Worried Sick

Expectations can make you ill. Fear can make you fragile. Understanding the nocebo effect may help prevent this painful phenomenon.

By Megan Scudellari | July 1, 2013

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Something strange was happening in New Zealand. In the fall of 2007, pharmacies across the country had begun dispensing a new formulation of Eltroxin—the only thyroid hormone replacement drug approved and paid for by the government and used by tens of thousands of New Zealanders since 1973. Within months, reports of side effects began trickling in to the government's health-care monitoring agency. These included known side effects of the drug, such as lethargy, joint pain, and depression, as well as symptoms not normally associated with the drug or disease, including eye pain, itching, and nausea. Then, the following summer, the floodgates opened: in the 18 months following the release of the new tablets, the rate of Eltroxin adverse event reporting rose nearly 2,000-fold.[1]

The strange thing was, the active ingredient in the drug, thyroxine, was exactly the same. Laboratory testing proved that the new formulation was bioequivalent to the old one. The only change was that the drugmaker, GlaxoSmithKline, had moved its manufacturing process from Canada to Germany, and in the process altered the drug's inert qualities, including the tablets' size, color, and markings.

So why were people getting sick? In June, it turned out, newspapers and TV stations around the country had begun to directly attribute the reported adverse effects to the changes in the drug. Following widespread coverage of the issue, more and more patients reported adverse events to the government. And the areas of the country with the most intense media coverage had the highest rates of reported ill effects, suggesting that perhaps a little social persuasion was at play.

But Eltroxin takers were not making up their symptoms. The feelings were real, but in the vast majority of cases they could not be attributed to the drug's pharmacological properties. The patients were victims of the nocebo effect.

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dastardly sibling of placebo ("I shall please"). In a placebo response, a sham medication or procedure has a beneficial health effect as a result of a patient's expectation. Sugar pills, for example, can powerfully improve depression when the patient believes them to be antidepressants. But, researchers are learning, the reverse phenomenon is also common: negative expectations can actually cause harm.

When Parkinson's patients undergoing deep brain stimulation were told that their brain pacemaker was going to be turned off, symptoms of their illness became more pronounced, even when the pacemaker was left on.[2] When people with and without lactose intolerance were asked to ingest lactose, but were actually given glucose, 44 percent of those with lactose intolerance and 26 percent of those without it still complained of stomach pain.[3] And men treated for an enlarged prostate with a commonly prescribed drug and told that the drug "may cause erectile dysfunction, decreased libido, [and] problems of ejaculation," but that these effects were "uncommon," were more than twice as likely to experience impotence as those who were not so informed.[4]

On paper, it sounds like psychobabble—a negative effect caused by a sham treatment based on a patient's expectations—but it is a real biochemical and physiological process, involving pain and stress pathways in the brain. And mounting evidence suggests that the nocebo effect is having a substantial negative impact on clinical research, medicine, and health.

"Nocebo is at least as important as the placebo effect and may be more widespread," says Ted Kaptchuk, director of Harvard's Program in Placebo Studies at Beth Israel Deaconess Medical Center in Boston, Massachusetts.

Now that this pernicious phenomenon is starting to receive the recognition it deserves, the question is: What exactly can be done about it?

Evil eects

In 1997, Fabrizio Benedetti, a neurophysiologist at the University of Turin Medical School in Italy, was busy mapping the biochemical pathways involved in placebo responses when he performed a simple study that revealed a distinct neural mechanism driving the body's nocebo response. He gave consenting postoperative patients reporting mild pain an injection that they were told would increase their pain within 30 minutes. The injection was either saline solution or proglumide, which blocks a hormone implicated in pain hypersensitivity and associated with anxiety. Neither substance actually causes any discomfort.

When saline was injected, patients experienced increased pain. When proglumide was injected, they had no pain increase—the nocebo effect was absent.[5] In one fell swoop, Benedetti identified a biochemical reaction responsible for the nocebo response, and he showed that it could be blocked.

It was Benedetti's work that finally convinced physician-bioethicist Howard Brody that the nocebo effect—allegedly first mentioned in the scientific literature in 1961 by physician Walter Kennedy, who called the phenomenon a "quality inherent in the patient rather than in the remedy"—was real.

ALLERGIC TO NOCEBO

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According to several recent studies, pain and itch appear to be especially susceptible to verbal suggestion. Recently, researchers in the Netherlands demonstrated that people who are told that a stimulus will cause itch feel the itch more intensely than those told that the stimulus is unlikely to cause itch. The finding could have implications for chronic itch conditions, says first author Antoinette van Laarhoven of Radboud University Nijmegen Medical Center. "More knowledge about nocebo effects on itch can give us some targets to reduce [those effects]."

Also last year, in a curious study of nocebo and rectal pain, a team at University Hospital Essen in Germany managed to recruit healthy volunteers to undergo multiple rectal balloon distensions, a procedure in which a balloon is inserted into the rectum and slowly inflated—in this case, until the moment it becomes painful. The procedures were exactly the same in control and nocebo groups, but there was a 20 percent increase in pain ratings among patients who had been told that doctors had observed an increase in pain sensitivity in response to repeated distensions. Those individuals who experienced more pain also had elevated levels of cortisol, again linking nocebo to anxiety. "We could show that a nocebo effect may be induced

"For many years, I dismissed the value of the term 'nocebo,' " says Brody, chair of family medicine and director of the Institute for the Medical Humanities at the University of Texas Medical Branch in Galveston, who first began studying the placebo effect in the 1970s. He and others had long assumed that nocebo and placebo were two sides of one coin, that the same process in the brain supported both illusory effects—one was just manifested as a positive outcome, while the other caused harm. But after reading Benedetti's work, Brody changed his tune: "I received my comeuppance," he laughs.

With that first biochemical evidence, others also began recognizing the importance of nocebo, and a few inquiring minds began to study it. Nevertheless, compared to placebo, the nocebo effect remains vastly understudied: a PubMed database search will turn up more than 163,000 publications on "placebo" and fewer than 200 on "nocebo." Of those, only a few dozen are empirical studies; most are reviews. "The placebo phenomenon has a tremendous fascination for the public—a gee-whiz thing with a positive spin, a way to be healthy without taking drugs," says Frank Miller, a bioethicist at the National Institutes of Health. "But nobody is very enthusiastic about the nocebo phenomenon."

In addition, the nocebo effect has become notoriously difficult to study. Few institutional review boards will allow scientists to induce pain in their subjects, and some even refuse to let researchers mislead their volunteers. "My ethics committee will not allow me to do it," says Paul Enck, a psychologist at the University of Tübingen in Germany, "unless I tell the subjects that I am deceiving them"—a requirement that obviously defeats the purpose of the deception. "It makes life really miserable as a [nocebo] researcher," says Enck.

The tragedy of this lack of investigation, researchers assert, is that controlled trials about the nocebo effect are needed to further understand and prevent nocebo's insidious effects on medicine and research. "In clinical drug trials, the placebo effect—and now we know the nocebo effect—can be really, really large," says Manfred Schedlowski, a clinical researcher at the University Hospital Essen in Germany. "This hinders the development of new drugs."

In December 2012, for example, a meta-analysis revealed the shockingly large impact of the nocebo effect in clinical trials: in 18 fibromyalgia drug studies, 11 percent of 3,546 patients in the placebo arm—meaning they were receiving a completely inert substance—dropped out of the study because of side effects including dizziness and nausea.[6] Other studies have calculated that nocebo effects cause between 4 and 26 percent of patients taking placebo to leave a clinical trial because of side effects from an inert treatment.

The nocebo effect may also have a worrisome effect on vaccine use. In 2011, researchers at the French vaccine manufacturer Sanofi Pasteur analyzed 33,275 vaccine side-effect reports and found that doctors and patients preferentially report disease-specific side effects, such as measles-like rash following measles immunization, even when the vaccine contains only proteins, sugars, or killed organisms that won't cause symptoms of the disease. The nocebo effect has "great potential" to exacerbate rumors and fears, and to cause a vaccine crisis similar to the Eltroxin events in New Zealand, the authors write.[7]

But the most common place where the nocebo effect makes an appearance is in everyday visits to clinics and hospitals. "In places like primary care, people are swimming in placebo and nocebo effects," says Kaptchuk.

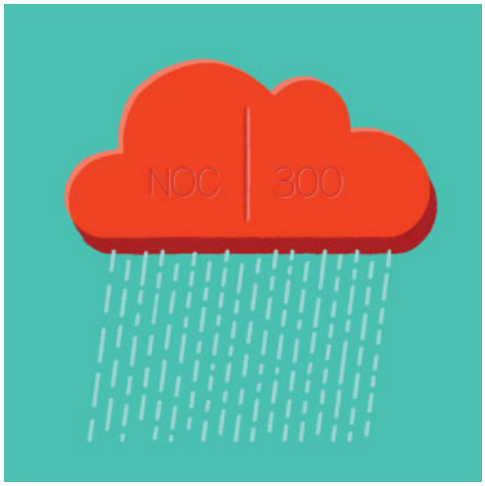
Thomas D'Amico, chief of thoracic surgery at Duke University Medical Center in Durham, North Carolina, says that even before he heard the term nocebo effect, he was aware of it in the clinic. "I've listened to some well-respected colleagues give information [to a patient], and I thought, 'Gosh, I know the operation and even I wouldn't want it,'" he says. "There's too much detail and too much emphasis about things that could go wrong." Measuring the effect of such detail on an individual patient is hard to quantify, he says, but fear and distress before an operation has been associated with slow postoperative recovery and delayed wound healing.

Another area of health that researchers suspect may be affected by nocebo is the increased incidence of asthma and allergies. "It's certainly possible," says Manfred Schedlowski, who studies placebo and the immune system at University Hospital Essen. "From experimental data, we know an allergic reaction can be conditioned."

In an oft-cited case from 1886, John Mackenzie, a surgeon in Baltimore, described how he'd "obtained an artificial rose of such exquisite workmanship that it presented a perfect counterfeit of the original," then exposed a woman with severe rose allergy to the fake flower. The woman, not knowing it was fake, had a full-blown allergic reaction, including a running nose, swollen nostrils, and a tight chest.12 Similarly, people allergic to dogs may begin sneezing when they simply see a dog across the way. Researchers have even shown that guinea pigs can be conditioned to release histamine, causing a local immune response, when presented with just an odor stimulus.

But the link between nocebo and allergy is far from concrete. "We're in such a primitive state of understanding this phenomenon, particularly in a clinically oriented way, that we just need to do more research," says bioethicist Frank Miller of the National Institutes of Health.

Nuts and bolts



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Despite the disproportionate amount of effort put into placebo research, since Benedetti's 1997 discovery there's been an uptick in the funding and time devoted to investigating the mechanisms behind nocebo, with impressive results. "Without a doubt, there's been a level of research and a sophistication of research that has made a quantum jump in the last decade or so," says Brody.

In 2007, for example, Benedetti discovered that the hypothalamic-pituitary-adrenal axis in the brain, an important part of the body's "stress system," is activated during a nocebo response, as detected by an increase in the secretion of the hormones ACTH, from the pituitary gland, and cortisol, from the adrenal gland, both markers of anxiety.[8]

Then, in 2008, Kaptchuk and colleagues at Harvard performed the first brain-imaging study of the nocebo effect. After conditioning healthy volunteers to expect pain on their right forearm, they watched as the hippocampus lit up when people experienced pain from a sham acupuncture device.

Through Benedetti's and Kaptchuk's work, it is now clear that a person's expectation of pain can induce anticipatory anxiety, triggering the activation of cholecystokinin, the hormone that Benedetti blocked with proglumide. Cholecystokinin-mediated pathways in turn facilitate pain transmission, which occurs in specific areas of the brain. The finding does not coincide with what is know about the biochemistry of the placebo effect—which seems to be at least partly regulated by opioid release—suggesting the two phenomena have distinct mechanisms.

"Even if placebo and nocebo are on a continuum of expectation, different mechanisms kick in at different points along that continuum," says Tor Wager, director of the Cognitive and Affective Control Laboratory at the University of Colorado, Boulder, who studies the brain pathways underlying pain.

Last year, Kaptchuk and colleagues added a surprising twist when they discovered nocebo can occur without conscious awareness. His team applied either high or low heat pain to the arms of 20 volunteers while showing them an image of one of two faces. The researchers then showed the volunteers the faces again, but with identical, moderate heat applied to their arms each time and the faces displayed at a much faster pace, preventing conscious recognition. When exposed to the faces associated with high pain levels, even without conscious awareness, the volunteers felt more pain.[9] "It was a really risky experiment," says Kaptchuk. "We were really surprised. We couldn't believe it, actually."

The biochemical and physiological discoveries about nocebo have made the phenomenon more credible in the medical community. "These brain measures provide objective evidence on the physical system implementing these squishy, fuzzy changes in emotion and expectation," says Wager.

Most nocebo research to date, however, focuses on basic mechanisms, not on how to deal with the phenomenon in the clinic. "Translational research has been a stepchild in scientific investigations of this phenomenon," says Miller. Understanding the mechanism is important, but at the end of the day, he says, the medical community needs a solution to the problem.

Controlling for nocebo

In 1987, a team of doctors in Ontario, Canada, suspected that medical consent forms might actually cause harm. Using the chance occurrence of two different consent forms being used for the same drug trial, they compared patient reactions to the wording of the forms. The trial pitted aspirin against sulfinpyrazone, a medicine already approved to treat gout, as a treatment for chest pain. Patients at two of the three centers hosting the trial were informed that "side effects are not anticipated beyond occasional gastrointestinal irritation and, rarely, skin rash." At the third center, patients' consent forms did not mention gastrointestinal effects. Seventy-six patients out of 399 (19 percent) given the first consent form that mentioned GI irritation withdrew from the study, citing GI issues, compared to just 5 out of 156 (3 percent) who received the second form.[10]

With the nocebo effect, doctors are caught between a rock and a hard place: their medical duty to primum non nocere, "First, do no harm," and the ethical and regulatory obligation of informed consent. What do you do when informed consent leads to harm?

Last year, Kaptchuk and colleague Rebecca Wells, also at Harvard Medical School, sparked a debate on this topic in the pages of the *American Journal of Bioethics*. They proposed a middle ground called contextualized informed consent. Doctors, they suggested, might choose not to tell patients every last

side effect of a treatment in great detail, but instead provide information to a patient tailored to his or her level of anxiety, such as leaving out nonspecific side effects—those that are not a direct result of the pharmacological action of the drug—including headache, nausea, and fatigue.

But the idea of not informing patients of all possible side effects is anathema to some ethicists. "I certainly don't think that we should be rethinking whether informed consent should be a basic norm in clinical practice," says Miller. Such a practice could promote mistrust in the health-care system and defeat recent efforts towards increased transparency. It may not be possible to have valid informed consent with no chance of the nocebo phenomenon, Miller admits, but he proposes two alterative techniques.

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>
> — Ted Kaptchuk, Program in Placebo Studies, Beth Israel Deaconess Medical Center, Harvard University

One is to frame information about treatments positively rather than negatively. A 1996 study from the University of Ottawa in Canada, for example, described the benefits and risks of a vaccine to 292 people, who had never been previously immunized, using two different approaches. Those who were told the percentages of vaccinated individuals who remain free of influenza and have no side effects had fewer side effects and missed less work than those told the percentages of people who acquire influenza and have side effects following vaccination.[11] "Since you're conveying the exact same information, why not just use positive framing?" says Miller.

Miller's second proposed technique is authorized concealment, in which a patient agrees to give up their right to informed consent—specifically, opting not to receive information on mild or transient side effects—in the hopes of avoiding a nocebo response. Yet with the increased access to information available online, such concealment might not be realistic or safe. "Based on my clinical experience, many patients go to the Internet or get their information from other people. The doctor is not gatekeeper," says Gerben Meynen, a philosopher at VU University Amsterdam and a psychiatrist who treats anxiety disorders. "Many patients just wait until they get a prescription, then they Google the name of the medication." And if a patient finds negative information online, he might simply stop taking the medication without informing his physicians, Meynen notes.

But unfortunately, while ethicists continue to debate how to balance the painful effects of nocebo with informed consent, "there's no engaging discussion of it in the medical community," says Kaptchuk.

"Most doctors don't know what nocebo means," agrees Y. M. Barilan, a practicing physician and associate professor of medical education at Tel Aviv University in Israel. That's not to say that they don't recognize the phenomenon. "They all know that the way you talk to a patient has enormous influence on side effects, mood, and state of mind," Barilan notes—but without guidelines on how to deal with the problem or even to recognize it, the nocebo effect remains a specter of illness haunting our health-care system.

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translational science, statistics, placebo, nocebo, disease/medicine and clinical trials

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Curtis R
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July 22, 2013

Loved the article! Thanks for calling attention to such an understudied (but very important) area of medical research. Too bad there isn't a more ethical way to induce the nocebo effect in humans.

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Peter Olins, PhD
Posts: 1

July 27, 2013

Excellent article!

The hundreds of fear-mongering websites and authors of health "news" items can no longer claim that they are merely entertaining or informing. We may have reached to point where these are actually have a net negative effect on our collective health.

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Lukas
Posts: 1

August 2, 2013

Interesting article.

I've had M.E. for 20 years or so, and for around the first 2 years took various vitamin and mineral supplements with no problems (or indeed positive effects either to my knowledge). I then caught a virus and shortly after I noticed I was reacting adversely to the supplements I was taking. I didn't realise at first, it took a few weeks of building agonising pain all over my body before I thought I'd stop taking them all just to check, to great relief.

Ever since then I've reacted to any and all medication or supplements, in various forms. I tried my fair share of alternative medicine as you do when you're desperate, nothing ever helped and I reacted to anything I ingested, even intravenous nutrition. I can get away with a few low dose painkillers and nothing else.

I no longer believe in most complementary medicine or therapies other than their placebo effects.

I tried some homeopathy tablets recently for the first time in years, just to appease a keen doctor. After a few days I was experiencing the usual pain all over my body that I always have in the past. I no longer believe in homeopathy though, so does this indicate a possible nocebo effect. If so, where to take it from here?

It's common for folks with M.E. to react adversely to medications and there are a few of us that seem to react to everything. One wonders how much of that, if any, may be a conditioned response?

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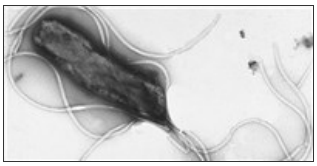

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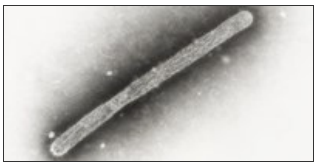

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By Abby Olena

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