

The Nocebo Effect: Placebo's Evil Twin

By Brian Reid

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Ten years ago, researchers stumbled onto a striking finding: Women who believed that they were prone to heart disease were nearly four times as likely to die as women with similar risk factors who didn't hold such fatalistic views.

The higher risk of death, in other words, had nothing to do with the usual heart disease culprits -- age, blood pressure, cholesterol, weight. Instead, it tracked closely with belief. Think sick, be sick.

That study is a classic in the annals of research on the "nocebo" phenomenon, the evil twin of the placebo effect. While the placebo effect refers to health benefits produced by a treatment that should have no effect, patients experiencing the nocebo effect experience the opposite. They presume the worst, health-wise, and that's just what they get.

"They're convinced that something is going to go wrong, and it's a self-fulfilling prophecy," said Arthur Barsky, a psychiatrist at Boston's Brigham and Women's Hospital who published an article earlier this year in the *Journal of the American Medical Association* beseeching his peers to pay closer attention to the nocebo effect. "From a clinical point of view, this is by no means peripheral or irrelevant."

Barsky's target is drug side effects, which cost the U.S. health system more than \$76 billion a year, according to a 1995 University of Arizona study. If even a small percentage of those costs are caused by patient expectations of harm, addressing the nocebo effect could save a nifty sum.

But convincing doctors that their patients' problems may be more than biochemical is no simple trick. The nocebo effect is difficult to study, and medical training leads doctors to seek a bodily cause for physical ills.

"Nocebos often cause a physical effect, but it's not a physically *produced* effect," said Irving Kirsch, a psychologist at the University of Connecticut in Storrs who studies the ways that expectations influence what people experience. "What's the cause? In many cases it's an unanswered question."

Looking for Trouble

The word nocebo, Latin for "I will harm," doesn't represent a new idea -- just one that hasn't caught on widely among clinicians and scientists. More than four decades after researchers coined the term, only a few medical journal articles mention it. Outside the medical community, being "scared to death" or "worried sick" are expressions that have long been part of the popular lexicon, noted epidemiologist Robert Hahn from the Centers for Disease Control and Prevention in Atlanta.

Is such language just hyperbole? Not to those who accept, for example, the idea of voodoo death -- a hex so powerful that the victim of the curse dies of fright. While many in the scientific community may regard voodoo with skepticism, the idea that gut reactions may have biological consequences can't be simply dismissed.

"Surgeons are wary of people who are convinced that they will die," said Herbert Benson, a Harvard professor and the president Mind/Body Medical Institute in Boston. "There are examples of studies done on people undergoing surgery who almost want to die to re-contact a loved one. Close to 100 percent of people under those circumstances die."

But the placebo effect can lead to more subtle outcomes as well.

Fifteen years ago, researchers at three medical centers undertook a study of aspirin and another blood thinner in heart patients and came up with an unexpected result that said little about the heart and much about the brain. At two locations, patients were warned of possible gastrointestinal problems, one of the most common side effects of repeated use of aspirin. At the other location, patients received no such caution.

When researchers reviewed the data, they found a striking result: Those warned about the gastrointestinal problems were almost three times as likely to have the side effect. Though the evidence of actual stomach damage such as ulcers was the same for all three groups, those with the most information about the prospect of minor problems were the most likely to experience the pain.

Despite the smattering of doctors' anecdotal reports and a few modest clinical studies, research on the phenomenon has not been robust, mostly for ethical reasons: Doctors ought not to induce illness in patients who are not sick.

Changing ethical standards have made it difficult to even repeat some of the classic placebo experiments. In one century-old effort, conducted long before anyone thought up the word placebo, doctors set an allergy sufferer wheezing by showing an artificial rose, proving that at least some aspect of the allergic response is stimulated by visual cues. In a study from the early 1980s, 34 college students were told an electric current would be passed through their heads, and the researchers warned that the experience could cause a headache. Though not a single volt of current was used, more than two-thirds of the students reported headaches.

Medical Distrust

But resistance to in-depth study of the placebo effect rests on more than ethical reservations, said the CDC's Hahn. Belief, he said, does not have a strong place in the anatomy-centered world of modern medicine.

"The fact is that phenomena that essentially come down to what people believe are conceptually difficult in our medical system," Hahn said. "Health is thought to be a biological phenomenon. More psychosomatic elements are hard to deal with."

Science is wearing away at the wall between mind and body. With the aid of high-tech imaging devices, neurologists are getting better at taking pictures of the brain in action. In one blinded study last year, researchers found that patients with Parkinson's disease given a placebo released a brain chemical called dopamine, just as the brain exposed to an active drug would do.

That flood of brain chemicals, it appears, has everything to do with what the mind expects. In most cases, like the Parkinson's study, the outcome is positive -- the placebo effect in action. But for some patients -- depressed, wary of medication or worried about drug side effects -- getting a prescription filled is an angst-ridden experience. And such patients appear even more likely to exhibit those side effects.

Barsky has even sketched out a profile of the kind of patient likely to experience the nocebo effect -- worse side effects and poorer outcomes -- on a given drug. When Barsky sees a patient with a history of vague, difficult-to-diagnose complaints who is sure that whatever therapy is prescribed will do little to battle the problem, he says, those low expectations are inevitably met. The treatments usually fail.

"Whether you trust your doctor or not probably makes a huge difference in whether you report side effects, but there's almost no data on that," Barsky said. He hopes to include information about a person's psychology in an upcoming placebo-controlled clinical trial to see if patients with a particular outlook on life fare better or worse than other subjects.

Far more esoteric factors may also shape both the placebo and nocebo response. A Dutch study, for example, found that most people considered red and orange pills to be stimulating, with blue and green-colored pills more likely to have a depressant effect.

"One of the most important things about a pill is [its] color," said Daniel Moerman, an anthropologist at the University of Michigan-Dearborn who has studied the placebo and nocebo effects across different cultures. "That seems to be fairly widespread."

But the mind is a funny thing, and generic responses to color go just so far in explaining the placebo or nocebo response. Consider this: In Italy, Moerman says, blue placebos made excellent sleeping pills for women but had the opposite effect on men.

The apparent reason? "The Italian national football team's color is azzurri," he said. "Blue."

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