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Kathryn T. Hall, Alia J. Crum

Placebo and Nocebo

Effects Placebos are sham versions of drugs, devices, or surgeries that lack the active compound, function, or procedure they are designed to simulate (Table 496-1). Administration of these “inactive” treatments can have significant therapeutic benefits called placebo effects, which accounts for their use as controls in clinical trials as comparators for active drugs, devices, or surgical interventions. Key drivers of placebo effects include the patient’s expectation and conscious or subconscious conditioning. Psychological studies demonstrated that expectations are shaped by factors intrinsic to the patient, including their past experi ences and core beliefs or mindsets, and extrinsic factors including environmental cues (e.g., white coat), clinical practice (e.g., physi cal examination), and information received about a treatment (e.g., expected benefits or side effects). Neuroimaging studies have identified consistent changes in the brain in response to placebo treatment that suggest that placebo effects work by integrating incoming information about extrinsic factors with prior experience and mindsets to update expectations of treatment benefit. When expectations are negative, TABLE 496-1 Glossary of Terms commonly used in Placebo Studies PART 20 Emerging Topics in Clinical Medicine TERM DEFINITION Additivity in clinical trials The assumption that placebo and drug treatment responses are additive is a fundamental assumption in clinical trials. However, there are notable exceptions to this assumption in pharmacogenomic and brain imaging studies where subsets of the population have been reported to have differential effects in placebo and drug treatment arms of a trial. Development and culture Our caregivers and social environment influence the psychological processes that underlie the placebo effect. These processes are continuously shaped throughout life by the ideas, institutions, and interactions that constitute the culture in which we live. Expectation A specific belief about the future based on a prediction of what is most likely to happen. Examples: “This drug will relieve my pain”; “I will experience side effects.” Gene-(drug/placebo) interaction Pharmacogenomic analysis has identified clinical trials in asthma, depression, pain, chronic fatigue, and cognitive function in which there are subpopulations based on genotype that have differential associations in the drug and placebo treatment arms. These differential effects often result in significant gene-(drug/placebo) interaction effects. Implicit learning The nonconscious acquisition of knowledge. Classical conditioning, a form of implicit learning, is implicated in certain instances of

the placebo effect (e.g., implicit association of sleepiness with the administration of blue pills). Mindset Core belief about a domain or category that orients an individual to a particular set of beliefs, associations, and expectations, and functions to guide attentional and motivational processes (e.g., “cancer is a catastrophe”; “symptoms are signs of efficacy”). Neurobiological mechanisms Dopamine, endogenous opioids, and endocannabinoids are three of the major neurotransmitter systems implicated in moderating the placebo effect. Placebo effects also work by activating biological properties of the body that facilitate healing, including homeostatic mechanisms and immune and inflammatory responses. These contribute to the natural history of a disease but can also be targets of placebo effects. Nocebo effect Sides effect or negative change in clinical outcome observed after exposure to negative information, interactions, or cues that can induce negative expectations. Open-label placebos (OLPs) OLPs are placebos administered to patients with their full knowledge that the treatment lacks the active pharmaceutical agent. OLP clinical trials have been conducted in irritable bowel syndrome, chronic back pain, allergic rhinitis, cancer-related fatigue, attention deficit hyperactivity disorder, major depression, and menopausal hot flushes. Meta-analysis of OLP trials found a significant overall effect. Patient-clinician relationship The patient-clinician relationship shapes the mindsets and expectations a patient holds about health, illness, and treatments, and affects the quality of care a patient receives. This relationship is influenced by the warmth and competence of the provider and is further shaped by characteristics like empathy and trust. Placebo Placebos are sham versions of drugs, devices, or surgeries that lack the active compound, function, or procedure they are designed to simulate. Placebos are often used in clinical trials as controls for placebo effects, natural history, regression to the mean, spontaneous remission, and Hawthorne effects (the tendency for people to change their behaviors when being observed). Placebo effect Positive change in clinical outcome observed after a placebo treatment; an exclusively attributed expectation mediated by psychological, neurological, or physiological placebo mechanisms. Placebo response Improvement observed among patients assigned to placebo treatment in a clinical trial. Placebome The genome-related products that modify placebo response. Several genes in neurotransmitter and other pathways have been implicated in modifying response to placebo treatment in clinical trials. The most well-studied of these is in the gene encoding catechol-Omethyltransferase (COMT). Social and observational learning Learning through direct observation of others undergoing treatment (i.e., other patients) and interactions with individuals who weild influence over the patient (i.e., physicians and nurses) both may powerfully drive placebo effects. Treatment characteristics The specific characteristics include factors like the shape, color, and labeling of the treatment; the method of administration; and the physical environment in which the treatment is administered.

they can result in negative outcomes, termed, “nocebo effects.” For many years, placebo effects were viewed as superfluous nuisance variables to be ignored, marginalized, and simply “controlled for” in clinical trials. With advances in psychology and neuroscience stud ies of placebo effects, the value of understanding their mechanism of action and harnessing these effects in clinical care and clinical trials has become increasingly apparent. INTRODUCTION TO PLACEBO EFFECTS:

A BRIEF HISTORY The word “placebo,” derived from the Latin placere, “to please,” first appeared in medical literature in clinical lectures of William Cul len, a leading physician in the eighteenth century. In 1792 he wrote, “I prescribed therefore in pure placebo, but I make it a rule even in employing placebos to give what would have a tendency to be of use to the patient.” Cullen was describing placebos being used to please, rather than treat; however, use of placebos was

commonplace at that time, especially when effective therapies were exhausted or unavailable. From the late eighteenth through the early twentieth centuries, sham treatments were also used to expose some unorthodox treatments as frauds—or, at least, as no better than placebos. In his highly publicized 1784 study of “animal magnetism,” a therapy developed by Austrian physician Anton Mesmer, Benjamin Franklin and a team of leading scientists in France simulated Mesmer’s elaborate rituals using fake practitioners and sham magnetism. This early placebo-controlled trial

demonstrated that the hugely popular and remarkably effective treat ment was no better than a placebo. Early trialists attributed the positive benefits of these therapies to the power of the “imagination,” reinforc ing the belief that placebo treatments were the product of wayward physicians, or “quacks,” who tricked gullible patients. After World War II, advances in metabolism, physiology, and clini cal pharmacology created a growing need for clinical trials to evaluate novel compounds for their ability to kill pathogens and alter disease processes. By the 1960s, the Declaration of Helsinki and KefauverHarris Amendments, introduced to protect patient safety by requiring informed consent, rendered use of placebos and the deception histori cally thought to promote placebo effects unethical, institutionalizing the transformation of placebos from salve to epistemic tool. Together, placebo controls, double-blinding, and randomization are considered the gold standard for acquiring the strongest evidence of efficacy or lack of efficacy for novel treatments. Notably, placebos are rarely used in trials of serious illnesses like cancer or when an effective treatment already exists. Then their use is limited to comparing novel treatments to standard of care plus placebo. In randomized placebo-controlled clinical trials, the effect of the drug is calculated by simply subtracting outcomes in the placebo treatment arm or placebo response from the drug response (Fig. 496-1A). Hence, in addition to controlling for placebo effects, placebos control for changes in the outcome of interest due to natural history (the tendency for a common cold to resolve on its own in 7–10 days), regression to the mean (a statistical phenomenon where extreme baseline measures tend to move toward the group mean), and the Hawthorne effect (the tendency for people to change behaviors when being observed). These variables, together with placebo effects, make up the placebo response. If the active treatment being tested significantly outperforms the pla cebo response, it is deemed efficacious and can progress through the U.S. Food and Drug Administration (FDA) approval process. However, if response to the drug is not statistically significantly greater than the placebo response, the active treatment is deemed lacking in efficacy. Clinical trials’ limited view of placebos obscures the reality that the effects associated with placebos are not, in practice, superfluous. Indeed, the effects of patient psychology (e.g., expectations, mindsets) and the social and cultural context (e.g., a clinician’s demeanor and drug label and advertising information) have a meaningful impact on health outcomes that warrant a more complete understanding. In addition, the effects of these factors are difficult to isolate. In fact, the total response to drug is the product of both the drug and the social and psychological context interacting with patient biology to bring about change (Fig. 496-1B). This perspective propels us into a new era of understanding placebo effects: not as treatment alternatives or as something to subtract, but as psychological, social, and biological mechanisms that can be considered an integral component of the overall treatment effect in medicine. By understanding placebo effects in this manner, we can optimize their benefits to improving drug discovery, maximizing existing treatments, and minimizing nocebo consequences to reduce harm. PLACEBO RESPONSE IN CLINICAL TRIALS Placebo effects, although often thought of in the context of a placebo pill, extend to many other treatment modalities, including sham surgeries, placebo acupuncture, and placebo diets. They have been documented in numerous

conditions and diseases, including pain, depression, Parkinson’s disease, anxiety disorders, cardiovascular dis orders, cancer-related fatigue, asthma, and gastrointestinal disorders. Not limited to patient-reported outcomes, placebo effects can affect objective physiologic outcomes, including blood pressure measure ments, immune biomarker levels, exercise endurance, and cognitive test scores. Recently, clinical trial sponsors have invested considerable resources in reducing the impact of placebo response by adjusting patient-level variables, such as reducing patient-clinician interactions and reducing patient expectations by providing neutral information about expected benefits and side effects. In conditions like Alzheimer’s disease, trial ists have modeled placebo response over time and set the optimal

treatment duration length to the time period beyond the 8-week period when placebo response is maximal. The placebo run-in design attempts to eliminate the influence of placebo responders by assigning all enrolled blinded patients to a placebo at the beginning of a study; patients who respond to placebo are subsequently excluded. Other more complex models, such as the sequential parallel comparison design (SPCD), randomize patients to placebo or drug at a ratio of 2:1. After a brief treatment period, placebo nonresponders are rerandom ized to placebo or drug. Unlike placebo run-ins, SPCD uses all patients and, thus, should have greater power to find an effect. Still, despite these and other considerable investments, no approach reliably reduces the impact of placebo response on clinical trial failure.

MECHANISMS OF PLACEBO EFFECTS ■ ■PSYCHOLOGICAL MECHANISMS Expectations Expectations, or beliefs about the likelihood of future events, are thought to be the key driver of placebo effects. Expecta tions can be conscious; for example, many patients expect nonsteroidal anti-inflammatory drugs (NSAIDs) will relieve pain, melatonin will improve sleep, and beta blockers will reduce anxiety. Expectations can also be consciously or subconsciously conditioned. Repeated use of blue sleeping pills can induce sleepiness by taking a blue placebo pill. Multiple sclerosis patients who received the immunosuppressant cyclophosphamide paired with flavored syrup later displayed drugconsistent immune responses to the flavored syrup alone. Obser vational learning can also play a role in eliciting placebo effects by altering expectations. Watching another person experience pain relief in response to a particular treatment can lead the observer to expect to experience similar relief, even if the stimulus is a placebo in both cases. CHAPTER 496 Mindsets Mindsets are core beliefs about a broader domain or category, such as the meaning of side effects or the nature of a disease or treatment. Mindsets orient individuals to a set of associations, expectations, and goals. A mindset such as “cancer is a catastrophe,” “statins are harmful,” or “my body is permanently damaged” can shape a patient’s experience of pain or other side effects. While mindsets and expectations are related, they are not identical. For example, a patient in pain may have the specific expectation that a treatment will relieve their pain. But they also could have broader mindsets in which those expectations are operating, such as “injections don’t work,” “my condi tion is hopeless,” or “I am in good hands.” Placebo and Nocebo Effects While specific expectations can be measured and assumed to influ ence placebo effects in studies, mindsets may be particularly powerful in the real-world practice of medicine where individual expectations do not exist in isolation. Mindsets may also be advantageous when con sidering how to harness placebo and minimize nocebo effects ethically. ■ ■SOCIAL AND CULTURAL MECHANISMS Language and Information Patients’ implicit or explicit pre existing mindsets, shaped by the broader culture in which they were raised and/or reside, can be updated and informed through verbal instructions. In “open-hidden design” studies, medication adminis tered openly by a health care professional who

informs the patient that they will experience benefit (e.g., “I’m going to administer a dose of morphine, a powerful painkiller that will alleviate your pain”) has a significantly greater analgesic effect compared to administering the same dose from a hidden pump without the patient’s knowledge. Thus, even potent opioid analgesics lose as much as 30% of their efficacy if the patient is unaware that they received the treatment. Effects of openhidden paradigms are also seen with objective outcomes, such as heart rate. Information is conveyed not just by a clinician’s words but also through information in the health care context more broadly, such as advertising and media related to drugs and health. Clinician Characteristics Beyond what the patient is told, trust in the source of information can also influence clinical outcomes. Socialpsychological research has shown that two qualities are key: patients’ perceptions of competence, or whether a physician “gets it” (i.e.,

Treatment Response Drug Effect

Placebo Response

DRUG PLACEBO Clinical Trials Clinical Practice A PART 20 Emerging Topics in Clinical Medicine

Treatment Response

DRUG a/a PLACEBO a/a DRUG PLACEBO DRUG PLACEBO WHAT WE EXPECT TO SEE WHAT WE OFTEN SEE WHAT WE SEE WITH PHARMACOGENETICS B FIGURE 496-1 A. Additivity of drug and placebo response in a clinical trial. B. (1) What we expect to see: Expected outcomes from the classic view of clinical trials in which the effect of the drug exceeds placebo response. (2) What we often see: Typical results from a clinical trial in which there is no significant difference between the drug and placebo responses. (3) What we can see with pharmacogenomics: Pharmacogenomic analysis demonstrating differential effects of a genetic locus in the drug and placebo arms of a trial such that the drug effect and placebo response of one version of a variant (patients who are homozygous for the “A” allele, A/A) are opposite that of homozygotes of the alternate allele at that locus (patients who homozygous for the “a” allele, a/a). The average effects of outcomes of the two subpopulations cancel each other to give the results we often see. displays of efficiency, knowledge, and skill), and patients’ perceptions of warmth, or whether a physician “gets me” (i.e., displays of personal engagement, connection, and care for the patient). Patients’ assessments of clinician warmth and competence shape their treatment expectations and impact their mindsets about illness and, therefore, can influence placebo effects. In one study, an allergic

Drug Effects Pharmaceutical or physical properties of drug or intervention Placebo Effects PSYCHOLOGICAL MECHANISMS

• Expectations

• Mindsets

• Implicit Learning SOCIAL AND CULTURAL MECHANISMS

• Language and information

• Clinician characteristics

• Symbols

• Rituals

• Environmental Cues BIOLOGICAL MECHANISMS

• Genetic predispositions

• Neurobiological processes Other Effects OTHER EFFECTS THAT CAN INFLUENCE PLACEBO RESPONSE in TRIALS

• Statistical regression to mean

• Blinding and bias

• Informed consent and uncertainty

• Hawthorn Effects TREATMENT Placebo responder Drug responder (but drugnonresponder) (but placebononresponder) DRUG A/A PLACEBO A/A reaction was induced in participants via a histamine skin prick fol lowed by the administration of a placebo cream. The information about the cream was varied to create either positive expectations (“this cream will reduce your rash and irritation”) or negative expectations (“this cream may worsen your symptoms”). When the ensuing wheal was measured 10 min later, the difference in information alone produced

differences in the size of the allergic reaction. Interestingly, the effect of the information differed depending on perceived clinician warmth and competence. When the physician exhibited cues of both compe tence (e.g., wearing a white coat with a badge that read “Fellow at the Stanford Allergy Center”) and warmth (e.g., making eye contact with the patient), the effect of the spoken message was significantly enhanced. However, when social cues were changed to induce ques tions about the level of competence (e.g., badge read “Student Doctor”) and warmth (e.g., staring at a computer screen or making a personal connection), the information about the cream no longer mattered: both placebo and nocebo effects were minimized. There is no one right way to signal warmth and competence, but there are many ways to fail to convey these qualities and, therefore, lose patients’ trust. Indications of warmth and competence are important for building patients’ trust not only with their medical providers but also with the broader clinic, hospital, or health care system. Trust in the social context can magnify placebo effects or minimize nocebo effects; it can also have a direct effect on patient care, influencing a wide array of outcomes, such as metabolic complications, immune response, symptoms, and adherence to medication. Symbols, Rituals, and Environmental Cues Medical treat ment occurs within a rich context of environmental cues, symbols, and rituals. Many patients, for example, exhibit a transient (albeit substan tial) rise in blood pressure when in a medical setting, a phenomenon known as the “white coat” hypertension. Seemingly inconsequential characteristics of a drug, such as color, drug brand name, and cost, have been found to impact treatment efficacy. Patients tend to perceive capsules as stronger and more effective than tablets and tend to have a reduced response to placebos referred to as discounted or generic. In a within-subjects, repeated-measures study to examine drug labeling in

migraine, patients were given either placebo or 10-mg rizatriptan labeled to create three information conditions ranging from negative (“placebo”), to neutral (“Maxalt or placebo”) to positive (“Maxalt”). While patients had significantly greater relief from Maxalt labeled as Maxalt compared to placebo labeled as placebo, there was no difference in the effect of Maxalt labeled as placebo compared to placebo labeled as Maxalt. These findings demonstrate the ability of labeling and brand names to influence the effect of a drug. Interestingly, drug companies have increased their use of the letters X and Z in drug names as stud ies show these visually distinct letters have fewer negative associations with other medications. Furthermore, marketing research has found Z is associated with efficacy, whereas T and S are associated with greater tolerability. ■ ■BIOLOGICAL MECHANISMS Pharmacologic evidence from the 1970s showing that naloxone, an opioid antagonist, could abrogate placebo effects in the experience of pain after molar tooth extraction laid the groundwork for demonstrat ing that psychological forces could affect patient physiology. Early neuroimaging studies revealed the release of endogenous opioids and dopamine signaling proportionate to the expectation and perception of how well a given placebo intervention worked. Using models of placebo analgesia, neuroscientists imaged the brains of healthy subjects exposed to various forms of thermal or mechanical pain-producing stimuli in the presence or absence of placebo treatments (e.g., inert creams or inactive transcutaneous electrical nerve stimulation devices) to induce placebo effects using conditioning or suggestion. These stud ies revealed activation of regions in the spinal cord and descending pain-control regions in the brainstem and reduced signaling in the spi nothalamic tract. Later meta-analyses of 20 of these studies confirmed reduced signaling proportionate to reported placebo analgesia in painrelated activity in the thalamus, insula, and habenula, while increased signaling was observed in frontal-parietal regions. Today, placebo treatments are hypothesized to influence brain sys tems involved in “meaning-making” by constructing internal models that guide our understanding of incoming signals and their source, as well as implications for anticipatory events. These internal models provide predictive signals that are incorporated with incoming sensory

signals to produce the sensations and symptoms experienced. In turn, these models inform our perceptions (mindsets) and shape our reac tions, amplifying or attenuating perceptual and affective circuits. Thus, contextual information around placebo treatments, including the sug gestion of benefit, the visual and behavioral cues provided via the ritual of treatment, and prior experiences of benefit, can modify the neural construction of the experience and, in turn, downstream physiologic consequences in the nervous, immune, endocrine, and cardiovascular systems.

THE CHALLENGE OF IDENTIFYING “PLACEBO RESPONDERS” In drug development, identifying and excluding placebo responders could lead to more precise, and potentially smaller and less expensive, clinical trials. Predicting which patients are likely to respond to pla cebos could allow clinicians to optimize patient interactions and even support gradual replacement of drugs with side effects with placebo by dosage titration. Research into psychological predictors of placebo responders found several personality traits and constructs to be associated with placebo responders, including optimism, habitual desire for control, fun and sensation seeking, neuroticism, self-efficacy, and internal locus of control. Functional magnetic resonance imaging (fMRI) has also been used to create brain-signaling profiles that are predictive of placebo responders. In a study of patients with chronic osteoarthritis pain, right midfrontal gyrus connectivity effectively identified placebo pill responders. Interestingly, in some subjects, the active drug in this study, duloxetine,

appeared to enhance the placebo response, but in others, duloxetine reduced it. This finding suggests that while drug and placebo were additive for some patients, the interaction with placebo response diminished the drug effect for others. CHAPTER 496 The observation that placebo effects are influenced by opioid and dopaminergic signaling suggested that genetic variation in the synthe sis, function, or metabolism of these neurotransmitters might influence the magnitude of placebo effects. This observation gave rise to the term “placebome” to describe the group of genome-related products that potentially influence individual response to placebo treatments. Mem bers of the placebome were identified in candidate and genome-wide association studies (GWAS) of the placebo control arms of clinical tri als. For example, there is evidence of differential effects associated with the genes COMT and MAO-A, which encode enzymes that metabolize dopamine; OPRM1, which encodes the opioid receptor; and TPH2 and HTR2A, which encode proteins involved in serotonin signaling. Of these genes, COMT has the strongest evidence for association with pla cebo response in clinical trials of irritable bowel syndrome (IBS) and pain. To date, there are 29 genes associated with response to placebo in the GWAS catalog. Placebo and Nocebo Effects Although numerous psychological, neuroimaging, and genetic profiles of placebo responders have been proposed, these biomarkers were mostly derived from small studies and have not yielded consistent results in prospective studies. This is in large part due to the broad het erogeneity in variables intrinsic to patients, including their conditions and disease severity and duration, and extrinsic study variables, includ ing treatment duration, inclusion criteria, study location, number of study visits, outcome measures, and information about the study drug (e.g., possible side effects). ■ ■ADDITIVITY IN CLINICAL TRIALS The study of placebo responders has also led to important evidence of nonadditivity in clinical trials. Additivity between drug and pla cebo outcomes has been a universal and fundamental, but unproven, assumption in clinical trials. Based on additivity, the drug effect is determined by subtracting the outcome in the placebo arm from the outcome in the drug treatment arm (Fig. 496-1A). As reported in the study investigating brain connectivity of patients with depression described above, in some patients, duloxetine enhanced brain connec tivity seen in the brain region associated with placebo response. How ever, in other patients, this connectivity was reduced with duloxetine. Similarly, in clinical trials of chronic pain, chronic fatigue syndrome,

cardiovascular disease, and asthma, significant genetic associations observed in placebo arms were null or found to be in the opposite direction in drug treatment arms. These unexpected gene-by-(drug/ placebo) interaction effects suggest that, in some clinical trials, there are subsets of patients for whom the drug and placebo response is not additive (Fig. 496-1B). Thus, the potential for differential outcomes in the drug and placebo arms could confound outcomes in clinical trials, warranting further investigation.

NOCEBO EFFECTS In part, because informed consent in clinical trials requires disclosure of all potential drug side effects, the side effects reported by patients randomized to placebo are often the same as those expected with ran domization to drug. When this phenomenon was first documented in 1961, the word nocebo, coined from the Latin nocere, “to harm,” was used to describe production of negative effects from negative verbal suggestions, contextual cues, or associative learning. Although the term nocebo was originally defined as an adverse effect from an inert treatment, nocebo effects, like placebo effects, are the product of underlying aspects of the patients’ psychology (in this case, negative expectations and mindsets) and the social context. In clinical trials, on average, 25% of participants randomized to placebo report side effects, and some

studies (such as those of statins) show that the rates of side effects do not significantly differ between the active drug and placebo. Because they did not receive the active drug, we can assume the side effects arose, in part, due to expectation and not due to any active ingredients in the treatment. Nocebo effects are not limited to clinical trials. While statins are effec tive cholesterol-lowering agents, the belief that they cause muscle pain is widespread, and treatment is often discontinued because of this reported side effect. This phenomenon has been extensively investigated. In one study, a “within-subjects” design was used in which each patient served as their own control. In this study, patients who reported side effects were blinded and randomized to take a placebo, statin, or no treatment on a monthly basis over a 1-year period. At the end of the study, there was no discernable difference between symptoms reported on placebo versus statin, and 50% of the patients in the trial were able to reinitiate statin therapy successfully. Negative expectations surrounding technology (e.g., wi-fi or cell phone signals), environmental agents (e.g., infrasound generated by wind turbines), or food (e.g., gluten) can also enhance the likelihood of negative symptoms related to their presence. PART 20 Emerging Topics in Clinical Medicine Ethically, it is hard to test nocebo effects deliberately, but random ized studies in laboratory contexts show that people who are told to expect side effects are more likely to experience those side effects than those who are not told to expect side effects. Expectations and mindsets can deepen negative effects through physiologic activation or by heightening awareness of symptoms that may have already been present, resulting in misattribution of their cause. Nocebo responses can also occur because of conditioned learning. For example, patients receiving chemotherapy can develop nausea when they see or smell a stimulus associated with their treatment, such as the treatment room or even a staff member. Key drivers of placebo and nocebo effects overlap with factors that create barriers to quality clinical care for black patients and other patients of color. Poor communication, perceived discrimination, and medical mistrust are all factors demonstrated to reduce the quality of care in racially discordant dyads. Prior experiences of discrimination in the health care setting may result in expectations of discrimination and suboptimal clinician communication, enhancing nocebo and reducing placebo effects during treatment encounters. Consequently, the pres ence of nocebogenic and absence of placebogenic influences associ ated with racially discordant dyads has the potential to generate and exacerbate racial and ethnic inequities in clinical outcomes and care. ETHICALLY AND DELIBERATELY HARNESSING PLACEBO EFFECTS If placebo effects are understood as an integral component of the overall treatment effect, mediated by neurobiological processes and social and environmental factors, they can be personalized and maximized in the

practice of medicine. Administering placebos without full knowledge of the patient is no longer acceptable for important ethical reasons. Moreover, administering “impure placebos”—pharmacologically active treatments that are prescribed at too low a dose to be effective or are known to be ineffective for the condition being treated—is reportedly common practice but still controversial and ethically problematic. The use of impure placebos varies by country. In the United States, a survey of 1200 internists and rheumatologists indicated that 62% of participants believed the practice of utilizing impure placebos—over-the-counter analgesics and vitamins—was ethically permissible. Notably, <5% reported using saline or sugar pills. The numbers are higher in Canada and the United Kingdom, where 80 and 77% respectively, of physicians surveyed reported prescribing impure placebos or treatments without proven or expected benefit. In Denmark, 86% of internists, 54% of hospitalists, and 41% of specialists in private practice report that they used placebo interventions at least one time within the previous year. Finally, the German Medical Association, after assessing placebos in medicine, published a

report in 2011 acknowledging the complexity of the strong effects that placebos can have, supporting their limited use when no other therapies were available. In addition to using impure placebos, there are several other alternatives that deliberately leverage benefits of placebo effects. ■ ■OPEN-LABEL PLACEBOS One way that researchers have addressed the ethical and legal limita tions on placebos is to simply tell patients the facts about placebos. In honest or open-label placebo (OLP) studies, patients are fully informed about the absence of the active agent in the placebo, but are also told that placebo treatments can sometimes result in clinical improvement. The patients are also informed that trying a placebo might yield some benefit; even if they do not believe this to be the case, they could con sider suspending their belief. To date, the findings on the effects of OLP are promising. Improvements have been observed in IBS, cancerrelated pain and fatigue, depression, posttraumatic memory intrusions, allergic rhinitis, attention deficits, and hyperactivity; however, OLP has yielded no benefit in wound healing and did not enhance the cognitive abilities of healthy volunteers. ■ ■DELIBERATELY LEVERAGING PATIENT EXPECTATIONS AND MINDSETS When understood as being driven by the psychological and social context, placebo effects can be evoked without the use of sham pills or procedures by deliberately shaping patient expectations and mindsets. At their best, doctors and patients alike already harness the forces behind placebo effects through interactions, branding, and language that inspire patients’ trust, as well as useful mindsets and expectations about their condition. Once aware of this fact, health care practitioners can work ethically to leverage these forces to improve health outcomes. In the PsyHEART trial, 124 patients undergoing coronary artery bypass surgery were randomized to standard care, supportive therapy, or an expectation of manipulation in which they were encouraged to develop clear expectations about how their life would improve after surgery (i.e., what activities they would be able to perform). Six months after surgery, patients who were randomized to the expectation manipulation showed significantly greater improvements in quality of life and reductions in disability. In the EMBRACE study, patients diag nosed with cancer were exposed to documentary-style films featuring experts in psychology and oncology and to cancer survivors who spoke about how their mindsets changed throughout and after their treatment, as well as challenges they faced along the way. Participants exposed to the films increased their health-related quality of life, such as their emotional well-being, physical health, and general functioning, by 10%, as measured by changes in industry-standard scales, compared to patients receiving treatment as usual. While these interventions were delivered directly to patients, trainings to help physicians and care teams more deliberately and effectively shape patients’ expectations and mindsets in the context of their care are being developed, evalu ated, and disseminated.

Revision #1
Created 2026-01-06 16:36:18 UTC by Omar Ayman
Updated 2026-01-06 16:36:18 UTC by Omar Ayman