Published in final edited form as:

JAMA. 2012 February 08; 307(6): 567–568. doi:10.1001/jama.2012.115.

Nocebo Effects, Patient-Clinician Communication, and Therapeutic Outcomes

Luana Colloca, MD, PhD,

National Center for Complementary and Alternative Medicine, and Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, Maryland

Damien Finniss, MSc Med

University of Sydney Pain Management and Research Institute, Royal North Shore Hospital, St Leonards, New South Wales, Australia

NOCEBO EFFECTS ARE ADVERSE EVENTS PRODUCED by negative expectations and represent the negative side of placebo effects. It is now recognized that nocebo effects exist and operate during routine treatments, negatively affecting clinical outcomes even when placebos are not administered. The nocebo effects and placebo effects are the direct result of the psychosocial context or therapeutic environment on a patient's mind, brain, and body. Both phenomena can be produced by multiple factors, such as verbal suggestions and past experience.[1] In the case of nocebo effects, negative information and prior unsuccessful therapies may be particularly important in mediating undesirable outcomes to routine therapy. Therefore, consideration of nocebo effects in the context of patient-clinician communication and disclosure in routine practice may be valuable in both minimizing the nocebo component of a given therapy and improving outcomes.

As with their placebo counterpart, nocebo responses demonstrate the powerful interaction between the therapeutic context and the patient's mind-brain interaction.[2] This phenomenon is demonstrated in elegant studies that show negative verbal information can convert nonnociceptive stimulation into the experience of pain, remarkably to the same level as painful stimuli.[3] Furthermore, just one occasion of negative information can induce long-lasting negative effects.[4] Negative expectations are not only experienced before administration of a treatment. Indeed, informing patients about interruption of treatment, such as an infusion of morphine for postoperative pain, has been associated with a significant increase in pain compared with when treatment is stopped without informing the patient. In this study, patients in one group were aware that the infusion would eventually cease, but not the exact time as the therapy was surreptitiously controlled by a computerized pump. In the other group, the cessation of therapy was made obvious through negative instructions from the clinician. The negative verbal instructions and manner in which the

Corresponding Author: Luana Colloca, MD, PhD, Department of Bioethics, Clinical Center, National Institutes of Health, 10 Center Dr, 10/1C118, Bethesda, MD 20892-1156 (luana.colloca@nih.gov).

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Disclaimer: The opinions expressed are those of the authors 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.

therapy was stopped altered clinical outcomes, not just in terms of pain but also motor performance and anxiety.[5]

The importance of information delivery and disclosure of potential adverse events in the clinical setting is highlighted in some clinical trials, involving significant nocebo responses. Studies have shown that different information about adverse events yields different clinical responses. In 1 study, patients with arm pain were randomized to receive either placebo pills or sham acupuncture. Among those patients given sham acupuncture, a quarter reported 1 or more adverse events that mirrored the disclosure information specific to needling technique.[6] Such significant nocebo responses have been demonstrated in other clinical trials, such as anti-migraine drugs and antidepressants, and these negative responses can potentially cause patients' withdrawal from the study and premature cessation of therapy.

Research on nocebo effects draws attention to the potentially important ways in which possible adverse effects are disclosed to patients in routine clinical care. Nocebo effects can modulate the outcome of a given therapy in a negative way, as do placebo effects in a positive way. Importantly, these effects operate in the absence of a traditional placebo, forming part of everyday treatments. To this extent, a balance must exist between communicating important clinical information and ensuring that every attempt is made to minimize negative instructions and a negative therapeutic context. This fine balance must take into consideration the patient's autonomy to make a decision based on all relevant information, with attempts to reframe how information may be delivered in a nondeceptive, yet reassuring way.

Such an example exists in women at term of gestation requesting labor epidural analgesia. In 1 study,[7] a small difference in framing the information provided along with labor anesthetic injection—"We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure" vs "You are going to feel a big bee sting; this is the worst part of the procedure"— produced different pain outcomes. The positive framing for the description of the procedure induced significantly lower pain compared with a neutral information deprived of positive words and encouragement.[7] An extension of appreciating and reframing the disclosure process is provided by a study in which informing men with benign prostatic hyperplasia about the potential sexual dysfunction induced by finasteride—"It may cause erectile dysfunction, decreased libido, problems of ejaculation but these are uncommon"—produced 43.6% of sexual adverse effects vs 15.3% when the same adverse effects were concealed.[8]

These differences in reported adverse effects indicate that the way in which adverse events are presented affects not only risk perception but, more importantly, clinical outcomes. Rather than merely delivering detailed lists of specific adverse effects, clinicians should incorporate in their communication positive framing and percentage formats as opposed to negative framing and frequency format, thus possibly reducing nocebo effects by minimizing attention on the negative aspects of medication. Furthermore, the process of tailoring information should account for what the patient wants to know and what the patient has already learned about his or her condition given the widespread access to information about treatments and their adverse effects. Guiding the patient in the knowledge process and

discussing valuable examples of nocebo effects engages him or her in the decision making process and potentially averts negative outcomes. Thus, clinicians in any discipline may benefit by considering the link between conveying information and nocebo effects. Reframing the disclosure process, continued thought about approaches to ethical alternatives surrounding disclosure, and educating clinicians and patients about the possible detrimental effects of nocebo processes are all particularly important strategies. Ultimately, clinicians should ensure adequate time and privacy, elicit patients' perspectives and expectations, and tailor the information delivery process to the needs of the patient.

The emerging evidence about nocebo effects in routine clinical practice suggests that there is a possibility of reducing this negative component of treatment outcomes. If negative information is conveyed about initiation of a therapy, as is ethically important, a negative context can be created. When this scenario is studied across clinical and laboratory settings and a placebo treatment is administered, a significant proportion of patients become worse. Upon adding the same disclosure of information to a routine clinical treatment, the negative contextual component is likely to still be present. Therefore, the net outcome of that treatment may be due to the overall positive effects of the treatment minus the negative effects attributable to nocebo. Such a conceptualization may represent an important addition to the way in which health care is delivered. Not only is there a focus on targeted treatments and the positive therapeutic context in which they are delivered, but also a focus on understanding and modulating nocebo effects and the negative therapeutic context.

Clinicians' efforts should be devoted to avoiding instilling negative expectations during the informed consent process, procedural information, and follow-up assessments so that the most effective patient-clinician communication can be pursued while unwarranted and untenable nocebo responses can be avoided.

Acknowledgments

Funding/Support: This work was supported by the Intramural Research Program of National Center for Complementary and Alternative Medicine, National Institutes of Health.

Role of the Sponsor: The National Institutes of Health had no role in the preparation, review, or approval of the manuscript.

REFERENCES

1. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. Lancet. 2010;375(9715):686–695. [PubMed: 20171404]
2. Brody H, Miller FG. Lessons from recent research about the placebo effect: from art to science. JAMA. 2011;306(23):2612–2613. [PubMed: 22187283]
3. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136(1–2):211–218. [PubMed: 18372113]
4. Rodriguez-Raecke R, Doganci B, Breimhorst M, et al. Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. J Neurosci. 2010;30(34): 11363–11368. [PubMed: 20739557]
5. Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol. 2004;3(11):679–684. [PubMed: 15488461]
6. Kaptchuk TJ, Stason WB, Davis RB, et al. Sham device v inert pill: randomised controlled trial of two placebo treatments. BMJ. 2006;332(7538):391–397. [PubMed: 16452103]

7. Varelmann D, Pancaro C, Cappiello EC, Camann WR. Nocebo-induced hyperalgesia during local anesthetic injection. Anesth Analg. 2010;110(3):868–870. [PubMed: 20042440]
8. Mondaini N, Gontero P, Giubilei G, et al. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo p