33. Placebo Effect vs. Nocebo Effect

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Definition

The concept of the placebo effect is widely known, but its counterpart, the nocebo effect, is still poorly recognized outside the scientific community. Although definitions may vary depending on context, the **placebo effect** ("I shall please" from the Latin *placere*) refers to clinical benefits observed after the administration of a substance or intervention without specific pharmacological action, triggered mainly by positive expectations and the therapeutic context. The **nocebo effect** ("I shall harm" from the Latin *nocere*), on the other hand, corresponds to the manifestation of real or perceived adverse reactions associated with negative expectations in response to an inert treatment (Chavarria et al., 2017). More broadly, both phenomena may arise not only from inactive substances but also from physical procedures such as injections, acupuncture, or sham surgeries (Tavel, 2022), or even as an additional component of the genuine pharmacological responses of a medication, indicating that every therapeutic intervention involves inseparable biological and psychosocial dimensions.

Mechanism

The placebo effect has been linked to the release of substances (endogenous opioids, endocannabinoids, dopamine, oxytocin, and vasopressin) whose effects are specific to the targeted system (e.g., pain or immune system) and the disease (e.g., arthritis or Parkinson's disease) (Colloca and Barsky, 2020). The main mechanisms underlying the placebo effect include expectation, through which the subject anticipates a future outcome, reducing anxiety and activating reward mechanisms, and learning, since previous experiences with effective treatments lead to substantial placebo effects. A central role in placebo effects also appears to be played by interactions between associative learning systems and cognitive evaluations (Frisaldi et al., 2023). Notably, a widely accepted theory suggests that the nocebo effect is mediated by neurobiological pathways similar to those of placebo effects (Colloca, 2024).

The fact that placebo effects are also observed in laboratory animals not only facilitates the study of the fundamental neurobiological mechanisms of placebo responses (Neyama et al., 2025) but also raises challenges in the preclinical evaluation of new drugs, similar to those described below for clinical studies.

Impact on drug discovery and development

The fact that the effect of an active pharmaceutical ingredient inherently includes a placebo component creates a major challenge for clinical studies designed to validate the efficacy of new drug candidates, especially when the control group receives a placebo.

The situation becomes even more complex because the relationship between the effects observed in placebo and active-treatment groups is not always additive (Chavarria et al., 2017), and because there is wide variability in placebo responses across individuals, sexes, and races (Tu et al., 2022). In many double-blind clinical trials for pain treatments or psychiatric disorders such as anxiety, placebo responses are similar to responses to the active treatment, and up to 19% of adults and 26% of older adults who receive placebos report adverse effects (nocebo effect), according to Colloca and Barsky (2020). Interestingly, a significant proportion of patients (about 25%) who receive a placebo in clinical trials discontinue treatment due to adverse effects caused by the nocebo effect (Colloca, 2024).

Currently, in most phase 2 and phase 3 clinical trials, a standard treatment is used as a control instead of a placebo, for ethical reasons when a safe treatment is available (See item 13 of this glossary). As a result, correctly assessing the true placebo effect becomes difficult, since it can only be accurately measured when a placebo group is compared with an untreated group. This is necessary because confounding factors can "mimic" the placebo effect, such as the natural course of the disease (Pardo-Cabello et al., 2022).

Impact in clinical practice

Placebo and nocebo effects occur frequently and are clinically relevant, yet they remain underrecognized in routine clinical care. The placebo effect is most evident in the relief of subjective symptoms such as pain, anxiety, fatigue, insomnia, and depression, but it can go beyond perception, modulating objective physiological responses such as immunological, autonomic, and endocrine changes (Tavel, 2022; Frisaldi et al., 2023). Aware of these effects, clinicians must apply strategies that enhance patient responses and quality of life by maximizing placebo effects and reducing nocebo effects in practice, such as fostering a strong doctor-patient relationship, increasing empathetic communication, providing information appropriately, reducing expectations of adverse effects, and promoting social contact among successfully treated patients (Chavarria et al., 2017).

References

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