The nocebo response

The pill may be inactive, but the side effects are real.

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About 20% of patients taking a sugar pill in controlled clinical trials of a drug spontaneously report uncomfortable side effects — an even higher percentage if they are asked. These effects are one kind of nocebo — a word that means in Latin "I will harm," as placebo means "I will please."

A placebo makes patients feel better for reasons unrelated to the specific healing properties of the treatment. A nocebo makes patients feel worse (or does other harm) in the same way. Common symptoms are drowsiness, headache, mild dizziness, difficulty concentrating, and stomach upset. Many health professionals are not aware of nocebos, yet the reaction can cause patients to drop out of clinical trials, stop taking drugs they need, or end up using other drugs that complicate their treatment.

The nocebo effect can result from conditioning, as when patients become nauseated or even vomit on entering a room where they have recently received chemotherapy. Medications and other treatments take on symbolic features that can have nocebo effects. Red is associated with stimulation, blue with sedation, so red and blue pills may produce those responses as unwanted side effects. Contagious rumor is another source of nocebo responses. Many people who have heard about penicillin allergies, wrongly think that they are allergic to penicillin, and report reactions.

Experiments show the potential of explicit suggestion in medical treatment for good or ill.

- Volunteers were told that a mild electrical current would be passed through their heads and might cause a headache. No electrical current was actually passed, but two-thirds of them developed a headache.
- Patients with asthma were divided into two groups. One was given a bronchoconstrictor, which ordinarily makes asthma symptoms worse, and told that it was a bronchodilator, which normally improves the symptoms. This placebo suggestion reduced their discomfort by nearly 50%. The second group was given a bronchodilator and told it was a bronchoconstrictor. The nocebo suggestion reduced the drug's effectiveness by nearly 50%.
- The same treatment can work as both a nocebo and a placebo. Experimenters gave subjects who believed they were allergic to various foods an injection they were told contained the allergen. It was only salt water, but it produced allergic symptoms in many of them. Then the experimenters injected salt water again, this time saying it would neutralize the effect of the previous injection — and in many cases it did.
- An active drug has more nocebo power than a mere sugar pill. In one study, experimental subjects were divided into four groups. The first was given a muscle relaxant, described correctly; the second group was given the same muscle relaxant but told it was a stimulant; the third group received a sugar pill described as a muscle relaxant, and the fourth received the same inert pill described as a stimulant. To no one's surprise, subjects who thought the pill was a stimulant were more likely to say they felt tense. But the muscle relaxant caused more reports of tension when described as a stimulant than the sugar pill did. Blood levels of the muscle relaxant were lower in people told it was a stimulant than in those told the truth. They may have absorbed less of the drug because the false information activated the sympathetic nervous system, which slows down movements of the intestinal tract.

Anyone can experience a nocebo effect, but it appears that the same people respond strongly to both nocebos and placebos. In one experiment, subjects in three groups were asked to keep a hand in ice water as long as they could. One group was told that this could have beneficial effects for a period of up to five minutes (placebo instruction). The second group was told that it could be harmful, so the experiment would be stopped after at most five minutes as a precaution (nocebo instruction). The third group was told only that their responses to cold were being tested (neutral instruction). People who indicated high anxiety about pain on a questionnaire before the experiment had the strongest responses — as measured by the time they kept their hands in the cold water — not only to the nocebo instruction, but also to the placebo instruction.

Anyone who is anxious, depressed, or hypochondriacal runs the risk of developing further symptoms in response to attempts at healing or comforting. In this case, the nocebo effect is related to somatization, the expression of emotional disturbances in the form of physical symptoms. Somatoform disorders, identified by recurrent medically unexplained physical complaints, have many sources in mood, personality, and social circumstances. Somatoform reactions may also be provoked and perpetuated by what some see as the advantages of being treated as an invalid. This so-called secondary gain is sometimes regarded as another form of nocebo response.

Patients need help in understanding and tolerating, minimizing, or ignoring nocebo and other somatoform responses. These responses may be at work whenever the side effects of a medication or other treatment are vague and ambiguous or the patient has been expecting it to cause problems. Patients can be asked about earlier disappointing experiences with medical procedures. If a patient says he or she is especially sensitive to drugs, the physician might point out that anticipating bad effects can be a self-fulfilling prophecy. It may help to emphasize the limits of medicine and explain the close relationship between emotions and physical sensations, especially as it involves stress hormones. Above all, in prescribing any drug or other treatment, physicians must act in a way that establishes trust and promotes the patient's participation and cooperation.

References

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