Understanding Parkinson's

The Placebo Effect & Research

To find out if a potential new treatment for Parkinson's disease (PD) is effective, it is necessary to test it in people, through clinical trials. It is through clinical trials that scientists investigate the effects of a treatment in people particularly its safety and efficacy. The advances we have made in understanding PD, and the medications that you may be taking, are available only because people before you volunteered to participate in clinical trials. In later stages of trials, researchers usually use a methodology known as the "double blind" trial. In this type of a trial, the experience of a group of participants who are taking the treatment is compared with that of a group of participants who are taking an inactive substance called a "placebo" — typically, a sugar pill. Participants go into the trial knowing that they will receive either the active treatment or a placebo. But neither the participants nor the researchers know who is taking the real treatment and who is taking the placebo.

Researchers use placebos and blinded trials to understand the true effectiveness of a new treatment. The placebo group is a "baseline" against which the treatment group can be measured. Theoretically, those participants who receive the placebo will not see any change in their symptoms. But in nearly every Parkinson's clinical trial, some people who take the placebo report that it eases their symptoms. We call this the placebo effect.

What causes the placebo effect? One cause may be a person's expectations. Trial participants typically receive more medical attention than usual, including frequent visits to the clinic. Studies have found that this may lead the participant to expect his or her symptoms to improve. This, partnered with the hope that the treatment will work, feeds the placebo effect. The placebo effect can be a wonderful thing because we want our patients to feel better. But in a clinical trial, it can confuse our results.

The Science Behind the Placebo Effect

The placebo effect is not a figment of the participant's imagination. There are biochemical changes occurring in the brain. We think the placebo effect may be so prominent in Parkinson's trials because of the neurotransmitter called dopamine — the same one that is reduced or lost in PD. Dopamine also underlies the placebo effect. When a person is motivated to participate in a trial and anticipates a reward — for example, the easing of symptoms — these all boost dopamine activation in the brain.

Studies have investigated how dopamine is involved in the placebo effect in Parkinson's. In one of these, people with PD were treated with a placebo and then given brain scans measuring dopamine activation in the striatum (the brain area that exhibits reduced levels of dopamine in Parkinson's). Some of the people in the study, as measured by the Unified Parkinson's Disease Rating Scale, experienced an improvement in their Parkinson's symptoms. The brain scans showed that in these people, dopamine activation in the brain was markedly higher than in those whose symptoms did not improve while on the placebo.

The Placebo Effect and PD Clinical Trials

In nearly every trial, some people who take a placebo will report that their symptoms have improved. And that means that the treatment being tested has to be not just better than before enrollment in the study, but also better than the placebo in order for its effects to be considered significant. The placebo effect "raises the bar" for a new treatment to be declared effective. Because of this, my own research team at Rush University Medical Center undertook a study to understand how the placebo effect impacts Parkinson's trials.

We looked at data from placebo groups of 11 published trials, comprising a total of 858 participants, exhibiting a wide range of PD severity with a variety of treatments. We defined placebo response as an improvement of 50 percent on the UPDRS. This means "placebo responders" had a

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reduction by half in disability simply by being involved in a clinical trial.

We found that 16 percent of people in placebo groups experienced improvement in Parkinson's symptoms. The improvement was markedly greater for surgical trials, in which 42 percent of the study participants receiving placebo experienced improvement in symptoms, than for drug trials, in which the rate of placebo response ranged from zero to 27 percent.

We also tested a common assumption that the placebo effect is strongest at the beginning of a study, and wears off. But we found no differences in placebo response rates at various stages of the studies. So we cannot filter out the placebo effect by ignoring data collected during a "placebo period."

The Investigator's Dilemma

The "gold standard" in establishing whether a new treatment works is whether it has a significant effect as compared to the placebo. When a clinical trial fails, one explanation is that the new treatment does not work. The other explanation is that the treatment does work, but that the evidence is overshadowed by the placebo effect. Our inability to "factor out" the placebo effect makes it difficult for treatments that have small, but important impacts on PD symptoms to succeed.

On the one hand, we can say that these studies should fail, because we're interested in treatments that can dramatically improve life for people with PD. But for many people, even a modest improvement may be seen as a welcome result. Besides which, in clinical trials that show a placebo effect, evidence that a treatment will have a significant impact would require the enrollment of hundreds of participants. This means asking people to volunteer just to overcome the placebo effect, not to get the data evaluating the true impact of the treatment. The time and money required for this will often be prohibitive.

Future Directions

Researchers are investigating ways to account for the placebo effect. One approach would be to identify people who respond to placebos, the "placebo responders," and screen them out of the trial. Then, the number of participants could be kept to a minimum. But, it may be that the same people who will respond to placebos have a very active dopamine system that would respond to treatments with small effects.

Many people ask, why not calculate the typical magnitude of the placebo effect and subtract it from our data to determine the "true" effect of the new treatment? For example, if we can say that on average, 16 percent of response is from the placebo effect, then anything more could be attributed to the treatment. The trouble with this idea is that the placebo response seems to be different in every trial, so we can't construct a reliable formula that fits all of them.

Another approach would be to design trials with three groups: those who receive active treatment, those who take a placebo and those who receive no treatment. Then we could compare the response of the people receiving the placebo to those receiving no treatment at all. But in this scenario, two thirds of participants would not receive the active treatment, meaning there is an even higher likelihood than in current trials, of a participant receiving no treatment. The difficulty would be in finding hundreds of people who are willing to go through the process to find that they are not receiving any treatment at all.

There is one other approach, used in some countries but not, for ethical reasons, in the United States. It is where participants are not informed that they could be receiving a placebo. To me, this breaches trust between doctor and patient, or investigator and study subject. But we will monitor the outcomes.

Harnessing Expectations

Researchers are working to understand how the placebo effect changes the brain, and how it affects the results of clinical trials. If we can characterize it more precisely, then perhaps we can turn it to our advantage to help people with Parkinson's feel better, and evaluate therapies more accurately.

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Adapted from the PDF News & Review, *Spring 2007*