

NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2018 Jan-.

Placebo Effect

Swapna Munnangi¹; Lambros D. Angus².

¹ Nassau University Medical Center

² Nassau University Medical Center

Last Update: July 16, 2018.

Introduction

Placebos have been in use since antiquity and may have been significant in improving health and quality of life when little was known about the etiology of most illnesses. In fact, most outcomes were likely due to a placebo effect since the available treatments were unproven. For example, the use of snake oil and bloodletting was a common practice of the past. However, those that responded positively to those treatments likely did so because of a placebo effect. The emergence of placebo-controlled clinical trials in the 1940s reintroduced the placebo effect to the modern day. The classic article “The Powerful Placebo” by Henry Beecher highlighted the placebo effect and emphasized a need to account for it to evaluate the efficacy of a treatment modality properly. Both research and clinical settings utilize the placebo effect.

The placebo effect is a fascinating phenomenon that occurs when a sham medical intervention causes improvement in a patient’s condition because of the factors associated with the patient’s perception of the intervention. Examples of placebo interventions include sugar pills, saline injections, and therapeutic rituals. Placebo effects are not limited to inert interventions. Proven effective treatments can also generate a placebo effect. Traditionally, the placebo effect was considered a nuisance variable to be controlled for; however, in light of some remarkable research demonstrating its potential to modulate treatment outcomes in recent decades, there has been a spiked interest in studying this phenomenon.

The placebo effect can be verbally induced or result from conditioning and prior experiences that shape patient expectations. The role of the placebo effect as a powerful determinant of health in certain disease conditions has been demonstrated in several research studies. Migraines, joint pain, arthritis, asthma, high blood pressure, and depression are some disease conditions that are more sensitive to the placebo effect. It is a complex phenomenon with several underlying psychological and neurobiological mechanisms. These underlying mechanisms that mediate placebo responses differ based on the medical condition and the investigated outcomes. Not all results of a placebo are beneficial, and as such, placebos can also result in undesirable outcomes. Indeed, the term “nocebo effect,” derived from the Latin *nocere* meaning “harm,” is commonly used when a placebo causes an unfavorable outcome. Both placebo and nocebo effects have the same mechanisms which presumably are psychogenic, but they can induce measurable changes in the body.

Mechanisms of Placebo Effect

Despite dramatic advances in scientific knowledge surrounding the placebo effect, efforts to characterize this phenomenon are in primitive stages. The complex nature of mind-body interactions, supplemented by the negative connotations associated with placebo effects in the past, have hampered understanding of it. However, researchers are beginning to unravel the neurobiological basis of placebo effects. Classical conditioning and expectancy are two hypothesized psychological mechanisms known to mediate the placebo effect. Classical conditioning is a form of learning where an association is formed between a stimulus and a response. The association is then remembered, affecting future experiences. Through this process of association, patients may acquire a behavior. For example, a patient may report a decrease in pain after receiving a placebo pill that looks similar to pain medication that was previously effective in easing the pain. Whenever the same stimulus is encountered in the future, the patient conditions himself by shaping expectations and shows a response that was previously imprinted in his memory. Learning and adaptation, therefore, drive a conditioned response.

Expectations of the patient also play a vital role in mediating a placebo effect. Expectations can impact the course of treatment by affecting the psychological and physiological responses to that treatment. Along with classic

conditioning, expectations can be induced by verbal instructions or social learning. For example, a research subject treated for pain with placebo in the context of a verbal cue that the placebo is in an effective analgesic may shape his expectations and elicit an analgesic response. Conditioning and expectancy are often entangled mechanisms mediating placebo responses. Neurobiological mechanisms underlying the placebo effect are best characterized in placebo analgesia. In addition to these mechanisms, several other influential elements are at work during the placebo effect. These include the patient-physician relationship, patient's psychological state and personality, the severity of the medical condition, and environmental circumstances. The patient's genetics may also influence the degree of placebo effect. Researchers are studying how genes can influence the placebo effect in various pathways, including the dopamine, opioid, serotonin, and endocannabinoid systems. Evidence also indicates that the therapeutic benefits of the placebo effect may not impact the pathophysiology of the underlying disease being studied, but rather address the subjective self-appraised symptoms of the disease. Elucidating the underlying mechanisms that mediate the placebo effect may prove beneficial to clinical practice and drug development.

Function

Placebo effects play a vital role in several areas. Primarily, placebo interventions serve as control treatments in experimental studies, enabling researchers to determine the specific effects of a particular treatment. Clinical investigators use randomized, double-blind placebo-controlled trials as a gold standard to validate treatments. Non-blinded trials may result in a disproportionately large placebo effect. In placebo-controlled trials, the placebo effect observed may be greater for psychological and self-rated measures relative to other more objective measures that are objective. Using a placebo in psychological and medical studies is advantageous as it helps minimize the influence of patient expectations on the outcome. Additionally, studying placebo effect at its core can help clinicians and researchers understand the context of how beliefs can shape various sensory and emotional perceptions. Identifying a physiological basis for the placebo effect may open doors to modulating processes that can improve mental and physical health. A clear understanding of the underlying mechanisms of placebo response with scientific work may enable clinicians to harness the placebo effect and improve the care provided to the patients.

Issues of Concern

It is challenging for medical professionals to sidestep the placebo effect and only measure the intrinsic activity of the treatment that they are testing. Therefore, therapeutic evaluations become difficult in medical conditions that are sensitive to the placebo effect. Interindividual differences also complicate the studies of the placebo effect. It is important that physicians separate the placebo effect from the treatment. Placebo research is challenging because of a certain degree of deception.

Clinical Significance

Understanding how placebo responses form is vital for clinical practice as it can play a crucial role in determining the therapeutic outcome of the patient. Although placebo effects frequently occur in clinical practice, they often go underrecognized. The therapeutic rituals and the psychosocial context surrounding the patient can mediate a placebo effect. The placebo effect is considered a melting pot of ideas in neuroscience. Translating the knowledge of the placebo effect to benefit the patient requires a thorough evaluation of the clinical effectiveness of the intended effect. Therefore, attempts to generate beneficial placebo responses should be done only under strict professional, legal, and ethical norms after obtaining appropriate informed consent.

Other Issues

Placebo effects have been a subject of ethical concern in clinical practice as well. Additionally, the ethical dimensions of placebo-controlled trials such as the use of sham invasive procedures, withholding potential proven treatments, or deception are issues of concern in studying the placebo effect.

Questions

To access free multiple choice questions on this topic, [click here](#).

References

1. Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* 2013 Jul;93(3):1207-46. [PMC free article: [PMC3962549](#)] [PubMed: 23899563]
2. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. *Neuroscience.* 2015 Oct 29;307:171-90. [PMC free article: [PMC5367890](#)] [PubMed: 26272535]
3. Dodd S, Dean OM, Vian J, Berk M. A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena. *Clin Ther.* 2017 Mar;39(3):469-476. [PubMed: 28161116]
4. Jakovljevic M. The placebo-nocebo response: controversies and challenges from clinical and research perspective. *Eur Neuropsychopharmacol.* 2014 Mar;24(3):333-41. [PubMed: 24393653]
5. Meissner K, Kohls N, Colloca L. Introduction to placebo effects in medicine: mechanisms and clinical implications. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* 2011 Jun 27;366(1572):1783-9. [PMC free article: [PMC3130411](#)] [PubMed: 21576135]
6. Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* 2013 Jul;93(3):1207-46. [PMC free article: [PMC3962549](#)] [PubMed: 23899563]
7. BEECHER HK. The powerful placebo. *J Am Med Assoc.* 1955 Dec 24;159(17):1602-6. [PubMed: 13271123]

Copyright © 2018, StatPearls Publishing LLC.

This book is distributed under the terms of the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>), which permits use, duplication, adaptation, distribution, and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, a link is provided to the Creative Commons license, and any changes made are indicated.

Bookshelf ID: NBK513296 PMID: 30020668