the growth of tumors.

What Beecher didn't foresee, however, was the explosive growth of the pharmaceutical industry. The blockbuster success of mood drugs in the '80s and '90s emboldened Big Pharma to promote remedies for a growing panoply of disorders that are intimately related to higher brain function. By attempting to dominate the central nervous system, Big Pharma gambled its future on treating ailments that have turned out to be particularly susceptible to the placebo effect.

The tall, rusty-haired son of a country doctor, William Potter, 64, has spent most of his life treating mental illness—first as a psychiatrist at the National Institute of Mental Health and then as a drug developer. A decade ago, he took a job at Lilly's neuroscience labs. There, working on new antidepressants and antianxiety meds, he became one of the first researchers to glimpse the approaching storm.

To test products internally, pharmaceutical companies routinely run trials in which a long-established medication and an experimental one compete against each other as well as against a placebo. As head of Lilly's early-stage psychiatric drug development in the late '90s, Potter saw that even durable warhorses like Prozac, which had been on the market for years, were being overtaken by dummy pills in more recent tests. The company's next-generation antidepressants were faring badly, too, doing no better than placebo in seven out of 10 trials.

As a psychiatrist, Potter knew that some patients really do seem to get healthier for reasons that have more to do with a doctor's empathy than with the contents of a pill. But it baffled him that drugs he'd been prescribing for years seemed to be struggling to prove their effectiveness. Thinking that something crucial may have been overlooked, Potter tapped an IT geek named David DeBrotta to help him comb through the Lilly database of published and unpublished trials—including those that the company had kept secret because of high placebo response. They aggregated the findings from decades of antidepressant trials, looking for patterns and trying to see what was changing over time. What they found challenged some of the industry's basic assumptions about its drug-vetting process.

Assumption number one was that if a trial were managed correctly, a medication would perform as well or badly in a Phoenix hospital as in a Bangalore clinic. Potter discovered, however, that geographic location alone could determine whether a drug bested placebo or crossed the futility boundary. By the late '90s, for example, the classic antianxiety drug diazepam (also known as Valium) was still beating placebo in France and Belgium. But when the drug was tested in the US, it was likely to fail. Conversely, Prozac performed better in America than it did in western Europe and South Africa. It was an unsettling prospect: FDA approval could hinge on where the company chose to conduct a trial.

Mistaken assumption number two was that the standard tests used to gauge volunteers' improvement in trials yielded consistent results. Potter and his colleagues discovered that ratings by trial observers varied significantly from one testing site to another. It was like finding out that the judges in a tight race each had a different idea about the placement of the finish line.

Potter and DeBrotta's data-mining also revealed that even superbly managed trials were subject to runaway placebo effects. But exactly why any of this was happening remained elusive. "We were able to identify many of the core issues in play," Potter says. "But there was no clear answer to the problem." Convinced that what Lilly was facing was too complex for any one pharmaceutical house to unravel on its own, he came up with a plan to break down the firewalls between researchers across the industry, enabling them to share data in "pre-competitive space."

After prodding by Potter and others, the NIH focused on the issue in 2000, hosting a three-day conference in Washington. For the first time in medical history, more than 500 drug developers, doctors, academics, and trial designers put their heads together to examine the role of the placebo effect in clinical trials and healing in general.

Potter's ambitious plan for a collaborative approach to the problem eventually ran into its own futility boundary: No one would pay for it. And drug companies don't share data, they hoard it. But the NIH conference launched a new wave of placebo research in academic labs in the US and Italy that would make significant progress toward solving the mystery of what was happening in clinical trials.

Visitors to Fabrizio Benedetti's clinic at the University of Turin are asked never to say the P-word around the med students who sign up for his experiments. For all the volunteers know, the trim, soft-spoken neuroscientist is hard at work concocting analgesic skin creams and methods for enhancing athletic performance.

One recent afternoon in his lab, a young soccer player grimaced with exertion while doing leg curls on a weight machine. Benedetti and his colleagues were exploring the potential of using Pavlovian conditioning to give athletes a competitive edge undetectable by anti-doping authorities. A player would receive doses of a performance-enhancing drug for weeks and then a jolt of placebo just before competition.

Benedetti, 53, first became interested in placebos in the mid-'90s, while researching pain. He was surprised that some of the test subjects in his placebo groups seemed to suffer less than those on active drugs. But scientific interest in this phenomenon, and the money to research it, were hard to come by. "The placebo effect was considered little more than a nuisance," he recalls. "Drug companies, physicians, and clinicians were not interested in understanding its mechanisms. They were concerned only with figuring out whether their drugs worked better."

Part of the problem was that response to placebo was considered a psychological trait related to neurosis and gullibility rather than a physiological phenomenon that could be scrutinized in the lab and manipulated for therapeutic benefit. But then Benedetti came across a study, done years earlier, that suggested the placebo effect had a neurological foundation. US scientists had found that a drug called naloxone blocks the pain-relieving power of placebo treatments. The brain produces its own analgesic compounds called opioids, released under conditions of stress, and naloxone blocks the action of these natural painkillers and their synthetic analogs. The study gave Benedetti the lead he needed to pursue his own research while running small clinical trials for drug companies.

Now, after 15 years of experimentation, he has succeeded in mapping many of the biochemical reactions responsible for the placebo effect, uncovering a broad repertoire of self-healing responses. Placebo-activated opioids, for example, not only relieve pain; they also modulate heart rate and respiration. The neurotransmitter dopamine, when released by placebo treatment, helps improve motor function in Parkinson's patients. Mechanisms like these can elevate mood, sharpen cognitive ability, alleviate digestive disorders, relieve insomnia, and limit the secretion of stress-related hormones like insulin and cortisol.

In one study, Benedetti found that Alzheimer's patients with impaired cognitive function get less pain relief from analgesic drugs than normal volunteers do. Using advanced methods of EEG analysis, he discovered that the connections between the patients' prefrontal lobes and their opioid systems had been damaged. Healthy volunteers feel the benefit of medication plus a placebo boost. Patients who are unable to formulate ideas about the future because of cortical deficits, however, feel only the effect of the drug itself. The experiment suggests that because Alzheimer's patients don't get the benefits of anticipating the treatment, they require higher doses of painkillers to experience normal levels of relief.

Benedetti often uses the phrase "placebo response" instead of placebo effect. By definition, inert pills have no effect, but under the right conditions they can act as a catalyst for what he calls the body's "endogenous health care system." Like any other internal network, the placebo response has limits. It can ease the discomfort of chemotherapy, but it won't stop the growth of tumors. It also works in reverse to produce the placebo's evil twin, the nocebo effect. For example, men taking a commonly prescribed prostate drug who were informed that the medication may cause sexual dysfunction were twice as likely to become impotent.

Further research by Benedetti and others showed that the promise of treatment activates areas of the brain involved in weighing the significance of events and the seriousness of threats. "If a fire alarm goes off and you see smoke, you know something bad is going to happen and you get ready to escape," explains Tor Wager, a neuroscientist at Columbia University. "Expectations about pain and pain relief work in a similar way. Placebo treatments tap into this system and orchestrate the responses in your brain and body accordingly."

In other words, one way that placebo aids recovery is by hacking the mind's ability to predict the future. We are constantly parsing the reactions of those around us—such as the tone a doctor uses to deliver a diagnosis—to generate more-accurate estimations of our fate. One of the most powerful placebo-generative triggers is watching someone else experience the benefits of an alleged drug. Researchers call these social aspects of medicine the therapeutic ritual.

In a study last year, Harvard Medical School researcher Ted Kaptchuk devised a clever strategy for testing his volunteers' response to varying levels of therapeutic ritual. The study focused on irritable bowel syndrome, a painful disorder that costs more than \$40 billion a year worldwide to treat. First the volunteers were placed randomly in one of

three groups. One group was simply put on a waiting list; researchers know that some patients get better just because they sign up for a trial. Another group received placebo treatment from a clinician who declined to engage in small talk. Volunteers in the third group got the same sham treatment from a clinician who asked them questions about symptoms, outlined the causes of IBS, and displayed optimism about their condition.

RX FOR SUCCESS

What turns a dummy pill into a catalyst for relieving pain, anxiety, depression, sexual dysfunction, or the tremors of Parkinson's disease? The brain's own healing mechanisms, unleashed by the belief that a phony medication is the real thing. The most important ingredient in any placebo is the doctor's bedside manner, but according to research, the color of a tablet can boost the effectiveness even of genuine meds—or help convince a patient that a placebo is a potent remedy.—*Steve Silberman*



Yellow pills make the most effective antidepressants, like little doses of pharmaceutical sunshine.



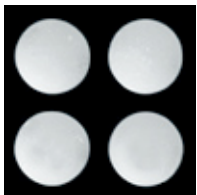
Red pills can give you a more stimulating kick. Wake up, Neo.



The color green reduces anxiety, adding more chill to the pill.



White tablets—particularly those labeled "antacid"—are superior for soothing ulcers, even when they contain nothing but lactose.



More is better, scientists say. Placebos taken four times a day deliver greater relief than those taken twice daily.



Branding matters. Placebos stamped or packaged with widely recognized trademarks are more effective than "generic" placebos.

Not surprisingly, the health of those in the third group improved most. In fact, just by participating in the trial, volunteers in this high-interaction group got as much relief as did people taking the two leading prescription drugs for IBS. And the benefits of their bogus treatment persisted for weeks afterward, contrary to the belief—widespread in the pharmaceutical industry—that the placebo response is short-lived.

Studies like this open the door to hybrid treatment strategies that exploit the placebo effect to make real drugs safer and more effective. Cancer patients undergoing rounds of chemotherapy often suffer from debilitating nocebo effects—such as anticipatory nausea—conditioned by their past experiences with the drugs. A team of German researchers has shown that these associations can be unlearned through the administration of placebo, making chemo easier to bear.

Meanwhile, the classic use of placebos in medicine—to boost the confidence of anxious patients—has been employed tacitly for ages. Nearly half of the doctors polled in a 2007 survey in Chicago admitted to prescribing medications they knew were ineffective for a patient's condition—or prescribing effective drugs in doses too low to produce actual benefit—in order to provoke a placebo response.

The main objections to more widespread placebo use in clinical practice are ethical, but the solutions to these conundrums can be surprisingly simple. Investigators told volunteers in one placebo study that the pills they were taking were "known to significantly reduce pain in some patients." The researchers weren't lying.

These new findings tell us that the body's response to certain types of medication is in constant flux, affected by expectations of treatment, conditioning, beliefs, and social cues.

For instance, the geographic variations in trial outcome that Potter uncovered begin to make sense in light of discoveries that the placebo response is highly sensitive to cultural differences. Anthropologist Daniel Moerman found that Germans are high placebo reactors in trials of ulcer drugs but low in trials of drugs for hypertension—an undertreated condition in Germany, where many people pop pills for *herzinsuffizienz*, or low blood pressure. Moreover, a pill's shape, size, branding, and price all influence its effects on the body. Soothing blue capsules make more effective tranquilizers than angry red ones, except among Italian men, for whom the color blue is associated with their national soccer team—*Forza Azzurri!*

But why would the placebo effect seem to be getting stronger worldwide? Part of the answer may be found in the drug industry's own success in marketing its products.

Potential trial volunteers in the US have been deluged with ads for prescription medications since 1997, when the FDA amended its policy on direct-to-consumer advertising. The secret of running an effective campaign, Saatchi & Saatchi's Jim Joseph told a trade journal last year, is associating a particular brand-name medication with other aspects of life that promote peace of mind: "Is it time with your children? Is it a good book curled up on the couch? Is it your favorite television show? Is it a little purple pill that helps you get rid of acid reflux?" By evoking such uplifting associations, researchers say, the ads set up the



Clever names can add a placebo boost to the physiological punch in real drugs. *Viagra* implies both vitality and an unstoppable Niagara of sexy.

kind of expectations that induce a formidable placebo response.

The success of those ads in selling blockbuster drugs like antidepressants and statins also pushed trials offshore as therapeutic virgins—potential volunteers who were not already medicated with one or another drug—became harder to find. The contractors that manage trials for Big Pharma have moved aggressively into Africa, India, China, and the former Soviet Union. In these places, however, cultural dynamics can boost the placebo response in other ways. Doctors in these countries are paid to fill up trial rosters quickly, which may motivate them to recruit patients with milder forms of illness that yield more readily to placebo treatment. Furthermore, a patient's hope of getting better and expectation of expert care—the primary placebo triggers in the brain—are particularly acute in societies where volunteers are clamoring to gain access to the most basic forms of medicine. "The quality of care that placebo patients get in trials is far

superior to the best insurance you get in America," says psychiatrist Arif Khan, principal investigator in hundreds of trials for companies like Pfizer and Bristol-Myers Squibb. "It's basically luxury care."

Big Pharma faces additional problems in beating placebo when it comes to psychiatric drugs. One is to accurately define the nature of mental illness. The litmus test of drug efficacy in antidepressant trials is a questionnaire called the Hamilton Depression Rating Scale. The HAM-D was created nearly 50 years ago based on a study of major depressive disorder in patients confined to asylums. Few trial volunteers now suffer from that level of illness. In fact, many experts are starting to wonder if what drug companies now call depression is even the same disease that the HAM-D was designed to diagnose.

Existing tests also may not be appropriate for diagnosing disorders like social anxiety and premenstrual dysphoria—the very types of chronic, fuzzily defined conditions that the drug industry started targeting in the '90s, when the placebo problem began escalating. The neurological foundation of these illnesses is still being debated, making it even harder for drug companies to come up with effective treatments.

What all of these disorders have in common, however, is that they engage the higher cortical centers that generate beliefs and expectations, interpret social cues, and anticipate rewards. So do chronic pain, sexual dysfunction, Parkinson's, and many other ailments that respond robustly to placebo treatment. To avoid investing in failure, researchers say, pharmaceutical companies will need to adopt new ways of vetting drugs that route around the brain's own centralized network for healing.

Ten years and billions of R&D dollars after William Potter first sounded the alarm about the placebo effect, his message has finally gotten through. In the spring, Potter, who is now a VP at Merck, helped rev up a massive data-gathering effort called the Placebo Response Drug Trials Survey.

Under the auspices of the NIH, Potter and his colleagues are acquiring decades of trial data—including blood and DNA samples—to determine which variables are responsible for the apparent rise in the placebo effect. Merck, Lilly, Pfizer, AstraZeneca, GlaxoSmithKline, Sanofi-Aventis, Johnson & Johnson, and other major firms are funding the study, and the process of scrubbing volunteers' names and other personal information from the database is about to begin.

In typically secretive industry fashion, the existence of the project itself is being kept under wraps. NIH staffers are willing to talk about it only anonymously, concerned about offending the companies paying for it.

For Potter, who used to ride along with his father on house calls in Indiana, the significance of the survey goes beyond Big Pharma's finally admitting it has a placebo problem. It also marks the twilight of an era when the drug industry was confident that its products were strong enough to cure illness by themselves.

"Before I routinely prescribed antidepressants, I would do more psychotherapy for mildly depressed patients," says the veteran of hundreds of drug trials. "Today we would say I was trying to engage components of the placebo response—and those patients got better. To really do the best for your patients, you want the best placebo response plus the best drug response."

The pharma crisis has also finally brought together the two parallel streams of placebo research—academic and industrial. Pfizer has asked Fabrizio Benedetti to help the company figure out why two of its pain drugs keep failing. Ted Kaptchuk is developing ways to distinguish drug response more clearly from placebo response for another pharma house that he declines to name. Both are exploring innovative trial models that treat the placebo effect as more than just statistical noise competing with the active drug.

Benedetti has helped design a protocol for minimizing volunteers' expectations that he calls "open/hidden." In standard trials, the act of taking a pill or receiving an injection activates the placebo response. In open/hidden trials, drugs and placebos are given to some test subjects in the usual way and to others at random intervals through an IV line controlled by a concealed computer. Drugs that work only when the patient knows they're being administered are placebos themselves.

Ironically, Big Pharma's attempt to dominate the central nervous system has ended up revealing how powerful the brain really is. The placebo response doesn't care if the catalyst for healing is a triumph of pharmacology, a compassionate therapist, or a syringe of salt water. All it requires is a reasonable expectation of getting better. That's potent medicine.

Contributing editor Steve Silberman (steve@stevesilberman.com) wrote about the hunt for Jim Gray in issue 15.08.