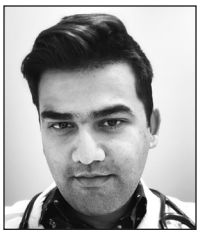

The nocebo effect in current practice

Kalpit Agnihotri MD CCFP ACBOM

In 2013, the *European Journal of Neurology* published a meta-analysis examining patient dropout rates owing to medication side effects in clinical trials for Parkinson disease treatments.[1] A review of more than a decade of various trials showed that nearly two-thirds of patients reported an adverse event after drug therapy. Worse still, nearly one-tenth (8.8%) of the patients in a specific arm of the studies experienced such horrific side effects that they were forced to stop treatment altogether. Strangely, this subset of patients had not been given any active medication at all—they had been given a placebo.

The placebo arm of a research study is crucial to the modern scientific method and is used to better understand the medication and confirm that it gives a true result beyond subjective experience. Much has been written about the placebo effect in recent years, but lesser known and understood is placebo's evil twin, the nocebo.

What is the nocebo effect?

Nocebo has been defined as

> a harmless substance or treatment that when taken by or administered to a patient is associated with harmful side effects or worsening of symptoms due to negative expectations or the psychological condition of the patient.[2]

To put it simply, bad expectations and "negative vibes" in a clinical encounter involving a prescribed medication lead to the patient experiencing real harm as an outcome.

The idea of "bad vibes" causing harm goes back centuries. Dr Walter Cannon (the Harvard physician who introduced us to the fight or flight response) discussed this in his well-known article on "voodoo death."[3] Dr Cannon wrote about this phenomenon in various cultures. He observed that the idea that death would result from a medicine man pointing a bone at his victim was a powerful cultural and spiritual belief. The victim often became hopelessly ill and fatigued over the course of days without any clear cause. It was the nocebo effect at its most extreme—a psychologically induced death:

> When Dr. Lambert arrived ... he learned that Rob was in distress .... Dr. Lambert made the examination, and found no fever, no complaint of pain, no symptoms or signs of disease. He was impressed, however, by the obvious indications that Rob was seriously ill and extremely weak. From the missionary he learned that Rob had had a bone pointed at him by Nebo and was convinced that in consequence he must die. Thereupon Dr. Lambert and the missionary went for Nebo, threatened him sharply that his supply of food would be shut off if anything happened to Rob .... At once Nebo agreed to go with them to see Rob. He leaned over Rob's bed and told the sick man that it was all a mistake, a mere joke—indeed, that he had not pointed a bone at him at all. The relief, Dr. Lambert testifies, was almost instantaneous; that evening Rob was back at work, quite happy again, and in full possession of his physical strength.[3]

A similar example in 20th-century medicine involved Mr Wright and his cancerous tumours.[4] Mr Wright suffered from advanced lymphosarcoma, but he had faith in a final resort—a horse-serum–derived substance called Krebiozen. He requested Krebiozen injections from his physician, and sure enough, his tumours shrank dramatically on x-ray scans. He spent several months in good health before reports came out stating that Krebiozen had no cancer-fighting properties. Then Mr Wright's tumours returned—visible and larger than ever.

His physicians chose to lie to him. They told him that Krebiozen did indeed cure cancer, but that he needed a much stronger dose for the full effect. Sham treatments with saline injections caused his cancer to presumably disappear completely. Mr Wright lived in good health for several months until a final review by the American Medical Association conclusively stated that Krebiozen was a useless drug. When Mr Wright learned this, his tumours reappeared. He was dead within days of admission to the hospital.

In an established patient-physician relationship, patients are often in a highly suggestible state. During such an encounter, a clinician's words might be as potent as a drug injection. Yet how much thought in medical education has been given to this idea?

Evidence for the nocebo effect

More than anecdotes support the nocebo effect. An article was published in 2011 titled "The nocebo effect and its relevance for clinical practice," in which researchers examined treatments for benign prostatic hyperplasia and their side effects, among other therapies for other conditions.[5] One group was informed about possible sexual side effects and the other was not. At 6-month and 12-month follow-up, "those patients who were informed

about the possibility of sexual dysfunction reported significantly greater sexual side effects (43.6%), as compared to those who were not informed (15.3%)."[5] Investigators concluded that the discussion of potential side effects during informed consent can induce the nocebo effect.

Various studies have confirmed physiologic mechanisms for the nocebo effect and its ability to produce a range of symptoms. An anesthesiology study examined physiologic processes during pain perception to explain increased pain in patients with negative expectations of pain and anticipatory anxiety.[6] Another study used functional magnetic resonance imaging to show that positive expectations toward the opioid remifentanil doubled its analgesic effect owing to associations with observable activity in endogenous pain modulation in the brain.[7] It has also been proposed that

> verbal suggestions of a positive outcome (pain decrease) activate endogenous μ-opioid neurotransmission, while suggestions of a negative outcome (pain increase) activate CCK-A [cholecystokinin A] and/or CCK-B receptors.[8]

Gastrointestinal effects can also be induced via nocebo. Myers et al found that simply mentioning possible gastrointestinal side effects "resulted in a sixfold increase ($P<0.001$) in the number of subjects in these centers withdrawing from the study because of subjective, minor gastrointestinal symptoms."[9] A similar nocebo response has been observed for muscle relaxants.[10] Researchers were able to cause (and measure) a decrease in the bronchodilator effect of isoproterenol simply by telling patients that it was a bronchoconstrictor, rather than a bronchodilator.[11]

A 2009 systematic review of antimigraine medication clinical trials also showed the power of nocebo:

> In addition, and most interestingly, the adverse events in the placebo arms corresponded to those of the anti-migraine medication against which the placebo was compared. For example, anorexia and memory difficulties, which are typical adverse events of anticonvulsants, were present only in the placebo arm of these trials. These results suggest that the adverse events in placebo arms of clinical trials of antimigraine medications depend on the adverse events of the active medication against which the placebo is compared. These findings are in accordance with the expectation theory of placebo and nocebo effects.[12]

If we see such measurable outcomes in controlled trials, how much more influence is carried by the words of a physician whom the patient has known and trusted for years? Thus, we face a balancing act with each clinical encounter.

Walking the fine line

Our profession obligates us to discuss the common and potentially serious side effects of medications with patients. No physician should mislead a patient. Potentially serious side effects should never be concealed and need to be outlined clearly. However, physicians should also be aware of the fine line between informing a patient of a medication's side effects and of *inducing* those side effects in a suggestible patient.

Additionally, some patients might "talk themselves out of" taking their medication. In my medical practice, an unnecessary and overly detailed review of a dozen possible side effects, often at the request of anxious patients, has occasionally kept them from starting medications that would have been beneficial for their overall health.

Further, some of the various listed side effects of medications often have little or no demonstrated causality and are generally taken from participant comments in drug trial reports without much further scrutiny.

The nocebo effect is, by its nature, challenging to study in a rigorous scientific setting. There are obvious ethical concerns with deliberately placing suggestions of negative outcomes in patients' heads. Nonetheless, there might be utility in studying which patient characteristics make them more susceptible to nocebo.

A study published in *JAMA* listed the following clinical risk factors for susceptibility to the nocebo effect[13]:

- the patient's expectations of adverse effects at the outset of treatment;
- a process of conditioning in which patients learn from previous experiences to associate taking medication with somatic symptoms;
- certain psychological characteristics such as anxiety, depression, and the tendency to somatize; and
- situational and contextual factors.

Research into further such clinical models might allow physicians to better navigate encounters with nocebo effect–prone patients. It is the responsibility of all clinicians to be aware of this effect and to diminish it as much as possible in their medical practices.

We must grow to appreciate the tangible power that our words hold over our patients. The challenge we face is how to create a more positive-minded environment for patients, while also remaining honest about their prognoses and the risks of the medical therapies we offer them.

Dr Agnihotri is a primary care physician with special interests in sports and exercise medicine and occupational injuries practising in Calgary, Alta.

Competing interests
None declared

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