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Placebo Effects in Medicine

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Placebo effects are often considered the effects of an “inert substance,” but that characterization is misleading. In a broad sense, placebo effects are improvements in patients’ symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions. These effects are distinct from those of discrete therapies and are precipitated by the contextual or environmental cues that surround medical interventions, both those that are fake and lacking in inherent therapeutic power and those with demonstrated efficacy. This diverse collection of signs and behaviors includes identifiable health care paraphernalia and settings, emotional and cognitive engagement with clinicians, empathic and intimate witnessing, and the laying on of hands.

Placebo effects rely on complex neurobiologic mechanisms involving neurotransmitters (e.g., endorphins, cannabinoids, and dopamine) and activation of specific, quantifiable, and relevant areas of the brain (e.g., prefrontal cortex, anterior insula, rostral anterior cingulate cortex, and amygdala in placebo analgesia).¹ Many common medications also act through these pathways. In addition, genetic signatures of patients who are likely to respond to placebos are beginning to be identified.² Such basic mechanistic discoveries have greatly enhanced the credi-

bility of placebo effects. Moreover, recent clinical research into placebo effects has provided compelling evidence that these effects are genuine biopsychosocial phenomena that represent more than simply spontaneous remission, normal symptom fluctuations, and regression to the mean.¹ So what have we learned about placebo effects to date, and what does our current understanding say about medicine?

First, though placebos may provide relief, they rarely cure. Although research has revealed objective neurobiologic pathways and correlates of placebo responses, the evidence to date suggests that the therapeutic benefits associated with placebo effects do not alter the pathophysiology of diseases beyond their symptomatic manifestations; they primarily address subjective and self-appraised symptoms. For example, there is no evidence that placebos can shrink tumors; however, experiments demonstrate that common symptoms of cancer and side effects of cancer treatment (e.g., fatigue, nausea, hot flashes, and pain) are responsive to placebo treatments. Similarly, an experiment in patients with asthma showed that placebos do not affect patients’ forced expiratory volume in 1 second (FEV₁) but can nonetheless dramatically relieve perceived symptoms.³ This conclusion tracks evidence related to many conditions, such as musculo-

skeletal, gastrointestinal, and urogenital disorders.

Second, placebo effects are not just about dummy pills: the effects of symbols and clinician interactions can dramatically enhance the effectiveness of pharmaceuticals. For example, a recent study of episodic migraine demonstrated that when patients took rizatriptan (10 mg) that was labeled “placebo” (a treatment that theoretically had “pure pharmacologic effects”), the outcomes did not differ from those in patients given placebos deceptively labeled “rizatriptan” (pure expectation effect). However, when rizatriptan was correctly labeled “rizatriptan,” its analgesic effect increased by 50%.⁴ Similar results have been observed when other drugs, including morphine, fentanyl, and diazepam, have been administered openly and covertly and with procedures such as deep-brain stimulation for mobility symptoms in Parkinson’s disease.

Third, the psychosocial factors that promote therapeutic placebo effects also have the potential to cause adverse consequences, known as nocebo effects. Not infrequently, patients perceive side effects of medications that are actually caused by anticipation of negative effects or heightened attentiveness to normal background discomforts of daily life in the context of a new therapeutic regimen. For example, nocebo effects were demonstrated in a study of

benign prostatic hypertrophy treated with finasteride: patients informed of the sexual side effect of this drug reported sexual side effects at three times the rate that patients who were not so informed did. In trials of anticonvulsants for migraine, patients receiving placebo report memory problems and anorexia, whereas in trials of triptans for migraine, patients receiving placebo report different side effects. Research reviews have estimated that 4 to 26% of patients who are randomly assigned to placebo in trials discontinue their use because of perceived adverse effects. It thus seems not unlikely that patients are often treated for adverse medication effects that are actually anticipatory nocebo effects. Finding a way to balance the need for full disclosure of potential adverse effects of drugs with the desire to avoid inducing nocebo effects is a pressing issue in health care.

Unfortunately, much of what is known about placebo effects has been discovered through laboratory experiments with healthy volunteers, employing deceptive techniques that are not directly pertinent to clinical practice. We need more research involving clinical interventions designed to elicit placebo effects in participants without deception and in a manner consistent with informed consent. We need to know precisely

 **An audio interview with Prof. Kaptchuk is available at NEJM.org**

when, how, in what “dose,” and in what temporal sequence these interventions can provide therapeutic benefit. What are the relationships among attention, gaze, touch, trust, openness, confidence, thoughtful words, and manner of speaking that can together reduce perceived discomfort, disability, and disfigurement?⁵ In addition, we believe that recent pilot randomized, con-

trolled trials using open-label (“honest”) placebos with full disclosure in patients with irritable bowel syndrome, depression, or migraine should be expanded.⁴ Furthermore, creative thinking and experimental research are needed to construct and test ethically appropriate methods of communicating with patients about potential side effects in order to minimize nocebo responses.

Placebo effects are often considered unworthy and illegitimate. They are thought to be unscientific and caused by bias and prejudice. This attitude obscures a core truth of medicine: medicine’s goal is to heal, which can include cure, control of disease, and symptom relief or provision of comfort. When no cure is available — an inevitable occurrence at some points — medicine’s ultimate mission is to relieve unnecessary suffering. Supportive and attentive health care (preferably with effective medications, but even without) legitimately creates a “therapeutic bias” in patients toward hope and an experience of relief and reprieve. Research suggests that distinct neurobiologic mechanisms are activated. Empathic health care creates a cognitive–affective–sensory orientation, tapping into conscious and non-conscious mechanisms that can predispose patients toward reduced symptom severity and lessened reactivity to underlying pathophysiology. Or to borrow terms from the behavioral social sciences, healing interactions “frame,” “anchor,” or “nudge” patients toward shifts in their perceptions of their symptoms and illness, making them less disturbed or perturbed. This shift is part of medicine’s moral imperative to relieve unnecessary suffering in a manner consistent with trust and transparency.

Medicine has used placebos as a methodologic tool to challenge, debunk, and discard ineffective and harmful treatments. But placebo effects are another story; they are not bogus. With proper controls for spontaneous remission and regression to the mean, placebo studies use placebos to elucidate and quantify the clinical, psychological, and biologic effects of immersion in a clinical environment. In other words, research on placebo effects can help explain mechanistically how clinicians can be therapeutic agents in the ways they relate to their patients in connection with, and separate from, providing effective treatment interventions. Of course, placebo effects are modest as compared with the impressive results achieved by lifesaving surgery and powerful, well-targeted medications. Yet we believe such effects are at the core of what makes medicine a healing profession.

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

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