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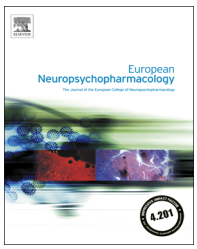

REVIEW

The placebo-nocebo response: Controversies and challenges from clinical and research perspective

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Abstract
Placebo and nocebo responses fascinate, confuse, mystify and challenge. They are genuine social, cultural and psychobiological phenomena which can significantly modify the overall treatment outcome. The placebo-nocebo phenomenon represents a very good model for our better understanding the role of treatment context and how the words, indices, symbols and icons act on our brains. Placebo response is associated with reward expectancy and relief of anticipatory anxiety, while nocebo response is related to lack of reward/positive expectancy and to increase of anticipatory anxiety. Placebo-nocebo responses are mediated through changes in various cortico-subcortical networks and psychophysiological systems. In spite of many existing complementary theories and still growing research on placebo and nocebo response, the implementation of our current knowledge to benefit basic research, clinical trials and routine clinical practice is still so scarce.

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1. Introduction

"Fortis imaginatio generat casum"
A powerful imagination generates the event
(Michel de Montaigne)

The placebo-nocebo phenomenon is subject to an increasing and heated debate, and extensive controversial research. For time being it represents a huge challenge to contemporary psychiatry as well as to medicine in general. Although "the history of medicine is the history of placebo" (Czerniak and Davidson, 2012), it is not only a conundrum (Jubb and Bensing, 2013), but a big puzzle wrapped into the great mystery of human body, brain and mind relationships. In modern clinical psychopharmacology neutral substance wrongly called placebo has been mainly used as a comparison factor rather than being studied while phenomenon of nocebo has been studied even less extensively than placebo. Placebo-nocebo challenge includes quite a number of conceptual, explanatory and moral questions and dilemmas. Conceptual questions are related to the cacophony regarding various definitions and meanings of terms like fake, slam or dummy treatment; pharmaceuticals and neutraceuticals; placebo treatment; multiple placebo effects; inert and active placebo, true and perceived placebo; pure and impure placebo, placebogenic and nocebogenic effects; placebo and nocebo effect or response; placebo and nocebo induction; negative placebo effect, placebo adverse reaction, placebo induced side-effect, negative placebo response, reverse placebo effect, antiplacebo; iatrogenic effects due to diagnosis and treatment, context effects and meaning responses. Questions concerning the function of neutral control treatment in research are very important from both ethical and methodological perspective. Explanatory or epistemological questions are relevant to mechanisms underlying placebo-nocebo phenomenon related to mind-body operating systems and psychosomatic networks, treatment context, doctor-patient relationship, suggestion and auto-suggestion, deception and self-deception and self-fulfilling prophecies, interactions between specific and nonspecific mechanisms of change and therapeutic action. Placebo-nocebo phenomenon is multifactorial, multidimensional and etiologically complex and that is why explanatory models should refer mostly to explanatory pluralism rather than to reductionism. Moral or ethical questions are about the supposed use of neutral or fake treatment should be used. These questions, although very important, are beyond the scope of this article.

The use of imprecise thinking and language in mind-body medicine associated with conceptual cacophony, mythology and misconceptions (see Table 1) has been leading to a confusion in placebo-nocebo research and understanding as well as to a widespread disconnect between clinical practice guidelines, patients' attitudes, and physicians' practice (Hull et al., 2013). As there is no consensus regarding terminology, this review focuses first on conceptual chaos and different connotations in placebo-nocebo medicine, then on some new perspectives on placebo-nocebo phenomenon in the frame of creative psychopharmacotherapy and transdisciplinary integrative psychiatry.

Table 1 Myths and misconceptions about placebo (Brown 1994 according Jopling 2008, McQueen et al. 2013).

Myth 1	Placebo is physiologically inert and it has no effect on physiological functions
Myth 2	Placebo only has an effect upon psychological symptoms, or conversely, if a placebo relieves symptoms, then it shows that the symptoms were unreal, imaginary, or 'psychosomatic'
Myth 3	Placebo is helpful only in psychogenic disorders, it is "a treatment for neurotic patients when the clinician has nothing better to offer"
Myth 4	Placebo differentiates between organic and mental disease (this is the cruelest and most dangerous myth")
Myth 5	Placebo use is ineffective if patients are told they are receiving placebo
Myth 6	Placebo use is unethical because it always involves tricking or deceiving patients
Myth 7	Placebo is the equivalent of no therapy.
Myth 8	A fixed fraction of patients responds to placebos —"about a third" often quoted
Myth 9	Placebo only affects subjective aspects of illness not objective measures of disease
Myth 10	Patients in double-blind trials do not know which condition they are in
Myth 11	In controlled trials, placebo never has a specific therapeutic effect upon the condition being treated
Myth 12	Patients will always give an honest and accurate account of their subjective well-being
Myth 13	Placebo is a catch-all for non-pharmacological effects in RCTs, a device for eliminating bias in trials and establishing the 'true' biochemical effect of drug treatments

2. Contradicting definitions: What's in the name?

The words placebo and nocebo are used with many different meanings associated with a lot of controversies. Regarding the neutral, inert, pharmacologically/biologically inactive, fake or deceptive treatment, given as if it was a real treatment, the very fundamental question is what is more appropriate to talk about "the effect of" or "response to" the such kind of treatment. Today an interchangeable use of the terms 'placebo effect' and 'placebo response' as synonyms is a trend (Benedeti, 2013).

According to the Encharta Concise Dictionary (2001) the word placebo (Latin: "I will please") has the following meanings: 1. prescription without physical effect, something prescribed for a patient that produces a psychological improvement rather than having a physical effect; 2. inactive substance, a preparation containing no active ingredients given to a patient participating in a clinical trial in order to