Review

The Placebo and Nocebo Phenomena: Their Clinical Management and Impact on Treatment Outcomes

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ABSTRACT

Purpose: This overview focuses on placebo and nocebo effects in clinical trials and routine care. Our goal was to propose strategies to improve outcomes in clinical practice, maximizing placebo effects and reducing nocebo effects, as well as managing these phenomena in clinical trials.

Methods: A narrative literature search of PubMed was conducted (January 1980–September 2016). Systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on placebo or nocebo effects in clinical practice were included in the qualitative synthesis. Search terms included: *placebo, nocebo, clinical, clinical trial, clinical setting, placebo effect, nocebo effect, adverse effects*, and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature.

Findings: Placebo and nocebo effects are psychobiological events imputable to the therapeutic context. Placebo is defined as an inert substance that provokes perceived benefits, whereas the term nocebo is used when an inert substance causes perceived harm. Their major mechanisms are expectancy and classical conditioning. Placebo is used in several fields of medicine, as a diagnostic tool or to reduce drug dosage. Placebo/nocebo effects are difficult to disentangle from the natural course of illness or the actual effects of a new drug in a clinical trial. There are known strategies to enhance clinical results by manipulating expectations and conditioning.

Implications: Placebo and nocebo effects occur frequently and are clinically significant but are underrecognized in clinical practice. Physicians should be able to recognize these phenomena and master tactics on how to manage these effects to enhance the quality of clinical

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Key words: adverse effects, clinical trial, nocebo, pharmacology, placebo, treatment.

INTRODUCTION

The placebo effect has been studied extensively throughout history.[1,2] The nocebo effect, also called "the evil brother of the placebo effect," has been less studied, but in recent years has become a subject of growing interest.[3–5] Both phenomena are composed of several intertwined biological and environmental mechanisms, displaying a complex interaction. Their operative mechanisms not only are affected by the characteristics of the individuals but also on the context in which they operate; thus, the search for a simple equation to predict the effect of placebo and nocebo has been met with limited success.

A precise definition of the placebo and nocebo phenomena is difficult to pinpoint, as different researchers have used different definitions, often depending on the context. A starting definition would be psychobiological events attributable to the overall therapeutic context[6]; herein, placebo effect would be the benefits provoked by an inert substance, and the nocebo effect is the induction of true or perceived harm after treatment with an inactive substance. Thus, a response to treatment, not attributable to the known mechanism of action of the treatment, is the core feature of both phenomena. This means that the definition can also be applied to an active substance treatment, then referring to the (extra) effects it elicits and that are not explained by its pharmacologic action. Many disorders have a natural course of illness in which symptoms fluctuate, making it difficult to differentiate between a placebo or nocebo response and the natural course of illness at an individual patient level. Similarly, many "side effects" occur commonly with or without pharmacotherapies (eg, headache), making it often difficult to disentangle, at an individual patient level, between a treatment-emergent adverse event that is a nocebo response or one that has occurred independently of treatment.

Paradigmatically, the placebo and nocebo phenomena have been most extensively studied in analgesia[7–10] and irritable bowel syndrome (IBS).[11] These phenomena have been studied more recently in the field of dermatology[12–14] and in psychiatry, particularly in depression.[15]

The underpinnings of placebo and nocebo are psychological and neurobiological. Psychological mechanisms include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning, and "placebo-by-proxy" induced by clinicians and family members.[16] Two principal mechanisms are well supported. The first aspect involves expectancy: the administration of placebo creates expectations in future responses by using simple verbal cues as modulators of expectations. Researchers can nudge a subject's expectations and boost the placebo effect. The second aspect involves classical conditioning: repeated associations between a neutral stimulus and an unconditioned stimulus (active drug) can result in the ability of the neutral stimulus by itself to provoke a response characteristic of the unconditioned stimulus.[4,17,18] In a study of placebo/nocebo in thermal pain, neither conditioning nor expectation alone seemed to be able to elicit placebo or nocebo effects; however, the combination of experience (conditioning) and expectation resulted in significant placebo (analgesia) or nocebo (hyperalgesia) effects.[19]

Misattribution is the inappropriate attribution of improvement or worsening to a treatment when it was actually caused by the disorder's natural fluctuation of symptoms or other causes.[20] Misattribution may have a more significant role in nocebo effects than in placebo effects, although this theory remains a focus of active debate.[21,22]

The neurobiology of the response to placebo and nocebo has been studied mostly in the paradigmatic field of analgesia and has been shown to be mainly related to the opioid and dopaminergic pathways.[6,23,24] A companion paper published in this issue of *Clinical Therapeutics* reviews the theoretical and biological underpinnings of the nocebo and placebo phenomena.[25]

It is important to note that placebo and nocebo responses are highly variable across individuals. Some individual differences have been associated with genetic polymorphisms or underlying neurologic impairments. For example, patients with frontal lobe impairment, especially prefrontal lobe, have decreased expectancy and learning, and thus they partially or totally lose their placebo response. In a study of Alzheimer's disease and pain, patients with reduced Frontal Assessment Battery scores exhibited a reduced placebo component of the analgesic treatment.[26] In intellectually disabled patients, a higher intelligence quotient was positively related with placebo response.[27]

Catechol-O-methyl transferase is involved in dopamine degradation, affecting the prefrontal lobe. The catechol-O-methyl transferase Val^{158}Met polymorphism