Review

A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena

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ABSTRACT

Purpose: Placebos are commonly used in experimental and patient populations and are known to influence treatment outcomes. The mechanism of action of placebos has been investigated by several researchers. This review investigates the current knowledge regarding the theoretical and biological underpinning of the nocebo and placebo phenomena.

Method: Literature was searched using PubMed using the following keywords: *nocebo*, *placebo*, *μ-opioid*, *dopamine*, *conditioning*, and *expectancy*. Relevant papers were selected for review by the authors.

Findings: The roles of conditioning and expectancy, and characteristics associated with nocebo and placebo responses, are discussed. These factors affect nocebo and placebo responses, although their effect sizes vary greatly, depending on inter-individual differences and different experimental paradigms. The neurobiology of the nocebo and placebo phenomena is also reviewed, emphasizing the involvement of reward pathways, such as the μ-opioid and dopamine pathways. Neurobiological pathways have been investigated in a limited range of experimental paradigms, with the greatest efforts on experimental models of placebo analgesia. The interconnectedness of psychological and physiological drivers of nocebo and placebo responses is a core feature of these phenomena.

Implications: Further research is needed to fully understand the underpinnings of the nocebo and placebo phenomena. Neurobiology pathways need to be investigated in experimental paradigms that model the placebo response to a broader range of pathologies. Similarly, although many psychological factors and inter-individual characteristics have been identified as significant mediators and moderators of nocebo and placebo responses, the factors identified to date are unlikely to be exhaustive. (*Clin Ther*. 2017;39:469–476) © 2017 Published by Elsevier HS Journals, Inc.

Key words: conditioning, dopamine, expectancy, μ-opioid, nocebo, pharmacology, placebo, treatment.

For the purpose of this review, a placebo response is an improvement in clinical symptoms when a person is administered an inert substance, whereas a nocebo response is a worsening of clinical symptoms or the experiencing of treatment-emergent adverse effects. Typically, a placebo tablet is administered in control arms of

Accepted for publication January 5, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.01.010
0149-2918/$ - see front matter

clinical trials and is manufactured to look identical to the tablet in the active arm of a trial. Nocebo and placebo responses are also sometimes used to describe unexpected responses to active treatments that are not explained by the known mechanism of action of the treatment. It may not be possible to discern at an individual participant level between true placebo or nocebo responses and fluctuations in symptom severity due to the natural progression of the illness; however, insightful placebo and nocebo response data can often be obtained at a cohort level. While the importance of the placebo effect is widely understood, this is much less so for the nocebo effect. The biological bases of the nocebo and placebo effects are only now beginning to be unraveled. Attempts to understand the causes of the placebo effect have increased in the last 50 years, as placebo-controlled clinical trials have become the only accepted method for efficacy testing of new pharmaceuticals and the problems associated with placebos have become more apparent. Insights have been gained from exploring theoretical causes and influencing factors of the effect, which have probed the mechanisms underlying the phenomenon. This article reviews the theoretical and biological underpinning of the nocebo and placebo phenomena. A separate article also published in this issue reviews the clinical importance of the nocebo and placebo phenomena.

PSYCHOLOGICAL UNDERPINNINGS

There are a multitude of psychological elements that have been identified as the leading factors underpinning the placebo and nocebo effects.

The most well-known theories pertaining to the placebo and nocebo phenomena are the conditioning and expectancy hypotheses. Conditioning can occur when a person was pre-exposed to an active substance and had a reaction that imprints in memory. When they are then given an inert substance, they might respond to the inert substance in the same or similar way as they would to the active substance. A conditioned response is a triggering of a memory loop and, therefore, is driven by learning and adaptation.[1] The effect is mediated by many variables. The conditioning hypothesis alone is insufficient to explain the placebo and nocebo phenomena, for example, the extinction phenomenon in classic conditioning does not necessarily occur with placebos.[1]

Expectancy occurs where a pre-existing belief, or information received before being given an inert substance (or before reporting a response[2]), elicits a response to the inert substance predicated on what the person thinks will happen. It is not necessary to have ever been exposed to an active substance to have an expectation of response. This may be responding to a treatment that is not pharmacologically active because of a pre-existing belief that the treatment either works or might cause a specific reaction, and can be an important factor in alternative therapies in which pharmacologically active compounds are not included in the treatment.[3] Similarly, expectation can be a driver of inappropriate or over-prescription of some medications, including antibiotics, in a phenomenon that shares much in common with the placebo effect.[4] As with conditioning, expectancy also requires learning, which may come through direct receipt of information, suggestion, social cues, or the interaction of all these learning modalities.[5] Suggestion has also been used experimentally to extinguish a conditioned placebo response.[6] Extinction of a conditioned response requires learning, which in the case of a placebo response can be facilitated by suggestion, but may not necessarily occur solely through repeated administration of a placebo.

Hope for improvement has also been suggested as a driver of the placebo effect[1] and this has face validity; however, data have not been presented to support this theory. A corollary, where despair is suggested to drive the nocebo effect, has not been proposed in peer-reviewed literature. However, personality traits have been associated with placebo response,[7] leaving the possibility open to an association between personality traits, such as optimism and pessimism, being factors in the placebo and nocebo phenomena. However, considerable work needs to be done to unravel the relationship between personality and placebo response, including expanding the theoretic underpinnings of the association through hypothesis-driven research in addition to the current works that have focused on association between personality measures and placebo response.[8] State and trait variance are a limitation with personality measures[9] and may be relevant for the placebo response, for example, where there is variance in dependence.

The nature of the therapeutic alliance may also be a driver of the nocebo effect, with a hostile–dependent relationship being an exemplar. This relationship pattern occurs when one party is dependent on another, and the former is hostile or mistrusting of other people. This is a not uncommon but poorly recognized pattern in clinical practice, where people with insecure attachment styles are forced into trusting a clinician, and their interactional style makes this difficult Figure.