The nocebo effect and its relevance for clinical practice

Luana Colloca, M.D., Ph.D[1,2] and **Franklin G. Miller, Ph.D**[2]

[1]National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health, Bethesda, MD, USA

[2]Department of Bioethics, Clinical Center, National Institutes of Health, Bethesda, MD, USA

Abstract

Negative expectations deriving from the clinical encounter can produce negative outcomes, known as nocebo effects. Specifically, research on the nocebo effect indicates that information disclosure about potential side effects can itself contribute to producing adverse effects. Neurobiological processes play a role in the nocebo effect and this paper provides a selective review of mechanistic research on the nocebo effect. Comparatively little attention has been directed to clinical studies and their implications for daily clinical practice. The nocebo response is influenced by the content and the way information is presented to patients in clinical trials in both the placebo as well as active treatment conditions. Nocebo effect adversely influences quality of life and therapy adherence, emphasizing the need for minimizing these responses to the extent possible. Evidence further indicates that the informed consent process in clinical trials may induce nocebo effects. This paper concludes with ethical directions for future patient-oriented research and routine practice.

Keywords

disclosure; expectation; ethics; side effects; suggestions; framing information

Introduction

Laboratory research on the nocebo effect — adverse effects produced by expectations — has demonstrated that this is a neurobiological phenomenon, which can be manifested by detectable bodily changes (1) and cause adverse health-related consequences (2). In placebo-controlled clinical trials, patients receiving placebo often report side effects that are similar to those experienced by patients receiving study treatment and that may be attributable to the mere communication of potential adverse effects in the informed consent process (3).

Nocebo effects do not merely encompass negative responses to inert interventions, as in placebo-controlled trials (3) and laboratory experiments (2). These effects can also be produced in clinical practice by negative expectations relating to disclosures of possible side

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.

Conflict of interests: The authors have not conflicts of interest to declare.

effects from prescribed treatments (4). For example, informing a patient that a prescribed drug may cause a side effect may itself produce the same side effect independent of the pharmacological properties of the drug (e.g. (5–8)). In this article, the term "side effect" is used to describe all signs and symptoms that are not the primary target effect of the intervention.

Just as the interpersonal and environmental dimensions of the clinical encounter have a potentially powerful therapeutic benefit (9, 10), negative aspects of the clinical encounter can have negative, nocebo effects. In daily clinical practice, nocebo effects can be a result of the interactions between clinicians and patients, and the general psychosocial context surrounding the patient. Harms and negative outcomes can be likewise related to the process of disclosing serious illness and prognosis (11) and, health information sources (12, 13). Here we focus on nocebo effects relating to information disclosure in clinical settings. After briefly introducing some methodological aspects and salient findings from mechanistic research on the nocebo effect, we discuss clinical research studying the relationships between negative expectations including social, psychological, and behavioral factors and bodily changes and well-being in humans. Translating research on mechanisms of the nocebo effect to behavioral and clinical observations and to clinical practice raises a distinctive challenge for clinicians. Clinicians have an obligation to convey truthful information to patients so that they can make informed decisions about their medical care. However, information disclosure can itself contribute to producing negative expectations and adverse side effects. We will examine this dilemma, and discuss relevant considerations for medical care. An understanding of the nocebo effect should help the medical community recognize its clinical implications and encourage strategies to minimize nocebo effects in an ethically acceptable fashion.

Definitions and methodological considerations

It is important to clarify the definition of "nocebo effect" and the methodology that relates to the identification of nocebo responses in the context of mechanistic research and randomized, placebo-controlled trials.

Although potential neurobiological pathways for nocebo are different from the pathways responsible for placebo effects, the term *nocebo effect* was originally coined to denote the negative counterpart of the placebo phenomenon and to distinguish the adverse from the beneficial effects of placebos (14, 15). The term *nocebo* has been used to indicate an inert substance or procedure intended to create negative expectations (e.g., giving a placebo along with verbal suggestions of worsening). Additionally, it is useful to distinguish the *nocebo effect* from the *nocebo response*. The former refers to the negative psychosocial context around the patient and the treatment and its neurobiological bases; the latter refers to the expectancy-induced changes in the patient's brain-body unit. It is clear that negative expectancies inducing a nocebo response occur frequently without any administration of inert substances. For example, words and elements of clinical encounter can produce nocebo responses that lead to worsening of patients' outcomes. Nocebos are used in research but, unlike placebos, they are not used in clinical practice. Whereas promoting placebo responses may be an intentional, and desirable, aspect of clinical practice, clinicians do not intentionally produce nocebo responses, as this would be contrary to the basic ethical norms of beneficence and non-maleficence.

Methodologically, with respect to clinical trials, Ernst and Resch distinguished the apparent and true placebo effect: the former is the response observed in the placebo group of a randomized controlled trial. The apparent placebo effect may be due to factors such as the natural history of the condition under study or regression to the mean rather than reflecting a

true placebo effect that can be attributed to the placebo intervention. Accurate detection of the true placebo effect requires comparison with a no-treatment control group (16). It has not been sufficiently appreciated that a similar distinction pertains to the nocebo effect. Apparent nocebo effects are adverse responses observed in the placebo arm of a randomized controlled trial. For example, a report of agitation or sexual dysfunction by depressed patients randomized to placebo might either reflect symptoms of depression or be due to expectations of side effects. Only the latter is a true nocebo effect. True nocebo effects in the context of clinical trials are adverse effects that can be attributed to the placebo intervention (including the informed consent disclosure relating to the side effects of study treatments), which can be detected accurately in specific clinical trials only by means of comparison with a natural history control group. Thus, nocebo effects can be appropriately identified from three-arm placebo-controlled trials that include a no-treatment group, which does not receive expectations of side effects related to a treatment (or masked placebo) intervention.

Assessment of side effects (and their attribution to nocebo effects) also poses methodological issues. In many studies, patients are simply asked whether they have experienced any side effects since the last visit; in other studies a structured list of possible adverse events is given to determine which have been experienced. Accordingly, the method of ascertaining side effects may have an impact on patient reports, suggesting the need for standardized assessments.

Mechanistic research on nocebo effects

Most studies on the nocebo effect come from the field of pain processing in healthy subjects due to the ease of delivering controlled painful stimuli and availability of sophisticated techniques of brain imaging (17, 18). The basic psychological mechanisms underlying the formation of negative expectations and thus nocebo responses are anticipation of and information about negative outcomes (19, 20), the prior experience of negative therapeutic outcomes (20, 21), and observation of other patients' negative outcomes (22).

In experimental settings, healthy subjects given a sham radiofrequency stimulus and informed that an electrical current was passing through their heads experienced headache (23), thus indicating that expectations created discomfort and head pain (24, 25). Moreover, mental processes can modify the action of medication paradoxically: the typical effect of 33% nitrous oxide (N_2O) (26) was reversed from analgesia to hyperalgesia – low level of pain perceived as higher - when healthy subjects received misleading information that they may experience an increase of pain. Negative information given verbally can convert typically painless stimulations into pain and induce nocebo responses as strong as those which are induced by direct experience of negative outcomes (20, 27).

These behavioral changes are supported by objective psychopharmacological (2, 28) and neuroimaging results (27, 29). On one hand, proglumide, a mixed cholecystokinin (CCK) type-A/B receptor antagonist, blocks nocebo hyperalgesic responses following the administration of placebos along with the verbal suggestion of increased pain, thus suggesting a specific involvement of the cholecystokinergic system in nocebo hyperalgesia (2, 28). On the other hand, information about the occurrence of pain increase even if given only once, can interfere with the natural course of pain perception by inducing a hyperactivity of the insular cortex over time periods as long as 8 and even 90 days (27). Interestingly, these observations have been supported by brain imaging findings. The brain analgesic effects induced by μ-opioid agonist remifentanil was completely over-ridden when subjects were told that the drug infusion was stopped (when it had not), suggesting that negative expectations may interfere with the drug pharmacodynamic profile (17, 30).

Overall, these experimental findings in the field of pain have relevance for patients with chronic pain and, probably for other clinical situations where mental processes act as a major factor affecting medical outcomes.

Nocebo effects in clinical research

Potential nocebo responses are common in clinical trials and practice. In clinical trials, a substantial proportion of patients in placebo control groups - those given supposedly inert therapies - experience negative side effects which match those associated with real drugs.

Meta-analyses of placebo-controlled trials including drugs with different side effect profiles provide suggestive evidence for these kinds of nocebo effects (31, 32). For example, Amanzio and colleagues performed a systematic review of adverse effects of anti-migraine randomized placebo-controlled clinical trials. The final sample consisted of 69 studies including 56 trials for triptans, 9 trials for anticonvulsants and 8 trials for non-steroids anti-inflammatory drugs. They found a high rate of adverse events in the placebo arms of trials with anti-migraine drugs matching those described for the specific type of real drugs under investigation. For example, anticonvulsant placebos produced anorexia, memory difficulties, paresthesia and upper respiratory tract infection — all adverse events reported in the side effect profile of this class of anti-migraine drugs (31). The linkage between reported side effects in the placebo groups and the known side effects of particular drugs suggests genuine nocebo effects from the informed consent process.

Similar results have been obtained for antidepressants. A comprehensive meta-analysis of 143 placebo randomized controlled trials for antidepressants including 21 trials for tricyclic (TCA) and 122 for selective serotonin reuptake inhibitor (SSRI) antidepressants reported a higher rate of adverse effects in the tricyclic trials than SSRI trials. This was true not only for the active drug arms but also for the placebo arms of tricyclic antidepressants. For example, patients receiving TCA placebos reported higher rates than those receiving SSRI placebos for dry mouth (19.2% vs. 6.4%), vision problems (6.9% vs. 1.2%); fatigue (17.3% vs. 5.5%), and constipation (10.7% vs. 4.2%). This indicates that information about adverse effects of different classes of drugs produce patient expectations that may influence the experience of side effects and may bias clinical trial outcomes (33).

Another common nocebo-related problem in clinical trials and practice is withdrawal of participation by research subjects and lack of adherence to treatment interventions. Frequently, this may be due to the occurrence of nocebo effects. For example, Myers et al. reported that communicating about potential side effects led to subsequent withdrawal from the study (4). They retrospectively analyzed the influence of consent forms that did and did not mention gastrointestinal side effects used by two of three centers involved in a randomized, double-blind, placebo-controlled trial that examined the benefit of aspirin, sulfinpyrazone, or both drugs, for unstable angina pectoris (34). They found that the inclusion of possible gastrointestinal side effects in the consent forms resulted in a remarkable increase (six fold) in both gastrointestinal symptoms and consequent patient-initiated cessation of therapy (4).

More recently, Rief and collaborators evaluated the occurrence of adverse effects and discontinuation rates in randomized placebo-controlled trials of statin drugs and in trial and general study populations. Although adverse effect assessment methods varied substantially across studies making it difficult to estimate the dropout rates accurately, the authors found that 4% to 26% of patients in the control groups of large trials of statin drugs discontinued placebo use because of perceived adverse effects (35).

While the examples described above have analyzed retrospectively the occurrence of (potential) nocebo responses, some experiments have been specifically designed to investigate prospectively the relation between informing patients and occurrence of side effects. For example, such a relation between disclosure and occurrence of side effects has been found for adverse sexual outcomes (8, 36, 37). Sexually active patients with benign prostatic hyperplasia (BPH) who received finasteride (5 mg) described as a "compound of proven efficacy for the treatment of BPH" were randomized to two different disclosures relating to side effects. One group was informed about the possible adverse sexual effects ("…it may cause erectile dysfunction, decreased libido, problems of ejaculation but these are uncommon"); the other group was not told about these side effects. Follow-up after 6 and 12 months revealed that 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%) (8). The nocebo effects relating to sexual dysfunction revealed by these studies may also be relevant to treatments of other conditions that are associated with sexual side effect, such as SSRIs for depression.

Verbal information conveyed during standard medical procedures can produce differential symptomatic pain worsening. This is illustrated by a study of verbal communication in pregnant women and prior experience of painful procedures in infants (20, 38). Women at term gestation requesting labor epidural analgesia or non-laboring patients presenting for elective cesarean delivery under spinal anesthesia were randomized to either a common description of the pain experience from local anesthesia injection ("You are going to feel a big bee sting; this is the worst part of the procedure") or a more reassuring description ("We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure"). Immediately after the local anesthetic injection, an observer blinded to the study design was called into the room for assessing patients' pain. Those women in labor informed to expect pain like a bee sting during the local anesthetic injection (nocebo group) rated pain significantly higher than those receiving the procedure along with gentle positive words (38).

Beyond harmful effects of disclosures, the exposure to cumulative experiences with pain can lead to anticipatory pain behaviors and conditioned nocebo hyperalgesia. An example of hyperalgesic conditioned responses has been reported in an observational study of hospitalized full-term infants of diabetic mothers who underwent repeated venipuncture (heel lancing without anesthesia) for monitoring blood glucose concentrations in the first 24 to 36 hours. The infants of diabetic mothers showed more pain than normal infants who underwent another venipuncture procedure for newborn screening (39). Additionally, they showed anticipatory pain behaviors when their skin was just cleaned prior to injection, suggesting that skin cleaning repetitively associated with venipuncture became a conditioned stimulus for inducing pain responses in absence of pain stimulation – an example of conditioned nocebo responses.

Nocebo effects are also involved in allergic disorders (40, 41) and severe symptoms such as nausea (and other symptoms) in cancer patients (42, 43) mostly related to verbally-induced and conditioned negative expectations (44–47). These adverse effects may reduce quality of life and negatively influence therapy adherence, emphasizing the need for minimizing nocebo responses to the extent possible.

Ethical implications

Traditionally, physicians have paternalistically controlled the disclosure of information to patients (48); however, both the law and medical ethics have endorsed informed consent and narrowly circumscribed the "therapeutic privilege" to withhold information (49). Physicians

have an obligation to convey truthful information to patients so that they can make informed decisions about their medical care. Accordingly, physicians face the ethical challenge of how they can communicate so that nocebo responses can be reduced to a minimum in clinical practice consistent with informed consent. In the literature on nocebo effects, no studies devoted to ethical issues are present. In this section, we suggest some strategies for addressing ethical concerns related to nocebo effects and disclosures about side effects of recommended treatments.

Before examining practical strategies aimed at minimizing nocebo effects, we note that nocebo research has an important ethical implication that has not been appreciated. One of the key purposes of informed consent is to communicate to patients the benefits and risks of recommended treatment interventions so that they can decide for themselves whether undergoing these treatments is a reasonable option for them, in light of their preferences and values. It appears to be assumed that such information disclosure merely describes independent facts that are relevant to patients' medical decisions. Nocebo research, however, reveals that the risks of treatment interventions relating to side effects are not necessarily independent of information disclosure. As demonstrated by the nocebo research that we have reviewed, communication about side effects can increase the probability that side effects will be experienced. It follows that the obligation to obtain informed consent is potentially in tension with the obligation of physicians to minimize risks to patients from medical interventions, including the risks associated with information disclosure (50).

How, then, can physicians simultaneously obtain informed consent and minimize nocebo-related risks? In light of nocebo research, the answer to this question calls for careful attention to the ways in which information about side effects is disclosed to patients.

Truthful information relating to side effects of treatments can be presented in various ways. A given side effect, such as headache or nausea, can be mentioned merely as a possibility. The probability of experiencing adverse effects, based on extant research, can be communicated qualitatively or statistically. And this information can be conveyed "negatively" (by focusing on the minority of patients who experience a particular side effect) or "positively" (by focusing on the majority of patients who do not experience the side effect). These different ways of framing side effect information may have differential effects on patients with respect to forming nocebo responses. Although a variety of studies have investigated the effects of framing information regarding risks and benefits of interventions on patient decision-making (51), little attention has been devoted to potential framing effects on nocebo responses. In one study, alternative ways of truthfully communicating risks of side effects to patients given a standard influenza vaccine influenced the reported adverse events as well as work absenteeism following immunization. Patients who were told the percentage of patients free of vaccine side effects based on available data (positive framing) reported significantly lower incidence of side effects than patients who were told the percentage reporting side effects (negative framing). While the logically equivalent information disclosures did not influence patient's decisions whether or not to be vaccinated, the positive framing reduced the probability of nocebo effects (52).

To minimize nocebo effects consistent with patient autonomy a technique of "authorized concealment" merits consideration. In an authorized concealment approach patients prescribed a particular drug would be asked if they are willing to agree not to receive information about certain types of side effects. Adverse effects with the potential for serious or irreversible harm should not be concealed, as patients cannot make informed choices without disclosure of serious risks, and negative expectations by themselves are unlikely to contribute to such effects. In contrast, authorized concealment may be appropriate for relatively mild and transient side effects. Consistent with this approach, a physician who is

recommending a given drug to a patient might communicate in the following way: "A relatively small proportion of patients who take Drug X experience various side effects that they find bothersome but are not life-threatening or severely impairing. Based on research, we know that patients who are told about these sorts of side effects are more likely to experience them than those who are not told. Do you want me to inform you about these side effects or not?"

Such an authorized concealment disclosure might be promising, but it has some limitations. First, not knowing about certain side effects such as sedation or dizziness might be harmful. These latter potential dangerous side effects would need to be disclosed (ideally, in ways that minimize nocebo effects). However, concealment of a range of other side effects, if not very prevalent for a given drug, might be reasonable: e.g., headache, mild fatigue, nausea. Second, many patients might be aware of the potential side effects of a treatment through the widespread access to internet websites containing information about medical treatments. (Whether learning about potential side effects is more likely to produce nocebo responses when the information is conveyed verbally by a trusted clinician versus by means of reading is a question that deserves study.) Third, some of the concealed side effects might be such that if they were disclosed they would influence patients not to take the drug in light of their preferences and values. For example, the sexual dysfunction related to taking finasteride for BPH, described above, might be the sort of side effect that would be material to some patients' decisions whether or not to undergo that treatment. Authorized concealment that includes these side effects might be inconsistent with patients' preferences and values, and thus contrary to autonomy. This latter problem might be addressed by giving patients a list of possible types of side effects and asking them which they would always want to know about before deciding on taking a drug and which they would prefer not to know about in advance.

In order to assess the feasibility and acceptability of authorized concealment, it would be valuable to survey patients regarding their attitudes towards this technique and the types of side effects that they think would be appropriate or inappropriate to conceal.

It might be objected that the authorized concealment approach is unethical because physicians adopting it would fail to disclose pertinent risk information to their patients, thus compromising informed consent. However, information disclosure is not a value in itself; rather, it is meant to serve patient autonomy. If patients autonomously decide not to receive certain types of risk information after being educated about the potential for this information to induce nocebo responses, then this deviation from standard practice of informed consent is not ethically objectionable. Authorized concealment constitutes a valid waiver by the patient of the right to receive information about certain types of treatment risks, making it consistent with autonomy (53).

The study of nocebo effects comparing different information disclosures relating to potentially painful anesthetic procedures for women in labor confirms earlier clinical observations emphasizing the influences of physician-patient interaction on clinical outcomes (54–57). Since verbal information has the power to elicit an immediate symptom worsening (e.g., increase of acute pain), clinicians should take care in verbal (and nonverbal) communication associated with medical procedures. In general, medical interventions should be accompanied by a reassuring, empathetic and supportive communication (58). Clinical training should include education regarding nocebo responses and strategies to minimize them, consistent with an ethical clinician-patient relationship.

The conditioned hyperalgesia in infants after heel lancing, reported above, is just one example of classically conditioned nocebo responses formed by an unwitting association of

neutral cues with invasive interventions (39). To the extent possible, conditioned development of hyperalgesic effects, with the potential for long-lasting adverse effects of painful experience, should be prevented through an effective management of pain during the invasive painful procedure. These kinds of adverse conditioned responses are not limited to pain or to infants. For example, anticipatory nausea and vomiting triggered by environmental cues may accompany cancer chemotherapy (42). Careful attention to minimizing adverse effects of medical procedures not only contributes to patient comfort but can prevent nocebo responses (59).

In summary, management of verbal communication and contextual cues associated with any treatment, and other aspects of the physician-patient interactions, are important elements of good clinical practice. Potentially promising methods of reducing nocebo effects include strategies of framing information, the authorized concealment approach, educating patients about the possibility of nocebo responses, promoting optimal doctor-patient interactions, and effective management of symptoms. Future empirical research is desirable to assess various communication strategies with respect to generating nocebo responses and their impact on patients' comprehension of what they need to know about adverse effects to make autonomous treatment decisions that reflect their values and preferences.

Conclusions

We have reviewed a diverse range of studies of nocebo responses, which raise important implications for both clinical practice and medical ethics. More clinically-oriented research is needed to assess techniques of clinician-patient interaction that can minimize nocebo effects consistent with informed consent and respect for patient autonomy.

List of abbreviations

N$_2$O	Nitrous Oxide
CCK	Cholecystokinin
SSRI	Selective Serotonin Reuptake Inhibition
TCA	Tricyclic antidepressants
BPH	Benign Prostatic Hyperplasia

Acknowledgments

References

1. Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. Neuron. 2008; 59(2):195–206. [PubMed: 18667148]

2. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. Neuroscience. 2007; 147(2):260–271. [PubMed: 17379417]

3. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002; 287(5):622–627. [PubMed: 11829702]

4. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. Clin Pharmacol Ther. 1987; 42(3):250–253. [PubMed: 3621780]

5. Flaten MA, Simonsen T, Olsen H. Drug-related information generates placebo and nocebo responses that modify the drug response. Psychosom Med. 1999; 61(2):250–255. [PubMed: 10204979]

6. Lancman ME, Asconape JJ, Craven WJ, Howard G, Penry JK. Predictive value of induction of psychogenic seizures by suggestion. Ann Neurol. 1994; 35(3):359–361. [PubMed: 8122889]

7. Luparello TJ, Leist N, Lourie CH, Sweet P. The interaction of psychologic stimuli and pharmacologic agents on airway reactivity in asthmatic subjects. Psychosom Med. 1970; 32(5):509–513. [PubMed: 4097491]

8. Mondaini N, Gontero P, Giubilei G, Lombardi G, Cai T, Gavazzi A, Bartoletti R. Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? J Sex Med. 2007; 4(6):1708–1712. [PubMed: 17655657]

9. 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]

10. Miller FG, Kaptchuk TJ. The power of context: reconceptualizing the placebo effect. J R Soc Med. 2008; 101(5):222–225. [PubMed: 18463276]

11. Lamont EB, Christakis NA. Complexities in prognostication in advanced cancer: "to help them live their lives the way they want to". JAMA. 2003; 290(1):98–104. [PubMed: 12837717]

12. Sakala C. Letter from North America: understanding and minimizing nocebo effects in childbearing women. Birth. 2007; 34(4):348–350. [PubMed: 18021151]

13. Grimes DA, Schulz KF. Nonspecific side effects of oral contraceptives: nocebo or noise? Contraception. 2011; 83:5–9. [PubMed: 21134497]

14. Kennedy WP. The nocebo reaction. Med World. 1961; 95:203–205. [PubMed: 13752532]

15. Kissel, P.; Barrucand, D. Placebos et effet placebo en medecine. Paris: Masson; 1964.

16. Ernst E, Resch KL. Concept of true and perceived placebo effects. BMJ. 1995; 311(7004):551–553. [PubMed: 7663213]

17. Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. Nat Med. 16(11):1277–1283. [PubMed: 20948533]

18. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. Curr Opin Anaesthesiol. 2007; 20(5):435–439. [PubMed: 17873596]

19. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, Evers AW. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011; 152(7):1486–1494. [PubMed: 21353388]

20. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008; 136(1–2):211–218. [PubMed: 18372113]

21. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010; 151(2):430–439. [PubMed: 20817355]

22. Mazzoni G, Foan L, Hyland ME, Kirsch I. The effects of observation and gender on psychogenic symptoms. Health Psychol. 2010; 29(2):181–185. [PubMed: 20230091]

23. Schweiger A, Parducci A. Nocebo: the psychologic induction of pain. Pavlov J Biol Sci. 1981; 16(3):140–143. [PubMed: 7290754]

24. Oftedal G, Straume A, Johnsson A, Stovner LJ. Mobile phone headache: a double blind, sham-controlled provocation study. Cephalalgia. 2007; 27(5):447–455. [PubMed: 17359515]

25. Stovner LJ, Oftedal G, Straume A, Johnsson A. Nocebo as headache trigger: evidence from a sham-controlled provocation study with RF fields. Acta Neurol Scand Suppl. 2008; 188:67–71. [PubMed: 18439225]

26. Dworkin SF, Chen AC, LeResche L, Clark DW. Cognitive reversal of expected nitrous oxide analgesia for acute pain. Anesth Analg. 1983; 62(12):1073–1077. [PubMed: 6650890]

27. Rodriguez-Raecke R, Doganci B, Breimhorst M, Stankewitz A, Buchel C, Birklein F, May A. Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. J Neurosci. 30(34):11363–11368. [PubMed: 20739557]

28. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J Neurosci. 2006; 26(46):12014–12022. [PubMed: 17108175]

29. Doganci B, Breimhorst M, Hondrich M, Rodriguez-Raecke R, May A, Birklein F. Expectations modulate long-term heat pain habituation. Eur J Pain. 2011; 15(4):384–388. [PubMed: 20951617]

30. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, Tracey I. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011; 3(70) 70ra14.

31. Amanzio M, Corazzini LL, Vase L, Benedetti F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain. 2009; 146(3):261–269. [PubMed: 19781854]

32. Reuter U, Sanchez del Rio M, Carpay JA, Boes CJ, Silberstein SD. Placebo adverse events in headache trials: headache as an adverse event of placebo. Cephalalgia. 2003; 23(7):496–503. [PubMed: 12950374]

33. Rief W, Nestoriuc Y, von Lilienfeld-Toal A, Dogan I, Schreiber F, Hofmann SG, Barsky AJ, Avorn J. Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials: a systematic review and meta-analysis. Drug Saf. 2009; 32(11):1041–1056. [PubMed: 19810776]

34. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, Jablonsky G, Kostuk WJ, Melendez LJ, Myers MG, Sackett DL, Sealey BJ, Tanser PH. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med. 1985; 313(22):1369–13675. [PubMed: 3903504]

35. Rief W, Avorn J, Barsky AJ. Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. Arch Intern Med. 2006; 166(2):155–160. [PubMed: 16432082]

36. Cocco G. Erectile dysfunction after therapy with metoprolol: the Hawthorne effect. Cardiology. 2009; 112(3):174–177. [PubMed: 18654082]

37. Silvestri A, Galetta P, Cerquetani E, Marazzi G, Patrizi R, Fini M, Rosano GM. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. Eur Heart J. 2003; 24(21):1928–1932. [PubMed: 14585251]

38. Varelmann D, Pancaro C, Cappiello EC, Camann WR. Nocebo-induced hyperalgesia during local anesthetic injection. Anesth Analg. 2010; 110(3):868–870. [PubMed: 20042440]

39. Taddio A, Shah V, Gilbert-MacLeod C, Katz J. Conditioning and hyperalgesia in newborns exposed to repeated heel lances. JAMA. 2002; 288(7):857–861. [PubMed: 12186603]

40. Liccardi G, Senna G, Russo M, Bonadonna P, Crivellaro M, Dama A, D'Amato M, D'Amato G, Canonica GW, Passalacqua G. Evaluation of the nocebo effect during oral challenge in patients with adverse drug reactions. J Investig Allergol Clin Immunol. 2004; 14(2):104–107.

41. Lombardi C, Gargioni S, Canonica GW, Passalacqua G. The nocebo effect during oral challenge in subjects with adverse drug reactions. Eur Ann Allergy Clin Immunol. 2008; 40(4):138–141. [PubMed: 19227649]

42. Colagiuri B, Zachariae R. Patient Expectancy and Post-chemotherapy Nausea: A Meta-analysis. Ann Behav Med. 2010; 40:3–14. [PubMed: 20387022]

43. de la Cruz M, Hui D, Parsons HA, Bruera E. Placebo and nocebo effects in randomized double-blind clinical trials of agents for the therapy for fatigue in patients with advanced cancer. Cancer. 2010; 116(3):766–774. [PubMed: 19918921]

44. Bovbjerg DH, Redd WH, Jacobsen PB, Manne SL, Taylor KL, Surbone A, Crown JP, Norton L, Gilewski TA, Hudis CA, Reichman BS, Kaufman RJ, Currie VE, Hakes TB. An experimental analysis of classically conditioned nausea during cancer chemotherapy. Psychosom Med. 1992; 54(6):623–637. [PubMed: 1454956]

45. Roscoe JA, O'Neill M, Jean-Pierre P, Heckler CE, Kaptchuk TJ, Bushunow P, Shayne M, Huston A, Qazi R, Smith B. An exploratory study on the effects of an expectancy manipulation on chemotherapy-related nausea. J Pain Symptom Manage. 2010; 40(3):379–390. [PubMed: 20579837]

46. Shelke AR, Roscoe JA, Morrow GR, Colman LK, Banerjee TK, Kirshner JJ. Effect of a nausea expectancy manipulation on chemotherapy-induced nausea: a university of Rochester cancer center community clinical oncology program study. J Pain Symptom Manage. 2008; 35(4):381–387. [PubMed: 18243641]

47. Stockhorst U, Wiener JA, Klosterhalfen S, Klosterhalfen W, Aul C, Steingruber HJ. Effects of overshadowing on conditioned nausea in cancer patients: an experimental study. Physiol Behav. 1998; 64(5):743–753. [PubMed: 9817589]

48. Katz, J. The Silent World of Doctor and Patient. New York: Free Pr; 1984.

49. Berg, JW.; Appelbaum, PS.; Lidz, CW.; Parker, LS. Informed Consent: Legal Theory and Clinical Practice. 2nd ed.. New York: Oxford Univ Pr; 2001.

50. Miller FG, Colloca L. The placebo phenomenon and medical ethics: Rethinking the relationship between informed consent and risk-benefit assessment. Theor Med Bioeth. 2011; 32(4):229–243. [PubMed: 21479794]

51. Edwards A, Elwyn G, Covey J, Matthews E, Pill R. Presenting risk information--a review of the effects of "framing" and other manipulations on patient outcomes. J Health Commun. 2001; 6(1): 61–82. [PubMed: 11317424]

52. O'Connor AM, Pennie RA, Dales RE. Framing effects on expectations, decisions, and side effects experienced: the case of influenza immunization. J Clin Epidemiol. 1996; 49(11):1271–1276. [PubMed: 8892495]

53. Dworkin, G. The Theory and Practice of Autonomy. Cambridge: Cambridge University Press; 1988.

54. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of Postoperative Pain by Encouragement and Instruction of Patients. A Study of Doctor-Patient Rapport. N Engl J Med. 1964; 270:825–827. [PubMed: 14108087]

55. Gracely RH, Dubner R, Deeter WR, Wolskee PJ. Clinicians' expectations influence placebo analgesia. Lancet. 1985; 1(8419):43. [PubMed: 2856960]

56. Greenfield S, Kaplan S, Ware JE Jr. Expanding patient involvement in care. Effects on patient outcomes. Ann Intern Med. 1985; 102(4):520–528. [PubMed: 3977198]

57. Kaplan SH, Greenfield S, Ware JE Jr. Assessing the effects of physician-patient interactions on the outcomes of chronic disease. Med Care. 1989; 27(3 Suppl):S110–S127. [PubMed: 2646486]

58. Brewin TB. Three ways of giving bad news. Lancet. 1991; 337(8751):1207–1209. [PubMed: 1673749]

59. Petrie KJ, Muller JT, Schirmbeck F, Donkin L, Broadbent E, Ellis CJ, Gamble G, Rief W. Effect of providing information about normal test results on patients' reassurance: randomised controlled trial. BMJ. 2007; 334(7589):7352.