

# Patients' DNA May Explain How Placebo Effect Occurs, Study Finds

Meg Tirrell Oct 24, 2012 12:01 am ET

Oct. 24 (Bloomberg) -- A patient's genetic makeup may explain the "placebo effect," in which people perceive that a fake treatment makes them feel better, according to a study that may help researchers design better clinical trials.

Patients with a certain variation on a gene linked to release of dopamine, a brain chemical that affects emotions and sensations of pleasure and pain, were more likely to respond to a placebo version of acupuncture than patients with a different variation, a study in the journal PLoS One found.

The findings may be useful for designing clinical trials, understanding why a placebo effect exists or trying to control it, researchers said. A stronger than expected response to placebo can make even a potentially effective drug appear to work less well, said Ted Kaptchuk, associate professor of medicine at Harvard Medical School and an author of the study.

"A clinical trial has one purpose: to show a difference in drug and placebo," Kaptchuk, who is also director of the Program in Placebo Studies & the Therapeutic Encounter at Beth Israel Deaconess Medical Center in Boston, said in a telephone interview. "If the placebo effect is very big, that makes things very difficult. It's the Holy Grail in drug development - - how we can predict and control placebo response is critical. This may be an opening to that question."

The research released yesterday, funded by the National Institutes of Health, was done in patients with irritable bowel syndrome who enrolled in an acupuncture trial that evaluated their self-reported change in areas like abdominal pain over three weeks.

## Trial Design

The patients were separated into three groups: one that received no treatment, called the "wait list" group; one that received fake acupuncture with little interaction with the caregiver, called the "limited" group; and one that received fake acupuncture with an enhanced interaction with the provider, called the "augmented" group.

The “validated sham acupuncture,” as the study called it, was done similarly to real acupuncture, except the needles were placed over non-acupuncture points, Kaptchuk said. Patients were able to receive real acupuncture after the three weeks of the placebo study, he said.

A genetic analysis based on blood samples separated patients by variations on the COMT gene, or catechol-O- methyltransferase, known to be related to dopamine release. The researchers focused on COMT variations because the gene had been shown in earlier studies to have a potential association to treatment response.

### Gene Variations

Patients with a variation referred to as met/met, for their two copies of the methionine allele, were shown to be more likely to respond to the placebo treatments, the study found. Those with a variation called val/val, for two copies of the valine allele, responded the least. Patients with one copy of each fell in the middle.

The study was unique in that it included a “wait list” arm, in which patients didn’t receive placebo or treatment. That enabled researchers to compare the two placebo groups with a non-treatment group.

The patients who saw the most improvement, those in the met/met group, responded more when they received care in the “augmented” placebo arm, reinforcing the importance of doctor- patient interaction, the authors wrote. They didn’t respond more than other patients in the “wait list” group, indicating met/met “is a predictor of the placebo effect, not just improvement in general,” the researchers wrote.

### Brain Chemical

Their response is thought to be tied to the availability of dopamine in their prefrontal cortex. Dopamine has been linked to reward and “confirmation bias,” or the adherence to a first impression, Kaptchuk said.

“People with met/met look for evidence to confirm their first impression or intuition that something will work versus people with val/val, who if the evidence switches they’ll switch more easily,” he said. As met/met people start getting better, “they start seeing more ways of getting better.”

If the results are replicated in future studies, they may enable designers of clinical trials to screen patients' genotypes and use that data to minimize placebo effects, said Kathryn Hall, the study's lead author and a fellow in integrative medicine at Beth Israel Deaconess.

The implications are most applicable to studies in which patients report their pain, fatigue, nausea, anxiety or depression, Kaptchuk said. Outcomes such as tumor shrinkage among patients on placebo aren't as well understood, Hall said.

The study's findings are likely to ignite research within existing databases of clinical trial results that showed strong placebo responses, Hall said.

"It's really interesting to now think that there's this potentially fundamental difference between people," Hall said in a telephone interview. "And it involves not just the placebo or the physical pill, but also involves this interaction that you have with your caregiver. It's really important to think about the ways in which we're similar and different, and design or develop medicines that are going to help us all heal."

--Editors: Angela Zimm, Andrew Pollack