NEUROSCIENCE

Nocebo effects can make you feel pain

Negative expectancies derived from features of commercial drugs elicit nocebo effects

By **Luana Colloca**

The mysterious phenomenon known as the nocebo effect describes negative expectancies. This is in contrast to positive expectancies that trigger placebo effects (*1*). In evolutionary terms, nocebo and placebo effects coexist to favor perceptual mechanisms that anticipate threat and dangerous events (nocebo effects) and promote appetitive and safety behaviors (placebo effects). In randomized placebo-controlled clinical trials, patients that receive placebos often report side effects (nocebos) that are similar to those experienced by patients that receive the investigational treatment (*2*). Information provided during the informed consent process and divulgence of adverse effects contribute to nocebo effects in clinical trials (*1*). Nocebo (and placebo) effects engage a complex set of neural circuits in the central nervous system that modulate the perception of touch, pressure, pain, and temperature (*1, 3, 4*). Commercial features of drugs such as price and labeling influence placebos (*5, 6*). On page 105 of this issue, Tinnermann *et al.* (*7*) show that price also influences nocebo effects.

Tinnermann *et al.* evaluated the responses of healthy participants who received two placebo creams labeled with two distinct prices and presented in two boxes that had marketing characteristics of expensive or cheap medication. The creams were described as products that relieve itch but induce local pain sensitization (hyperalgesia). All creams, including controls, were identical and contained no active ingredients. Nocebo hyperalgesic effects were larger for the "more expensive" cream than for the "cheaper" cream. Combined corticospinal imaging revealed that the expensive price value increased activity in the prefrontal cortex. Furthermore, brain regions such as the rostral anterior cingulate cortex (rACC) and the periaqueductal gray (PAG) encoded the differential nocebo effects between the expensive and cheaper treatments. Expectancies of higher pain-related side effects associated with the expensive cream may have triggered a facilitation of nociception processes at early subcortical areas and the spinal cord [which are also involved in placebo-induced reduction of pain (*8*)]. The rACC showed a deactivation and favored a subsequent activation of the PAG and spinal cord, resulting in an increase of the nociceptive inputs. This suggests that the rACC–PAG–spinal cord axis may orchestrate the effects of pricing on nocebo hyperalgesia.

The anticipation of painful stimulation makes healthy study participants perceive nonpainful and low-painful stimulations as painful and high-painful, respectively (*9*). Verbally induced nocebo effects are as strong as those induced through actual exposure to high pain (*9*). Moreover, receiving a placebo after simulating an effective analgesic treatment, compared to receiving the same placebo intervention after a treatment perceived as ineffective, produces a 49.3% versus 9.7% placebo-induced pain reduction, respectively (*10*). The relationship between prior unsuccessful or successful pain relief interventions and placebo analgesic effects is linked to a higher activation of the bilateral posterior insula and reduced activation of the right dorsolateral prefrontal cortex (*11*).

Informing patients that a treatment has been stopped, compared to a covert treatment interruption, alters the response to morphine, diazepam, or deep-brain stimulation in postoperative acute pain, anxiety, or idiopathic Parkinson's disease, respectively (*12*). Patients openly informed about the interruption of each intervention experience a sudden increase of pain, anxiety, or bradykinesia (a manifestation of Parkinson's disease), whereas patients undergoing a hidden interruption do not (*12*). Neuroimaging approaches support the clinical observation. For example, the action of the analgesic remifentanil is overridden by activation of the hippocampus that occurs when healthy participants that receive heat pain stimulations are misleadingly told that the remifentanil administration was interrupted (*13*). These findings provide evidence that communication of treatment discontinuation might, at least in part, lead to nocebo effects with aggravation of symptoms.

In placebo-controlled clinical trials, nocebo effects can influence patients' clinical outcomes and treatment adherence. It was shown in a clinical trial that atorvastatin induced in the same individuals an excess rate of muscle-related adverse events in the nonblinded (i.e., patients knew they were taking atorvastatin), nonrandomized 3-year follow-up phase but not in the initial blinded 5-year phase when patients and physicians were unaware of the treatment allocation (atorvastatin or placebo) (*14*). Furthermore, misleading information about side effects for statins via public claims has led to treatment discontinuation and an increase in fatal strokes and heart attacks (*14*).

Given that nocebo effects contribute to perceived side effects and may influence clinical outcomes and patients' adherence to medication, we should consider how to avoid them in clinical trials and practices (*15*)—for example, by tailoring patient-clinician communication to balance truthful information about adverse events with expectancies of outcome improvement, exploring patients' treatment beliefs and negative therapeutic history, and paying attention to framing (i.e., treatment description) and contextual effects (i.e., price). Through an understanding of the physiological mechanisms, strategies could be developed to reduce nocebo effects. ■

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