YOU, A RESEARCH SUBJECT:
Take the pill the pleasant doctor gives you // Feel better, just as you thought you would // Suffer the side effects she warned you about // Confuse trial results because your sugar pill works just as well as the genuine article.

The Placebo Problem

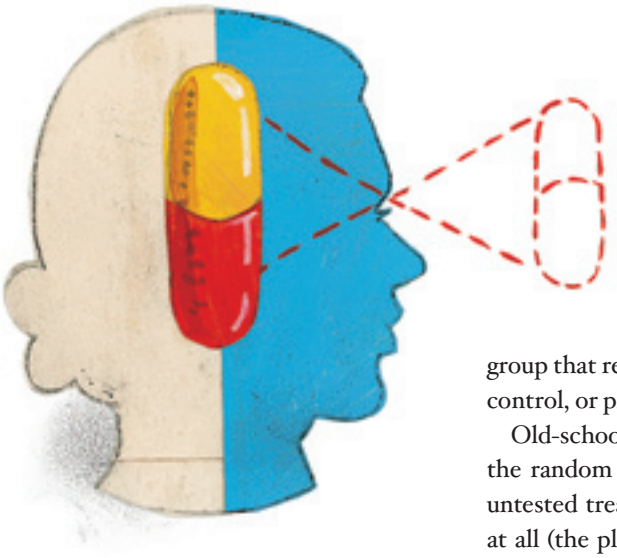
BY RACHAEL MOELLER GORMAN // ILLUSTRATIONS BY LEIGH WELLS

"People were crying," recalls Ted Kaptchuk. "They said they were drowsy all the time and wanted to cut their dosage in half. Two weeks into the study, nearly 30% of the subjects were experiencing adverse effects." Yet most patients' pain also subsided—strangely so, because no one in Kaptchuk's clinical trial had received "real" treatment.

Kaptchuk, an assistant professor of medicine at Harvard Medical School's Osher Institute, had devised the pain-relief study to compare two placebos—an inert pill and sham acupuncture—and the outcome, reported in the *British Medical Journal* in February, was remarkable: Both placebos reduced patient pain, though to differing degrees. (People who thought they were receiving acupuncture—but in fact were being "treated" with sham needles that retracted into a hollow shaft—experienced greater relief over six weeks than did those taking inactive pills.) What's more, subjects in the two groups suffered entirely different side effects, depending on what they were told during informed consent at the beginning of the trial. People receiving the sham acupuncture had been warned of the potential side effects of real acupuncture, such as redness or swelling, while subjects getting the placebo pills heard about the drowsiness and dry mouth that may bother patients taking amitriptyline, a pain medication. Those were the side effects subjects from each group reported.

These surprising results come from the latest of several recent studies that are changing the way science understands placebos. While it has long been known that taking a sugar pill may produce a measurable physiological effect, the new research reveals more about what actually goes on in the body and how variable the impact can be. The placebo effect is visible on brain scans, showing activity in areas involved in the response to pain; it disappears when a drug is given covertly, presumably because subjects don't expect any benefit. Moreover, as Kaptchuk's study shows, the magnitude of the placebo effect depends strongly on the circumstances of treatment—a new, unexpected finding. Patients taking pills at home alone responded quite differently than did those getting acupuncture in clinical settings surrounded by concerned caregivers.

Still, curious as they are, these findings might be nothing more than medical oddities if not for the huge role of the placebo group in modern medicine. Randomized double-blind placebo-controlled trials (RCTs), the biggest and best medical research studies science has to offer, sort out the effectiveness of new drugs and treatments by comparing people on real regimens with those in placebo groups (as long as patients are healthy enough to forgo treatment or no good treatment exists). Subjects randomly assigned to a placebo group go through a trial experience identical to that of those getting actual treatment, except that for the placebo group the active ingredient in a pill or the key action in a treatment has been left out.



Neither subjects nor doctors know their group assignment—hence, double-blind—and so such trials are supposed to reveal what really works and what doesn't.

Establishing causal links between treatments and clinical results is crucial, particularly in evaluating drugs being considered for U.S. Food and Drug Administration (FDA) approval. In passing judgment on new treatments—at a cost, factoring in countless failures, of about $800 million per drug—the FDA requires a series of human trials, the last and most important of which is an RCT involving hundreds or even thousands of subjects.

For decades, scientists have assumed that subjects receiving placebos formed a reliable control group, a static baseline against which a treatment's safety and efficacy could be gauged. But what if, as the latest research suggests, the placebo effect is not only powerful but also inconsistent? What if some drugs actually work through the same brain pathways as does the placebo effect? Will RCTs have to be redesigned to take this new understanding into account? And will the placebo, medical wallflower no more, have to be factored into treatment plans and drug designs? If, for example, a compassionate physician can heighten the positive effects of a placebo, doesn't that argue for paying greater attention to how care is delivered?

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Before WWII, physicians chose treatments based on expert opinion, and science largely stayed in the laboratory. But by mid-century, many doctors had begun to recognize the need to denounce quack treatments and validate new drugs. They came up with a human trial in which they compared results from a randomly assigned test group to results of a group that received sham treatment—a control, or placebo, group.

Old-school physicians denounced the random assignment of patients to untested treatments and no treatment at all (the placebo group) as unethical. In a letter to the *British Medical Journal* in 1951, one physician wrote, "Patients [are being] degraded from human beings into bricks in a column, dots in a field, or tadpoles in a pool; with the eventual elimination of the responsibility of the doctor to get the individual back to health."

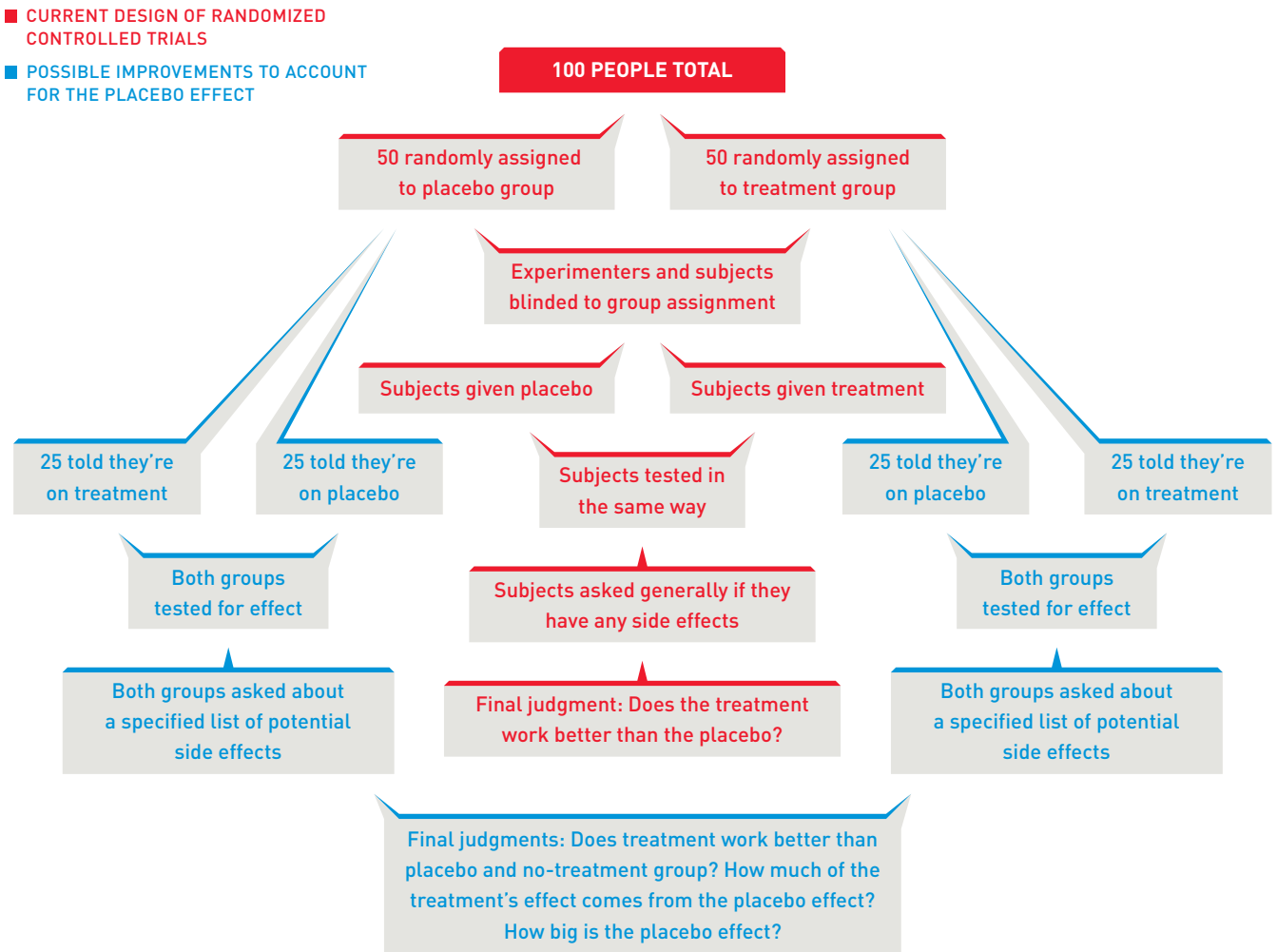
Then, in an influential paper, "The Powerful Placebo," published in the *Journal of the American Medical Association* in 1955, Henry Beecher of the Massachusetts General Hospital and Harvard Medical School swung the debate toward the modern point of view. Beecher showed that in 15 of the first RCTs, which tested treatments for a variety of diseases, a certain percentage of people in the control group actually got better. RCT proponents used this to argue that without putting half the subjects from any trial into a control group, no one would ever know whether a treatment inherently worked or whether the placebo effect—the combination of expectation, physician care and nature just taking its course—experienced by those receiving the actual treatment as well, was responsible for the improvement. Beecher believed that the effectiveness of any drug resulted in part from its active ingredients and in part from a placebo effect, and that remains the prevailing view.

With support from Beecher's persuasive arguments and the momentum of post-WWII science—in which research was venturing out of the laboratory and into the clinic—the randomized controlled trial became the gold standard. But this powerful new research tool was based on the assumption that

Building a Better Trial—But Is It Ethical?

Accounting for the varying (and newly discovered) effects of placebos could improve randomized controlled trials. But doing so may involve deceiving test subjects, which defies the Declaration of Helsinki, the World Medical Association's ethical principles governing research on humans. This creates a catch-22: Deceive subjects and you may glean lifesaving information about the drugs being tested (though at the cost of behaving unethically); tell them exactly what you're up to and you'll probably compromise the outcome of the trial, because the information alters subjects' expectations, a major part of the placebo effect.

Researchers have suggested several ways to clear both the scientific and ethical hurdles. One ethically compromised idea involves misleading half of the treatment group and half of the placebo group about whether they are receiving real treatment or placebo (see diagram). This would help determine the size of the placebo effect in both groups. Though healthy patients can be deceived (as long as they are debriefed later), sick patients cannot. Rather than lie, researchers could ask subjects at the trial's end which arm they thought they were in and analyze the data according to that belief. Studies have shown that placebo-group subjects who believe they are receiving real treatment often improve more than treatment-group subjects who think they're on placebo.



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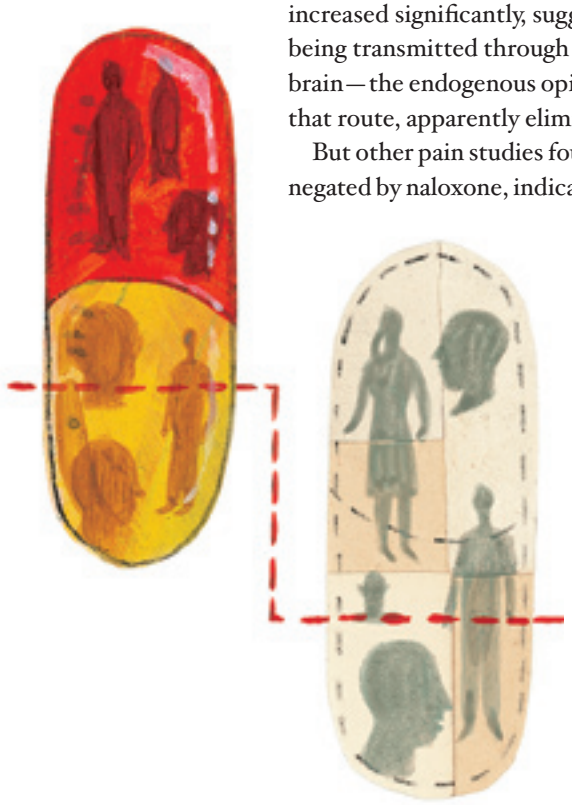
there was a static placebo baseline that varied little across trials. Now, half a century later, Kaptchuk's study and other recent work suggest there's a lot more to the story.

Modern placebo research began with the study of pain. In 1978, Jon Levine, a researcher at the University of California at San Francisco, gave a placebo painkiller to patients after dental surgery, and some felt better. To those subjects he then gave naloxone, a drug that prevents the body from sensing a class of naturally occurring painkillers known as endogenous opioids. The patients' pain increased significantly, suggesting that the placebo effect was being transmitted through a specific chemical pathway in the brain—the endogenous opioid system. Naloxone, by blocking that route, apparently eliminated the placebo effect.

But other pain studies found placebo responses that weren't negated by naloxone, indicating that the effect must also work through non-opioid brain pathways. One possible route is the body's conditioning response. Like Pavlov's dog, which salivated when a bell rang because researchers had previously paired a ringing bell with food, we may be conditioned to respond in a certain way to an expected stimulus. In studies published in the late 1990s and early 2000s, Parkinson's disease patients who took a powerful anti-Parkinsonian drug saw their motor skills improve even when the drug was replaced by a placebo. The study's authors concluded that the patients' brains had been conditioned to release dopamine, and continued to do so even when the placebo was substituted.



Other studies have delved deeper into the expectation aspect of the placebo response. In the 1980s and 1990s, researchers at the University of California at San Francisco and at the University of Torino Medical School, in Italy, studied postoperative patients hooked up to intravenous lines. Either a doctor openly injected a painkiller or a computer fed it into the line without the patient's knowledge. Remarkably, a hidden injection of morphine worked no better than an open injection of saline that the patients thought was morphine. What's more, in another study, an open injection of a painkiller called buprenorphine worked immediately, whereas a hidden one lagged by nearly two hours. In other words, much of the drug's effectiveness derived from a patient's expectation.

Brain-imaging studies have identified a sort of "expectation" pathway in the brain that might help explain some of these intriguing results. In 2004, a team led by Tor Wager, a cognitive neuroscientist at Columbia University, scanned subjects with functional magnetic resonance imaging (fMRI), which shows small changes in blood flow to precise areas of the brain, an indicator of neuronal activity. As subjects watched a computer screen, Wager flashed a cue indicating that pain would follow shortly, and a few seconds later he shocked their wrists. Next Wager rubbed placebo pain-relief cream on the wrists of some subjects, and repeated the cue and shock. On the fMRI scans, brain areas associated with pain—including the thalamus, insula and anterior cingulate cortex—lit up with the shock but then dimmed in patients rubbed with the sham cream.

Wager's study also looked at another part of the brain, the prefrontal cortex, which seems to be associated with generating expectations of pain and pain relief. That region showed

increased activity on the scans when patients expected the placebo to reduce the pain they felt. Says Wager, "We think the prefrontal cortex participates in decision-making about how much pain you should feel and how you should respond." Patients whose prefrontal cortex lit up in anticipation of pain relief also showed less activity in the pain-processing regions of the brain, and reported less pain.

Though much of the research into the placebo effect has involved pain relief, other studies have examined depression, Alzheimer's disease and immune suppression. Scientists have even found a "nocebo" effect, the side effects of taking a placebo, including the dry mouth and fatigue patients in Kaptchuk's trial experienced. In a study published this past January, Arthur Barsky, a Harvard Medical School psychiatrist, looked at the side effects experienced by the placebo group in RCTs of cholesterol-lowering statins. As many as one in four subjects (the percentage was quite variable) dropped out because of "perceived side effects." Barsky thinks this is because doctors—who don't know which patients are on the real drug and which ones are on the placebo—must tell all patients about the potential side effects of the real drug. Subjects then may be more focused on that area of the body and redefine pre-existing sensations as the suggested side effects.

Though the placebo effect is proving to be far more complex, variable and powerful than scientists had long believed, most researchers don't see fundamental flaws in the basic design of RCTs, which still provide vital information on whether a new drug works better than a placebo. Yet many also agree that the standard trial regimen needs an update to improve the information it provides, and that more placebo research (which is still in its infancy) is needed.

One improvement would expand studies to include a no-treatment arm, with subjects on a waiting list who are monitored but not treated, even with a placebo. That would provide a baseline against which the placebo effect can be measured and help sort out whether a drug works through placebo pathways. Another possibility, suggested by research into patient expectations, is to give a new drug surreptitiously, through an existing IV or disguised as something else. That, too, could help determine how much of a patient's improvement comes from a placebo. (Doctors would inform patients that they may or may not receive the drug at different points in the trial.)

Randomizing researchers so they see an equal and arbitrary set of patients is another idea. That way, an experimenter whose personality is warm and empathetic—and thus may generate a large placebo effect—is involved with the same number of patients as a more stoic experimenter. Patient expectations, too, could be manipulated. "You could tell some people they're getting the drug when they're really not, and tell others they're getting nothing though they are getting it and so on," suggests Wager. That would let researchers factor out the expectation aspect of the placebo effect, another step in determining how different elements of a trial affect the results.

If the goal in RCTs is to minimize the placebo effect to obtain more standardized data across all trials, in other areas of medicine it might pay to exploit it—for example, as a tool to help pharmacologists design more effective drugs. "We typically have a machine model for how drugs work—you take the drug and it does something to you," explains Wager. "But that's not really the case at all. Drugs interact with your expectations and beliefs in an ongoing process. You need to ask, how effective is a drug when you believe X about it?" In some cases, what a patient believes could become part of the treatment plan—say, by giving more suggestible people a lower drug dosage than that prescribed for those who are less susceptible.

Physicians might also use the placebo effect to improve care—for example, by taking advantage of research showing that a doctor's compassion may produce a measurable improvement in the patient. "Great doctors can do great things in 10 minutes," says Kaptchuk. "It's not just about good drugs." ■

DOSSIER

1. **"Sham Device v Inert Pill: Randomised Controlled Trial of Two Placebo Treatments," by Ted J. Kaptchuk et al., *British Medical Journal*, Feb. 18, 2006.** Kaptchuk's study which found that the placebo effect not only exists but also that its magnitude differs depending on the type of placebo given and that each placebo produces unique side effects.
2. **"Powerful Placebo: The Dark Side of the Randomised Controlled Trial," by Ted J. Kaptchuk, *The Lancet*, June 6, 1998.** A thought-provoking history of the placebo and its tumultuous relationship with randomized controlled trials.
3. ***Science of the Placebo: Toward an Interdisciplinary Research Agenda*, edited by Harry Guess, Arthur Kleinman, John Kusek and Linda Engel [Blackwell BMJ Books, 2002].** An exciting series of articles on the biological, cultural and ethical aspects of the placebo effect by researchers in various fields that resulted from a groundbreaking National Institutes of Health conference in 2000.