

EDITORIAL

Clin. Invest. (2013) 3(1), 5–7

## The nocebo effect: should we be worried?

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“Research on nocebo effects affirms the need for rethinking the ethics of patient–clinician communication, informed consent and, perhaps more importantly, the decision-making processes.”

Lack of adherence to therapeutic regimes and side effects observed in placebo arms are common problems in randomized clinical trials and practice [1]. These effects can be partially due to the occurrence of negative placebo effects, the so-called ‘nocebo effects’. Nocebo effects rely on a phenomenon that is opposite to placebo, in which expectations of worsening play a crucial role. Recent neuroanatomical and neurochemical advances support the notion that specific modulators and brain areas are involved in the formation of nocebo effects. Negative expectations can produce increases in pain experienced and can interfere with the therapeutic action of active drugs. It has been reported that the negative and positive disclosures interfere with the analgesic efficacy of the  $\mu$ -opioid agonist, remifentanyl [2]. A positive communication such as, “you are going to receive a potent analgesic medication,” substantially enhanced (doubled) the analgesic effect of remifentanyl. Conversely, a negative disclosure such as informing a health volunteer that the painkiller is going to be stopped when in actuality, was continuously administered, abolished the remifentanyl-induced pain relief. The subjective pain reports correlated significantly with modifications in specific brain regions that are known to be involved in pain processing [2]. Studies in human models have also indicated that the CCK system is linked to nocebo effects, at least in the field of pain. Verbal cues of increased pain produce the anticipated effects and these effects can be reversed by administering the nonspecific CCK-antagonist proglumide, suggesting that blocking CCK-A and -B receptors antagonizes verbally induced increases in pain. Furthermore, sensorial stimulations that would never normally produce pain began to do so under verbal suggestions of hyperalgesia [3]. Nocebos can produce deleterious effects as nonpainful tactile stimuli can become painful and hyperalgesic responses in which low-intensity painful stimuli are perceived as high-intensity stimuli [4]. Apparently, direct experience matters in nocebo responses, but less than the placebo counterpart in which learning from previous positive experience is fundamental for consolidating positive outcomes. We can speculate that nocebos induce short-term innate responses that are aimed at enhancing the perceptual processing and at anticipating negative outcomes, which in turn help initiate potentially defensive behavioral reactions. On the other hand, perpetuation of unsuccessful experiences may promote the consolidation of negative outcomes and the severity of symptoms.

From a clinical point of view, it is plausible to think that if nocebos and negative verbal cues are powerful in eliciting negative outcomes in laboratory settings, it is licit to postulate that the doctor’s words and attitudes can induce immediate worsening of symptoms [5]. For example, communication about the interruption of a therapy (pharmacological or non-pharmacological) results in the occurrence

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**Keywords:** communication • disclosure • expectation • informed consent  
• placebo • verbal suggestion

of a certain symptom. According to an open/hidden paradigm, the anxiolytic diazepam was given by means of a computer-controlled pump of infusion and patients either were or were not alerted by a health practitioner about the interruption of treatment [6]. Patients overtly informed about the interruption of treatment experienced a sudden increase of anxiety, while hidden covert interruption (controlled by computer) induced no worsening, suggesting that the communication of treatment interruption can aggravate patients' symptoms. Similarly, patients with Parkinson's disease who were treated with high-frequency stimulation showed an exacerbation of symptoms such as bradykinesia and an impairment of the velocity of movement when they were told of the deactivation of the deep stimulation of their subthalamic nuclei [6].

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Other studies have illustrated the impact of communication on clinical outcomes. Two such studies have explored how verbal cues modulate pain experience associated with lumbar puncture in medical and surgical patients. In 1981, patients from Gilbert Island, likely unaware of the adverse event of lumbar puncture, were randomly told that they might experience a headache afterwards, or were not informed. Of the 15 patients informed about the potential adverse event, seven reported headaches. Of the 13 subjects undergoing the same procedure, but not being told to expect headaches, none reported having had a headache when asked later [7]. More recently, women at term gestation requesting labor epidural analgesia or non-laboring patients presenting for elective cesarean delivery under spinal anesthesia were randomized to one of two groups. The first group received a common description of the pain experience from local anesthesia injection – expecting pain like a bee sting during the procedure. The second group was informed in a more reassuring way, emphasizing that the local anesthetic will numb the area making the overall procedure comfortable. After the local anesthetic injection, a blinded observer assessed patients' pain. Those assigned to group one rated pain significantly higher than those receiving the procedure along with positive words [8].

Communication of potential side effects might also lead to patient-initiated cessation of therapies. Myers and collaborators retrospectively analyzed the influences on outcome of mentioning gastrointestinal side-effects in the consent forms of two of three centers

involved in a randomized, double-blind, placebo-controlled trial examining the benefit of aspirin, sulfipyrazone, or both drugs, for unstable angina pectoris. They found that the inclusion of possible gastrointestinal side effects in the consent forms resulted in a remarkable increase (approximately six-times) in both gastrointestinal symptoms and consequent patient-initiated cessation of therapy, suggesting that communicating potential side effects led to subsequent withdrawal from the study [9].

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Research on nocebo effects affirms the need for rethinking the ethics of patient–clinician communication, informed consent and, perhaps more importantly, the decision-making processes. While clinicians must convey truthful information to patients so that patients can make informed decisions about their medical care, this information should be framed in a way that mitigates symptomatic worsening [10]. Information regarding risks and benefits of interventions should be wisely framed during the patient decision-making processes, by considering the impact of informing patients of the potential adverse effects. Additionally, patients might be warned about the possibility of experiencing some adverse events as a result of being informed. This approach is consistent with informed consent and respect for patients' autonomy allowing clinicians and trialists to benefit from considering the potential link between conveyed information and observation of certain negative outcomes.

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#### Disclaimer

*The opinions expressed are those of the author and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.*

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#### Financial & competing interests disclosure

*This research was supported by the Intramural Research Program of the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Mental Health (NIMH). The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

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