Harvard Mental Health Letter

New insights into the nocebo response

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Research is providing clues about a phenomenon that is the exact opposite of the placebo response.

All drugs cause side effects, but it turns out that placebo pills also cause them. This is puzzling, because placebo pills are usually made of sugar or some other inert substance and so theoretically should have no biological effect. Even more intriguing, the research suggests that the *type* of side effect a placebo causes will vary depending on the active drug being tested.

For example, researchers analyzed the findings of 69 randomized clinical trials that compared different classes of migraine drugs with placebos. All studies were "blinded" so that neither the researchers nor the participants knew who was receiving the placebo. In studies evaluating nonsteroidal anti-inflammatory drugs (NSAIDs), patients assigned to the placebo arm most often reported nausea, vomiting, and other gastrointestinal problems — side effects that can occur after taking NSAIDs. In studies assessing anticonvulsants, patients taking placebo most often reported loss of appetite, memory problems, and upper respiratory infections — all side effects of anticonvulsants.

This phenomenon is not just observed in studies of migraine medication. Another analysis of placebo-controlled trials concluded that 23% of patients taking a placebo reported uncomfortable side effects.

These effects are testaments to the existence of the nocebo effect — the dark side of the better-documented placebo effect. In Latin, nocebo means "I will harm," while placebo means "I will please." A placebo can enhance healing or pain relief, while a nocebo has the opposite effect — making patients feel worse.

Multiple mechanisms

Several factors contribute to the nocebo response — as they do to the placebo response.

Psychology. Anxiety, depression, and hypochondria increase susceptibility to the nocebo response. It's not clear why, but one theory is that these psychological states may cause somatization, the expression of emotional disturbances in the form of physical symptoms.

Conditioning. When patients have had a negative experience or developed side effects in the past, they may do so again in response to sights, sounds, or other cues associated with that treatment. For example, as many as one in three patients become nauseated or even vomit on entering a room where they have recently received chemotherapy.

Context. Medications and other treatments take on symbolic features that can have nocebo effects. Red, orange, and yellow are colors associated with stimulation, while blue and green suggest sedation. Studies have found that participants who take blue placebo pills are more likely to say they feel drowsy afterward than people who take pink placebos.

Suggestion. The words a clinician uses to describe possible side effects of treatment — or even the forms used to provide informed consent — can create expectations of outcomes. In one placebo-controlled study of aspirin for unstable angina (a type of chest pain), researchers used two variations of a consent form. One specifically listed "gastrointestinal irritation" as a possible side effect, while the other did not. In the placebo arm, patients who had signed the consent form listing gastrointestinal irritation not only were more likely to experience this distress, but were also more likely to drop out of the study as a result.

Other research in healthy subjects has shown that the use of certain words — such as experimenters who warn that a mild electric shock might hurt a great deal — increases participants' own rating of pain severity.

Many questions

The biology of the nocebo response remains largely unknown. One theory holds that just as a placebo activates endorphins in the brain to provide pain relief, so too a nocebo may activate other receptors that stimulate the production of stress hormones like cortisol and in other ways affect perception of pain. Benzodiazepines, drugs used to treat anxiety, can blunt the nocebo effect on pain — suggesting that the chemical imbalances that contribute to anxiety may also underlie the nocebo response.

Although many questions remain about the mechanisms, the existence of the nocebo effect is an important reminder of the need to consider the context in which treatment takes place. Clinicians are wise to establish trust and address a patient's concerns about treatment in a positive way whenever possible. As research continues, the hope is that clinicians will have better guidance about how to invoke the placebo response — and avoid invoking the nocebo response — to help ensure that patients have every chance of healing and pain relief.

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For more references, please see www.health.harvard.edu/mentalextra.