Sham Surgeries, Real Risks

As a rule, researchers believe in sham treatments. Some patients aren't so sure.

BY JOEL HAVEMANN

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Tom Intili was thrilled when he was chosen in 2007 to participate in a trial of a surgical procedure to treat Parkinson's disease. He felt it was his last chance to combat the crippling disease.

The drug company told Intili that one-third of the patients in the trial would undergo all the surgical procedures up to—but not including—the introduction of medication deep into the brain. None of the patients would know if they had received the real treatment or the sham, in order to make sure the actual treatment—instead of just the expectations of participants—was responsible for any improvements.

Intili figured his prospect of leading a normal life depended on gaining access to the medication. His chances of getting the drug were two out of three if he joined the trial, zero if he didn't. So he gave his "informed consent," which is a patient's legal authorization to undergo a medical intervention.

A year after the operation, Intili, who was 50, felt better than he had for a long time. He went with his wife and two kids from their New Jersey home to Florida's Disney World. But for the first time in 10 years, he didn't need a wheelchair. He was sure he had received the real treatment.

Then his neurologist told him he had undergone the sham surgery. When Ceregene, the sponsoring drug company, observed that the treated patients had not improved any more than the untreated patients, it pulled the plug on the trial. Left without reason to believe he was profiting from a new medication, Intili saw his condition lapse to what it had been before the trial.

THE PLACEBO EFFECT

Researchers structure clinical trials to separate the placebo effect—the tendency of patients to improve if they merely believe they are receiving good medical care—from the impact of the treatment itself. Accident victims tend to feel relief from pain, for example, when they are given a placebo—a medically inactive substance that looks like a pain pill. Some trial subjects (known as the treatment group) undergo the actual therapy; others (the control group) receive a placebo. Therapies that can't outperform the placebo are typically abandoned. Those that can do better than the placebo cross another regulatory hurdle on the way to your pharmacy shelves.

Most researchers endorse the use of sham surgical treatments. In their view, the information gained from sham surgery, by keeping ineffective treatments off the market for tomorrow's patients, is worth the risk and inconvenience to some of today's patients.

But Intili's brush with medical science exposed a raw nerve in relations between patients and researchers. From Intili's point of view, not only was he asked to undergo a dangerous procedure—he was under anesthesia for most of six hours—but the trial did not prove that the new therapy had failed. To a desperate patient, a procedure works if it arrests the disease's progress or at least relieves some of the symptoms, whatever the reason. The alternative is to watch helplessly as the disease slowly disables you.

In short, researchers want to make sure risky, ineffective treatments don't make it to market. Patients don't want effective treatments blocked or delayed by trials erroneously judged to have failed.

THE RESEARCH PERSPECTIVE

These clashing perspectives were on display June 30 and July 1 during a workshop on sham surgery sponsored by the National Institutes of Health (NIH). Two questions formed a backdrop to the conversation: Is it ethical to make patients believe they have undergone a potentially helpful operation? And how useful are the clinical results of trials based on sham surgeries?

Separating out the placebo effect can be tricky enough with pills. But brain surgery is something else. At best, sham brain surgery causes considerable discomfort and inconvenience. At worst, it can cripple or even kill.

A few of the researchers at the NIH workshop expressed misgivings about the use of sham surgery. "As a doctor, I want to amplify the placebo effect," said Christopher G. Goetz, M.D., a neurologist at Rush University in Chicago. "But I don't want to treat

people by fooling them."

Most of the researchers argued that sham surgery was necessary to separate the treatment's value from the placebo effect. "There's no scientifically valid alternative," said Don M. Gash, Ph.D., a neuroscientist at the University of Kentucky.

In clinical trials, subjects receiving the experimental treatment feel the placebo effect just as surely as does the control group. If the treatment group fares no better than the control group, researchers attribute whatever improvement there is to the placebo effect.

This, from the researchers' perspective, insulates future patients from the trauma of surgeries that don't work. In a survey of its members in 2004, the Parkinson Study Group, which represents several hundred researchers across the United States, found that 90 percent agreed that sham surgery's advantages outweighed its drawbacks.

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> —PERRY COHEN

THE PATIENT PERSPECTIVE

What made the NIH workshop extraordinary was the presence of two patients, one an outspoken patient advocate and one a veteran of a clinical trial, who formally addressed the 35 researchers.

The view of patient advocates was quite different from the researchers'. In an unscientific survey this year by the Parkinson Pipeline Project (a group of activist patients seeking a greater voice in the formulation of research policy) only one of 35 patients acknowledged a willingness to participate in a trial involving sham surgery.

Some patients are beginning to wonder if it would be better to exploit the placebo effect. Perry Cohen, founder of the Pipeline Project, an initiator of the NIH workshop, and the activist patient who addressed it, is one.

"Researchers are treating the placebo effect as an error to be eliminated," Cohen says. "I say if it helps, I will take it."

Consider the case of Peggy Willocks, a subject in one of the "failed" trials of Parkinson's surgeries. She was one of six subjects in the trial's initial phase who received surgical implantations in the brain of retinal cells from an eye bank. At her early trial stage, the drug company, Titan Pharmaceuticals, was testing whether its prospective therapy was safe for humans. All the trial volunteers got the real thing, and they knew it.

Willocks' symptoms improved considerably after the surgery, and the gains have persisted for about 10 years now. But during the next phase of trials, to check for effectiveness, a control group receiving sham surgery did just as well as a treatment group. So Titan halted the trial.

Willocks, a retired Tennessee school principal, says she doesn't care what was responsible for her improvement. "If this is the placebo effect," she says, "they ought to bottle it and sell it."

Only in the last couple of decades have researchers begun to understand how the placebo effect works. It may be in people's heads, but it's not in their imagination.

A placebo—as long as the patient thinks it may be real—causes the brain to unloose a cascade of chemicals whose makeup depends on the disease. Prominent among them in Parkinson's is dopamine, the very substance whose shortage is responsible for Parkinson's tremor, walking difficulties, and other movement problems. And the placebo effect grows with the stakes and the risks. Sham brain surgery, which is about as high-risk as it gets, produces a more prominent placebo effect than lesser-risk procedures.

The Parkinson Pipeline Project found a similar pattern in the data for each of the failed clinical trials that have reported results. After dramatic improvements over long periods of time in early tests for safety, all the trials failed after sham surgery was introduced, and the treatment groups did not do significantly better than the placebo groups.

"Patient advocates are fed up with the track record of sham failures," Cohen says. "Sham neurosurgery is an extensive and costly intervention, quite different from the usual conception of a placebo as an inert sugar pill." As a basis for comparison, he would rather use a real therapy such as the highly successful deep brain stimulation, which entails the surgical placement of electrodes in the brain.

The researchers at the sham surgery workshop agreed to prepare a list of recommended principles to guide the design and conduct of sham surgery trials. These principles include greater patient participation.

"There was a full discussion of the issues but no resolution of the differences," Cohen says. "But at least we are at the table for the first time to help researchers understand the different perspective of patients. I hope we are invited back."

As for Intili, he was asked by Ceregene to be in the safety stage of its revamped trial, which included a second target in the brain. He would be guaranteed to get the real treatment. Intili accepted and, on the eve of his 6 a.m. date with a New York surgeon, was staying in Manhattan hotel near the hospital.

But Intili couldn't sleep, because he was still conflicted about whether to go ahead. After four hours of lying awake in the bathtub to relax, he made up his mind. At 5:55 a.m., five minutes before his operation was to begin, he phoned his neurologist and said thanks but no thanks. Because he didn't want to risk putting his family through another cycle of disappointment, he was dropping out. NN