REVIEW ARTICLE

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Placebo and Nocebo Effects

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Placebo and nocebo effects are the effects of patients' positive and negative expectations, respectively, concerning their state of health.[1,2] These effects occur in many clinical contexts, including treatment with an active agent or a placebo in clinical practice or in a clinical trial, the informed-consent process, the provision of information about medical treatments, and public health campaigns. Placebo effects cause beneficial outcomes, and nocebo effects cause harmful and dangerous outcomes.

Variation in the ways that patients respond to treatments and experience symptoms is partly attributable to placebo and nocebo effects.[3-6] The frequency and intensity of placebo effects in clinical practice are difficult to determine, and the range of effects in experimental settings is wide.[7] In many double-blind clinical trials of treatments for pain[8] or psychiatric disorders,[9] for example, the responses to placebo are similar to the responses to active treatment, and up to 19% of adults and 26% of elderly persons taking placebos report side effects.[10] Furthermore, as many as one quarter of patients receiving placebo in clinical trials discontinue it because of side effects,[11,12] suggesting that a nocebo effect may contribute to discontinuation of or lack of adherence to active treatments.

Neurobiologic Mechanisms of Placebo and Nocebo Effects

Placebo effects have been shown to be associated with the release of substances such as endogenous opioids,[13,14] endocannabinoids,[15] dopamine,[16,17] oxytocin,[18] and vasopressin.[19] The effects of each of these substances is specific to the target system (i.e., pain, motor, or immune system) and the illness (e.g., arthritis or Parkinson's disease). For example, dopamine release plays a role in placebo effects of treatment for Parkinson's disease[16,17] but not in placebo effects of treatment for chronic pain[20] or acute pain.[21]

Exacerbation of experimentally produced pain through verbal suggestion, a nocebo effect, has been shown to be mediated by the neuropeptide cholecystokinin[22] and blocked by proglumide, a mixed cholecystokinin type A and type B receptor antagonist.[22,23] This type of verbally induced hyperalgesia has been associated with increased activity of the hypothalamic–pituitary–adrenal axis in healthy persons. Both hyperalgesia and hypothalamic–pituitary–adrenal hyperactivity are antagonized by the benzodiazepine diazepam, suggesting a role of anxiety in these nocebo effects. However, proglumide blocks hyperalgesia but not hypothalamic–pituitary–adrenal hyperactivity, which suggests involvement of the cholecystokinin system in the hyperalgesia component of the nocebo effect but not in the anxiety component.[22] Genetic influences on placebo and nocebo effects have been linked to haplotypes of single-nucleotide polymorphisms in the dopamine, opioid, and endocannabinoid genes.[24-26]

A participant-level meta-analysis of 20 functional neuroimaging studies in 603

healthy participants indicated that placebo effects related to pain have only small effects on the functional imaging correlates of pain,[27] termed "neurologic pain signature."[28] Placebo effects are likely to act at the level of several brain networks that subserve affect and the influence of affect on the multidetermined subjective experience of pain. Brain and spinal cord imaging have shown that nocebo effects cause increased pain signaling from the spinal cord to the brain.[29,30] In experiments that tested the response to placebo creams that were described as causing pain and were labeled as having either high or low prices, regions for pain transmission in the brain and spinal cord were activated when people expected that they would have more pain with a higher-priced treatment.[29] Similarly, some experiments tested pain that was induced by heat and ameliorated by the potent opioid remifentanil; in participants who believed that remifentanil had been stopped, the hippocampus was activated and a nocebo effect blocked the therapeutic efficacy of the drug, suggesting a role of stress and memory in this effect.[31]

EXPECTATIONS, VERBAL SUGGESTION, AND FRAMING EFFECTS

The molecular events and neural network changes underlying placebo and nocebo effects are mediated by expectancies, or anticipated future outcomes. When expectancies are accessible consciously, they are called expectations, which can be measured and are affected by changes in perception and cognition. Expectations can be acquired in a number of ways, including prior experience of medication effects and of side effects (e.g., analgesia after taking a medication), verbal instructions (e.g., being told that a medication will reduce pain), or social observation (e.g., directly observing symptom relief in another person taking the same medication).[6,32-34] However, some expectancies and placebo and nocebo effects are not accessible consciously. For example, it is possible to condition an immunosuppressive response in patients who have undergone renal transplantation.[35] This has been shown by administering a neutral stimulus that was previously paired with an immunosuppressive agent. Administration of the neutral stimulus alone results in a reduction in T-cell proliferation.[35]

In clinical settings, expectancies are affected by the way in which a medication is described, or "framed." In postoperative settings, morphine administered along with the instructions "the treatment that you are about to receive is potent in relieving your pain" induced a substantially greater benefit than covert administration in which the patient was unaware of the timing of the administration.[36] A direct suggestion of side effects can also become self-fulfilling. In a study involving patients taking the beta-blocker atenolol for cardiac disease and hypertension, the incidence of sexual side effects and erectile dysfunction among patients who were specifically informed of these potential side effects was 31%, as compared with an incidence of 16% among those who were not told of the side effects.[37] Similarly, among patients taking finasteride for benign prostatic hypertrophy, 43% of patients who were informed explicitly of the sexual side effects had side effects, as compared with 15% of those who were not informed of them.[38] In a study involving patients with asthma who inhaled nebulized saline and were informed that it was an allergen, approximately half the patients had dyspnea, increased airway resistance, and decreased vital capacity.[39] And among persons with asthma who inhaled an active bronchoconstrictor, dyspnea and airway resistance were more severe in those who were told it was a bronchoconstrictor than in those who were told it was a bronchodilator.[40]

Furthermore, verbally induced expectancies can elicit specific symptoms such as pain,[23] itchiness,[22] and nausea.[41] After verbal suggestion, a stimulus associated with low-intensity pain can be experienced as high-intensity pain, and tactile stimulation can be experienced as painful.[23] In addition to inducing or exacerbating symptoms, negative expectations diminish the therapeutic efficacy of active medications. The effect of a topical analgesic can be blocked by falsely informing patients that the drug will worsen rather than alleviate their pain.[26] Falsely labeling rizatriptan, a serotonin (5-hydroxytryptamine) receptor agonist, as placebo can reduce its efficacy against migraine attacks[42]; similarly, negative expectancy can prevent the analgesic effect of an opioid on experimentally induced pain.[28]

LEARNING MECHANISMS IN PLACEBO AND NOCEBO EFFECTS

Learning and classical conditioning play roles in both placebo and nocebo effects. There are many clinical situations in which neutral stimuli

that have previously been associated with either beneficial or adverse drug effects through classical conditioning subsequently evoke the benefit or the side effects without administration of the active drug.[29]

For example, when environmental cues[43] or gustatory cues[44] are repetitively paired with morphine, the same cues subsequently paired with placebo rather than with morphine can produce analgesia.[45] Among patients with psoriasis in whom reduced glucocorticoid doses were interspaced with placebo (so-called dose-extending placebo[46]), relapse rates were similar to the rates among patients who received the full dose of glucocorticoids.[47] In a control group of patients who underwent the same glucocorticoid tapering regimen but without interspersed placebo, the relapse rate was three times as high as the rate in the group that received dose-extending placebo. Similar conditioned effects have been reported for the treatment of chronic insomnia[48] and for amphetamine treatment in children with attention deficit–hyperactivity disorder.[49]

Prior therapeutic experiences and learning mechanisms also drive nocebo effects. Thirty percent of women undergoing chemotherapy for breast cancer have anticipatory nausea when exposed to a previously neutral environmental cue that they have come to associate with the infusions, such as traveling to the hospital, encountering the medical personnel, or entering a room that resembles the infusion room.[50] After repeated venipunctures, neonates cry and show pain behaviors as soon as their skin is cleansed with alcohol before the phlebotomy.[51] Asthma attacks can be precipitated by showing an allergen in a sealed container to patients with asthma.[52] A liquid with a characteristic taste and no beneficial biologic effects that is given with an active drug that has prominent side effects (e.g., a tricyclic antidepressant) can elicit those side effects when the liquid is given with a placebo.[53] Visual cues such as lights and images that are paired with experimentally induced pain can subsequently trigger pain when they are provided alone.[54,55]

Learning about the experience of others can lead to placebo and nocebo effects. Observing pain relief in someone else elicits placebo analgesic effects[56,57] that are similar in magnitude to the analgesic effects induced by previous firsthand therapy.[57-61] There is experimental evidence that social context and modeling can induce side effects. For example, witnessing a person who reports side effects of a placebo, reports pain from the application of an inert ointment, or inhales room air that is described as "potentially toxic" causes side effects in study participants who are exposed to the same placebo, inert ointment, or room air.[59,62]

Reports in the mass media and lay press, information obtained from the Internet, and direct exposure to others who are having symptoms all foster nocebo responses.[63] For example, the rates of reported adverse effects of statins have been associated with the intensity of negative statin-related media coverage.[64,65] In a particularly vivid example, negative stories in the press and on television about harmful changes in the formulation of a thyroid medication were followed by an increase by a factor of 2000 in the number of reported adverse events, and the increase occurred only in the specific symptoms featured in the publicity.[66] Likewise, publicity campaigns that lead community residents to mistakenly believe they have been exposed to a toxic substance or hazardous waste are followed by an increased incidence of symptoms that the residents ascribe to the supposed exposure.[63,67]

IMPLICATIONS OF PLACEBO AND NOCEBO EFFECTS FOR RESEARCH AND CLINICAL PRACTICE

It may be helpful at the outset of treatment to identify persons who are more likely to have placebo and nocebo effects. Some of the characteristics that are associated with these responses are known, but future studies could provide better empirical evidence for these features. Optimism and suggestibility do not appear to be closely associated with placebo responsiveness.[68] There is some evidence that among persons taking active drugs, the nocebo effect is more likely to occur in those who are more anxious,[69] have a history of medically unexplained symptoms,[70] or have greater psychological distress.[71] Evidence of the role of sex in placebo or nocebo effects is not conclusive.[62] Imaging, polygenic risk, genome-wide association studies, and twin studies could help elucidate how brain mechanisms and inheritance contribute to biologic changes that underlie placebo and nocebo effects.

The interaction between the patient and the

clinician influences the likelihood of placebo effects[72] and the reporting of side effects of placebos and active drugs.[49] Trust in the clinician and a positive relationship, with open communication between patient and physician, have been shown to palliate symptoms. Thus, patients with common colds who perceive their clinicians as empathetic report symptoms that are less severe and of shorter duration than those of patients who do not perceive their clinicians as empathetic; patients who perceive their clinicians as empathetic also have reduced levels of objective measures of inflammation such as interleukin-8 and neutrophil counts.[73] Positive expectations on the part of the clinician also play a role in the placebo effect. A small study comparing narcotic analgesic treatment with placebo after dental extraction showed that the physician's knowledge that the patient was receiving the analgesic agent was associated with greater pain relief.[74]

One way to capitalize on placebo effects in a nonpaternalistic manner in order to enhance therapeutic outcomes is to describe treatments in a realistic yet positive way. Heightened expectations of a treatment benefit have been shown to increase the response to morphine, diazepam, deep-brain stimulation,[36] intravenous remifentanil,[31] topical lidocaine,[75] complementary and integrative approaches (e.g., acupuncture[76]), and even surgical interventions.[77]

Exploration of the patient's expectations can be a starting point for routinely incorporating these expectations into clinical practice. Expectations can be clinically evaluated by asking the patient to rate expectations about a benefit of treatment on a scale from 0 (no benefit) to 100 (maximum imaginable benefit).[78] Helping patients to understand their expectations of elective cardiac surgery reduced disability outcomes 6 months after surgery,[79] and educating patients about coping strategies before they underwent intraabdominal surgery resulted in a significant 50% reduction in postoperative pain and narcotic use.[80] These framing effects can be used by providing information not only about the appropriateness of a given treatment but also about the proportion of patients who benefit from it.[81] For example, patient-controlled postoperative analgesic requirements can be diminished by emphasizing the effectiveness of the medication being administered.[81]

There may be other ethically acceptable ways of capitalizing on the placebo effect in clinical practice. Some research supports the efficacy of an "open-label placebo" approach, in which the treatment effect of an active drug is enhanced by concurrently administering a placebo and informing the patient (truthfully) that the addition of a placebo has been shown to enhance the beneficial effects of active drugs.[82] It may also be possible to use conditioning effects to sustain the effect of an active drug while progressively decreasing the dose by pairing the drug with a sensory cue, a conditioning process that would be particularly advantageous for drugs that are toxic or addictive.

In contrast, worrisome information, mistaken beliefs, pessimistic expectations, negative prior experiences, social messaging, and the therapeutic milieu can lead to side effects and can reduce the benefits of symptomatic and palliative treatments. Nonspecific side effects of active drugs (side effects that are intermittent, idiosyncratic, not dose-dependent, and not reliably reproducible) are common.[83,84] Such side effects lead to nonadherence to the prescribed regimen (or drug discontinuation), substitution of another agent, or additional medications to treat the effects. Although more research is necessary to establish a definitive link, these nonspecific side effects are probably attributable to the nocebo effect.

Closely coupling information about side effects with information about benefits can be helpful,[85] as can describing side effects in a supportive yet nondeceptive way. For example, presenting the proportion of patients who do not have the side effects, instead of the proportion of patients who do, reduces the incidence of such effects.[86]

Physicians are obligated to obtain valid informed consent from patients before administering treatment. As part of the informed-consent process, physicians are expected to provide complete information to help patients make informed decisions about treatment. All potentially dangerous and medically significant side effects must be clearly and accurately described, and patients are instructed to report all side effects. Since enumerating benign, nonspecific side effects that are not of medical concern makes them more likely to occur, however, physicians face a dilemma. One potential solution is to educate patients about the nocebo effect and

Table 1. Implications of Placebo and Nocebo Effects for Research, Clinical Practice, and Clinical Trials.

Laboratory, genetic, and other investigations
Assess placebo and nocebo effects and include the appropriate control groups (including a no-intervention group when feasible) in designing laboratory studies
Explore the molecular and genetic mechanisms underlying placebo and nocebo effects (e.g., use genomic investigations and animal models)
Conduct large studies that allow clustering and machine-learning approaches to better understand the driving factors for individual placebo and nocebo responsiveness
Recommend replication studies and data sharing for creating large data sets to improve phenotype discoveries
Clinical practice
Become familiar with the mechanisms of placebo and nocebo effects
Present patients with the mechanisms of placebo and nocebo effects as a basis for promoting healing processes
Favor positive associations and minimize negative associations between the therapeutic intervention and contextual factors
Consider administering interventions in a positive context, suggesting coping strategies and providing multisensory cues (e.g., sight, smell, and taste stimulations associated with the active medication) to promote conditioning
Encourage patients to recount their previous positive or negative experiences with interventions
Present patients with realistic possible effects of the intervention to avoid a discrepancy between what is expected and what actually occurs[94]
Collect information about patients' expectations concerning treatment and outcomes as part of the medical history
Encourage discussion to align patients' expectations with anticipated therapeutic outcomes
Frame information about side effects in such a way as to minimize nocebo effects
Use communication strategies to reduce the likelihood of nonadherence to the treatment regimen or discontinuation of the drug
Consider using educational strategies (e.g., video clips of patients recounting positive treatment experiences) to improve outcomes
Clinical trials
Ask patients at baseline how much improvement they would expect from the active treatment
Ask patients whether they believe they received the active treatment (assessment of group assignment)
Standardize the language used to present the benefit–risk profile of the intervention under investigation
Standardize the duration and number of therapeutic visits across study sites
Standardize framing strategies used to present information about side effects
Standardize questions and use structured checklists to collect data on side effects

then ask whether, in light of that effect, they wish to be informed of the benign, nonspecific side effects of a treatment. This approach has been termed "contextualized informed consent"[87] and "authorized concealment."[84]

Since mistaken beliefs, worrisome expectations, and prior negative medication experiences can produce nocebo effects, exploring them with patients may be helpful. What prior bothersome or dangerous side effects have they had? What worried them about the side effects? If they are currently troubled by benign side effects, what do they presume is the significance of the side effects? Does the patient expect them to worsen over time? Answers to these questions may enable the physician to allay the patient's concern about a side effect, thereby making it more tolerable. Reassurance that a side effect may be bothersome but is not harmful or medically dangerous may relieve the anxiety that is contributing to it. Conversely, patient–clinician interactions that fail to assuage the patient's anxiety, or that even heighten it, amplify side effects. A qualitative review of experimental and clinical studies has suggested that negative nonverbal behaviors and a cold communication style (e.g., not making empathetic remarks, not making eye contact with the patient, speaking in a

monotone, and not smiling) contribute to nocebo effects, lead to lower pain tolerance, and diminish placebo effects.[88] Putative side effects often turn out to be preexisting symptoms that were ignored or dismissed and that have now been attributed to the drug. Correcting this misattribution can make the drug more tolerable.

Reported side effects can be a covert, nonverbal expression of doubts, reservations, or anxiety about the medication, the regimen, or the doctor's expertise.[2] Side effects provide a less embarrassing and more acceptable reason for discontinuing a medication than explicitly confronting the clinician with misgivings. In these situations, elucidating and openly discussing the patient's concerns may prevent drug discontinuation or nonadherence to the treatment regimen.

Research on placebo and nocebo effects has implications for the design and conduct of clinical trials, as well as interpretation of the findings. First, when feasible, clinical trials should include a no-intervention group to account for confounding factors related to placebo and nocebo effects, such as regression of symptoms to the mean.[89] Second, the longitudinal design of a trial influences the rate of occurrence of placebo responses,[90,91] particularly with crossover designs, because positive prior experience creates expectations in persons who receive the active drug first, rather than placebo first.[92] Since informing patients about specific benefits and side effects of treatment may increase their incidence, information about benefits and side effects provided during the informed-consent process should ideally be uniform across trials investigating a particular agent. Caution is needed in interpreting the results of meta-analyses that lack such uniformity of information. The research personnel who collect data on side effects should ideally be unaware not only of treatment assignments but also of side-effect profiles. A structured symptom inventory is preferable to open-ended inquiry for the collection of side-effect data.[93] The implications of the placebo and nocebo phenomena for neurobiologic research, clinical practice, and the design and conduct of clinical trials are outlined in Table 1.

CONCLUSIONS

Placebo and nocebo effects are powerful, pervasive, and common in clinical practice. Neurobiologic mechanisms, information offered in relation to treatment, patients' expectations, previous encounters with a drug or procedure, and the therapeutic milieu can all generate these effects. Strategies to promote placebo effects and to prevent nocebo effects can improve therapeutic outcomes and minimize the unintended exacerbation of symptoms in clinical practice and clinical trials.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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