*Review*

# Unsolved, Forgotten, and Ignored Features of the Placebo Response in Medicine

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## ABSTRACT

**Purpose:** We aimed to identify topics of research that have been neglected, undervalued, or overseen in the past 2 decades of placebo/nocebo research.

**Methods:** A highly specialized literature database containing >3200 articles on the placebo or nocebo effects or response was screened for articles covering placebo effects in nutrition, sports medicine, physical therapy, and psychotherapy; for article covering gender, age, and culture as influencing factors; for articles dealing with long-term outcome, multimodality; and for articles related to technical (eHealth, mHealth) aspects of placebo effects.

**Findings:** Although placebo research has gained substantial progress over the past 2 decades, it has not resolved all its puzzles, it has ignored some obvious and some less obvious facets of the placebo topic, and it has overlooked that during these years, medicine has further developed and progressed, as has the doctor–patient relationship and the social environment in which this communication happens.

**Implications:** The biggest threat for placebo research is that it may outdate itself by declaring all and everything as a placebo effect even if there may be better terms and concepts (eg, patient expectations, doctor–patient communication, empathy), and by ignoring that medicine continuously changes its face, for patients as well as for clinical researchers. Its biggest opportunity is the fact that it, as no other topic in medicine, requires both medical and psychological experts for its exploration and to stay updated. (*Clin Ther*. 2017;39:458–468) 

**Key words:** clinical trials, designs medicine, methodology, nocebo, placebo.

## INTRODUCTION

Placebo effects (PEs) and placebo responses (PRs) are immanent components of all and every medical intervention, be it during placebo-controlled randomized clinical trials (RCTs) of new diagnostics and therapeutics or during clinical routine management of patients at his/her physician's office or hospital. Evidently, PRs and PEs are to be minimized and to be controlled for during RCTs for the development of better therapies, but to maximize and harness in medical routine for the benefit of the individual patient.[1]

We understand PEs here as any improvements in a symptom or physiologic condition of individuals after a placebo treatment. There are different mechanisms underlying this phenomenon, including spontaneous remission, regression to the mean, natural course of a disease, biases, and PRs. We understand PRs as the outcomes caused by a placebo manipulation. The PR reflects the neurobiological and psychophysiologic response of an individual to an inert substance or sham treatment and is mediated by various factors that make up the treatment context. Importantly, PRs are not restricted to placebo treatments and can also modulate the outcome of any active treatment.[1]

Over the past 20 years, placebo research has fostered a much better understanding of the underlying neurobiological and psychological mechanisms of PRs (and to a lesser extent also the nocebo responses).[2] These include learning and expectations, to which we refer to

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throughout this article. For a more detailed description of their operation, please see a recent publication.[2]

Although there appears to be general agreement that PE is based on some form of learning (conditioning, prior history, social learning, and expectations), mediators of the PR may as well include factors that bridge across different diseases and therapeutic modalities and that may explain PRs independently of learning. Age and sex may be such factors that we discuss below. More recently, the search for genetic predictors of the PR have replaced the long and fruitless search for individual "personality" markers of placebo responders,[3] and new designs of RCTs and experimental approaches have taken increasing PRs in a number of clinical conditions into account.[4] These aspects will not be covered here because of the lack of space, but readers are referred to previous publications.[1,2]

The number of genuine publications dealing with the placebo and nocebo effect has risen from a few hundreds to now >3500 and highlights the relevance in medicine and beyond.

Despite this progress, however, a number of issues have remained unsolved in placebo research during the past decade, or even have been generated by the recent progress but require new solutions. They will be discussed here with respect to (1) experimental placebo research, (2) clinical components of the PE, and (3) societal and (4) technical dimensions of it.

## METHODS

Since 2004, we searched PubMed for articles using the search term "placebo" both retrospectively and prospectively to select articles dealing with the PE.

For all ~100,000 citations retrieved in 2004, we (P.E., K.W.) screened their titles and abstracts retrospectively and excluded articles describing placebo-controlled trials of individual drugs and other medical interventions that "only" assessed differences between drug and placebo for evaluation of therapeutic benefits of the therapy. We also excluded meta-analyses of placebo-controlled trials and respective reviews. After exclusion of letters and editorials, we were left with ~1000 articles (or ~1% of all articles screened) that discussed different aspects of the PR, Pes, or both in different medical and psychological subspecialties. These were predominantly experimental data (exploring the different mechanisms of the PR) and reviews, systematic reviews, re-analyses, and meta-analyses of RCT data. PDFs of these articles were retrieved and stored in an EndNote database. Since 2004, we prospectively screen all articles published on a weekly basis ever since (total article count: 194,680 as of November 11, 2016) using the same search term placebo. In 2015, we added the search term "nocebo" (414 citations as of November 11, 2016).

To manage these >3400 references (as of November 11, 2016), a few tools are available and have been used for this review: All articles are included in a self-designed literature database (operating similar to EndNote) for quick title, author, abstract, and MESH term search, available through our *Journal of Interdisciplinary Placebo Research* (www.jips.online). A detailed full-article semantic analysis was made possible via the semantic analysis program Luxid of TEMIS Expert System (www.expertsystem.com), courtesy of the company.

The summary reported here is a combination of both a heuristic and an empirical analysis, first presented during a meeting in Porto, Portugal, April 2016.[5]

## RESULTS

### Experimental Placebo Research

Although we all acknowledge that the PE is an immanent component of all medical (and many non-medical) interventions, we still lack systematic knowledge on a number of experimental issues related to the intra-individual stability of the response, on the cross-modality of the response, the contribution of age and sex, cross-cultural aspects, and long-term efficacy.

#### *Intra-individual Stability*

Only a few studies have attempted to assess whether a person (a healthy volunteer or a patient) who has responded to a placebo treatment will exhibit a similar response when tested a second time, either under the same condition or under different circumstances.

Kaptchuk et al,[6] in summarizing the existing older literature before 2008, concluded that "much of the existing evidence […] was performed before 1967. This early evidence is contradictory, methodologically weak and is sufficiently old to be considered medical history" (p. 587). Since then, the results of respective research "are not unequivocal, and may not be equivalent to non-deceptive conditions" (p. 587).

Whalley et al[7] argue that stability of response requires the within-subject response to be equal with two identical placebo tests (eg, of placebo analgesia)