

Η ΕΠΙΔΡΑΣΗ ΤΟΥ ΦΑΙΝΟΜΕΝΟΥ NOCEBO ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΚΑΡΚΙΝΟ

THE EFFECT OF NOCEBO ON CANCER PATIENTS

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«ΑΝΑΠΤΥΞΗ ΝΕΩΝ ΦΑΡΜΑΚΩΝ:ΕΡΕΥΝΑ, ΚΥΚΛΟΦΟΡΙΑ ΚΑΙ ΠΡΟΣΒΑΣΗ»

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NOCEBO: DEFINITION

The nocebo effect is defined as the effect which occurs when a harmless substance or active treatment is taken by, or administered to, a patient and is associated with harmful side effects or worsening of symptoms **due to:**

- **negative expectations of the patient**
- **negative psychological condition of the patient**
- **negative verbal and nonverbal communications on the part of the treating person**

NOCEBO: HISTORY

The term nocebo ('I shall harm' from *noceō*, 'I harm' in Latin) was introduced in contraposition to the term placebo ('I shall please') by a number of authors in order to distinguish pleasing from the noxious effects of placebo.

Kennedy first introduced the concept of “nocebo reaction” in **1961**.

In its most extreme, nocebo-stimuli may cause death, as in voodoo-death in primitive societies, an example of the fear-paralysis reflex. In records of anthropologists and others who have lived with primitive people in widely scattered parts of the world is the testimony that when subjected to spells or sorcery or the use of “black magic”, men may be brought to death.

NOCEBO: WHY IS IT IMPORTANT?

- ▶ Decrease in overall treatment efficacy
- ▶ Increase of the unpleasant treatment side effects
- ▶ Increase of the unintended secondary effects of a treatment
- ▶ Decreased compliance on treatment
- ▶ Drop-out of studies resulting to altered final results
- ▶ Has been proven that in certain situations, this kind of side effects can cause symptoms that are serious enough to require hospitalization and medical intervention

In a recent systematic review, 3544 patients who received placebo showed that 64.5% of the patients reported at least one adverse event during the study and nearly 10% of patients discontinued placebo treatment because of intolerance, showing that placebo-treated subjects closely mimicked those seen in the active treatment arm in terms of side-effect type and severity.

MECHANISMS UNDERLYING THE NOCEBO EFFECT

Due to ethical limitations, because nocebo effect causes unwanted experiences to the patients, the number of available studies designed to specifically understand the nocebo mechanisms of action are considerably limited.

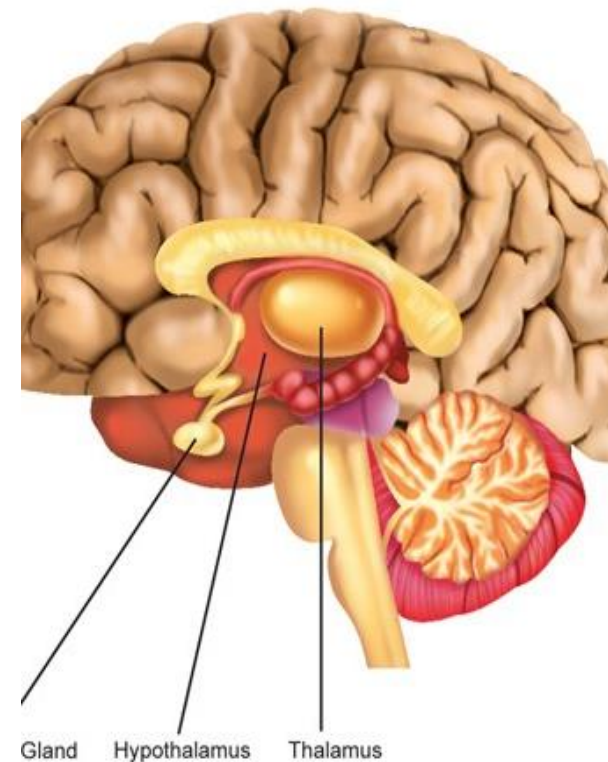
Most research on the nocebo effect has been focused on the appearance of pain and changes in its intensity among healthy people, mainly because of the ease of controlling painful stimuli and observing the effects of these stimuli with the aid of advanced methods for imaging the central nervous system.

MECHANISMS UNDERLYING THE NOCEBO EFFECT

The role of hypothalamic–pituitary–adrenal axis in nocebo response

The nocebo effect through exacerbation of experimentally induced pain via verbal suggestion, has been shown to be mediated by the neuropeptide cholecystikinin and blocked by proglumide, a mixed cholecystikinin type A and type B receptor antagonist. Cholecystikinin is a peptide hormone of the gastrointestinal system that is involved in anxiety states.

This type of verbally induced hyperalgesia has been associated with increased activity of the hypothalamic–pituitary–adrenal axis in healthy persons. Both hyperalgesia and hypothalamic–pituitary–adrenal hyperactivity are antagonized by the benzodiazepine diazepam, suggesting a role of anxiety in these nocebo effects. However, proglumide blocks hyperalgesia but not hypothalamic–pituitary–adrenal hyperactivity, which suggests involvement of the cholecystikinin system in the hyperalgesia component of the nocebo effect but not in the anxiety component.



MECHANISMS UNDERLYING THE NOCEBO EFFECT

The role of spinal cord in nocebo response

The experience of pain belongs to the most common symptoms in many maladies. The individual pain experience can be substantially modulated by many interventions, such as nocebo hyperalgesia can be increased by negative expectations. Nocebo-induced hyperalgesia increases pain along with activity in cortical pain-processing areas. However, the processes leading to increased cortical pain activations are unknown.

MECHANISMS UNDERLYING THE NOCEBO EFFECT



Expectations

When expectancies are accessible consciously, they are called expectations, which can be measured and are affected by changes in perception and cognition. In addition to inducing or exacerbating symptoms, negative expectations diminish the therapeutic efficacy of active medications. In the context of a study, has been proven that the effect of a topical analgesic can be blocked by falsely informing patients that the drug will worsen rather than alleviate their pain.



Nonconscious activation

A further correlation analysis between high pain reports during conditioning and amygdala activity during nonconscious nocebo trials demonstrated that high pain ratings during conditioning correlated with high activation of the amygdala during nonconscious trials, both for the right amygdala and the left amygdala but not for conscious nocebo trials

MECHANISMS UNDERLYING THE NOCEBO EFFECT



Genetic influence

Experimental and clinical data document a large interindividual variability in nocebo responses, however, data on psychological, biological or genetic predictors of nocebo responses are lacking.

The results of Wendt et al suggest that COMT Val158Met, specifically the Val158/Val158 genotype, is a potential genetic marker for nocebo responders.

THE ROLE OF NOCEBO EFFECT ON PATIENTS WITH CANCER

The nocebo effect has been poorly studied specifically on cancer patients, however the main adverse reactions of cancer treatment, such as pain, nausea and vomiting, have need widely studied the last years in other patient population.

The available therapies for cancer are most of the time associated with side effects that significantly affect the patient's quality of life even though medical advances have improved cancer survival.

It is of important notice to highlight that therapy toxicities are always taken into consideration by the patients when deciding to start chemotherapy and has been shown to be one of the three major predictors of treatment discontinuation in the palliative setting.

THE ROLE OF NOCEBO EFFECT ON PATIENTS WITH CANCER

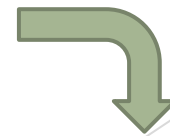
- ▶ Patients' positive or negative perception of a treatment does not only contribute to placebo and nocebo effects, but also adds to the **efficacy of pharmacologically active drugs**.
- ▶ Determining the **causality** of an adverse event with the treatment is challenging, especially in early cancer drug development when a control arm is lacking. The results of some recent studies revealed that expected AEs from chemotherapeutic agents with side effects are also commonly presented in the placebo arms.
- ▶ However, this phenomenon causes high rates of treatment discontinuation, resulting to a **confounding factor for the assessment of investigational drug safety profile**.

MEASURES TO MINIMIZE THE NOCEBO EFFECT IN CANCER TREATMENT

Nocebo effect is a known risk for treatment **nonadherence**, **discontinuation**, and **alteration of clinical trials results**, so it is fundamental to understand this phenomenon and take any possible **measure to minimize the risk**.

One of the main underlying mechanisms for the development of nocebo effects is **expectations**. These are formed based on:

- prior experiences (either specific to the treatment or in general to medical procedures)
- social learning
- the information received about the treatment by the treating physician



MEASURES TO MINIMIZE THE NOCEBO EFFECT IN CANCER TREATMENT

- ▶ Doctor-patient communication and the patient's treatment expectations can have considerable consequences, both positive and negative, on the outcome of a course of medical therapy.
- ▶ Nocebo responses may result from unintended negative suggestions by physicians or nurses. There are some studies in different therapeutic areas that examine the impact of educating patients about the nocebo effect. This type of intervention is fast, simple, cost-effective and ethically feasible; therefore, it could potentially serve as a component of adverse effect management. Moreover, it requires no alteration to clinical routine or informed consent.



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