Med Clin (Barc). 2017;xxx(xx):xxx–xxx

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

Placebo effect and therapeutic context: A challenge in clinical research☆

Antoni Morral[a,*], Gerard Urrutia[b], Xavier Bonfill[b]

[a] Facultat de Ciències de la Salut Blanquerna, Universitat Ramon Llull, Barcelona, Spain
[b] Centro Cochrane Iberoamericano, Institut d'Investigació Biomèdica, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 14 March 2017
Accepted 28 March 2017
Available online xxx

Keywords:
Placebo effect
Nocebo effect
Therapeutic context

ABSTRACT

When we apply a physical or pharmacological treatment, there are many things that may explain the clinical improvement experienced by a patient. The drugs or physical agents applied are important, but we must also add other elements in the context of the patient–therapist relationship. Scientific evidence has proven that the placebo effect exists. This is a true biopsychosocial phenomenon produced by the context in which an intervention is carried out. Biases aside, placebo and nocebo responses are changes in patients' symptoms, due to their participation at the therapeutic meeting, with its rituals, symbols and interactions. This multitude of signals inherent, in any intervention, is perceived and interpreted by patients and can create positive or negative expectations.

Efecto placebo y contexto terapéutico: un reto en investigación clínica

Palabras clave:
Efecto placebo
Efecto nocebo
Contexto terapéutico

RESUMEN

Cuando administramos un tratamiento físico o farmacológico, existen muchas variables que pueden explicar la mejoría clínica que experimenta un paciente. El principio activo del fármaco o el agente físico aplicado son importantes, pero también hay que sumarle otros elementos presentes en el contexto de la relación paciente-terapeuta. La evidencia científica ha demostrado que el efecto placebo existe. Se trata de un auténtico fenómeno biopsicosocial producido por el contexto en el cual se lleva a cabo una intervención. Sesgos al margen, las respuestas placebo y nocebo son cambios en los síntomas de los pacientes atribuibles a su participación en el encuentro terapéutico, con sus rituales, símbolos e interacciones. Esta multitud de señales inherentes a toda intervención son percibidas e interpretadas por los pacientes, generando expectativas positivas o negativas.

Definition

The word *placebo* and the expression *placebo effect* have different meanings. Placebo means an inert treatment, without therapeutic properties. Placebo effect is the response produced by the administration of a placebo. Placebo effect and placebo response are equivalent. These definitions contain a great paradox: How is it possible that something inert generates a response? If something is inert, by definition, it is incapable of producing responses.

The word *placebo* is a conjugation of the Latin verb *placere*, which means to please, to gratify, to satisfy. The placebo effect appeared with force in the scientific community after World War II, following Henry Beecher's article "The powerful placebo" published in the *JAMA* journal, in 1955. Beecher treated soldiers that had been wounded during the war. He observed that in some of them, the pain could be mitigated with a saline solution and that this produced effects similar to morphine. Thirty-five percent of patients responded positively to placebo treatment.[1]

Beecher's work on placebo was the beginning of medicine's modern era, where the randomized clinical trial represents the gold standard for evaluating the efficacy of an intervention. However, Beecher overestimated the placebo effect because it did not

☆ Please cite this article as: Morral A, Urrutia G, Bonfill X. Efecto placebo y contexto terapéutico: un reto en investigación clínica. Med Clin (Barc). 2017. http://dx.doi.org/10.1016/j.medcli.2017.03.034

* Corresponding author.
E-mail addresses: antonimf@blanquerna.url.edu, antonifm@blanquerna.url.edu (A. Morral).

2387-0206/

differentiate it from other bias or confounding factors, such as, for example, the natural course of the disease or regression to the mean. Since then there has been a growing interest in researching the placebo effect, especially in the last 15 years.

In a broad sense, the placebo effect refers to improvements in the symptoms of patients that are attributable to their participation in a therapeutic encounter, with its rituals, symbols and interactions.

The patient–therapist relationship implies a therapeutic ritual composed of a multitude of signs and symbols that are consciously and unconsciously perceived. These perceived messages are interpreted by patients, generating expectancy and conditioning.[2] We emphasize verbal and non-verbal communication, empathy, touch, gaze, enthusiasm, predisposition to listen and respond, trust, diagnostic and therapeutic tools, technology use, office or hospital room appearance, appearance of the waiting room, the white dressing gown, the stethoscope and the type of intervention (a pill or a physical agent).[3] This context is always present when a patient is subject to an intervention, whether we administer a tablet containing sugar or a tablet containing a potent analgesic. The tablet may be inert but the context is not.[4]

The placebo effect is based on complex neurobiological mechanisms involving neurotransmitters (e.g. endorphins, cannabinoids and dopamine) and the activation of specific and quantifiable areas of the brain: the prefrontal cortex, the anterior insular cortex, the rostral anterior cingulate cortex, and the amygdala, areas related to anticipation and reward.[5,6] Many drugs also act through these pathways.

Recently, genes that predispose to a higher placebo response are being identified.

Current evidence shows that the therapeutic benefits associated with the placebo effect exist, but do not alter the pathophysiology of the diseases, only their symptomatic manifestations. For example, there is no evidence that placebos can reduce the size of a tumour. However, clinical trials demonstrate the efficacy of placebos to alleviate the more frequent symptoms of cancer and decrease the side effects produced by chemotherapy, such as fatigue, nausea, hot flashes and pain.

Placebo effect and bias

When we administer a drug or an intervention, there are many variables that can influence the clinical improvement of a patient. We have talked about the placebo effect, but we must assess other phenomena that also act as biases. These phenomena may confuse us and we could be attributing to the placebo effect responses that are unrelated.[7]

Hawthorne effect

The act of participating in a clinical trial may produce an improvement in symptoms due to the observations the patient receives from the investigators. The Hawthorne effect was described in the 1920s. After years of work, researchers at a Chicago plant (USA) concluded that part of the benefit observed in the workers' production was due to the fact that they were being studied, rather than to the effect of the production process being implemented.[8]

Regression to the mean

In statistics, regression to the mean is the phenomenon in which if a variable is extreme in its first measurement, it will tend to be closer to the mean in its second measurement. Regression to the mean is closely related to the natural history of some diseases that occur with variations or exacerbations.[9] Patients affected by chronic pain due to musculoskeletal disorders are a good example. These patients usually ask for help when they are experimenting an acute exacerbation. Thus, in subsequent observations, the patient is more likely to be better off, to abandon one of the extremes and return to the mean.

Natural course of the disease

All diseases have a natural course that includes spontaneous remissions and fluctuations in symptomatology. It is an important bias to attribute these changes to the treatment or the placebo effect.[10]

Rosenthal effect

Also, known as the Pygmalion effect, it was described by R. Rosenthal in 1963. A person's beliefs and expectations about another individual affect his/her behaviour to such an extent that the latter tends to confirm them. A very close relationship is generated between the researchers and the participants of a study. There is a great commitment on the part of patients with what is expected of them in terms of results. This is the basis of the Pygmalion effect, which psychology explains as a principle of action based on the expectations of others.

Other biases

There are other biases that may affect the internal validity of the studies and raise doubts about the authenticity of the placebo responses. In clinical epidemiology, bias is a deviation from truth. Unlike random errors, bias represents a systematic distortion that can be minimized through rigorous and creative designs. In studies on the placebo effect, we highlight (a) *biases due to the selection of participants*; (b) *biases for cointerventions*: patients who do not receive treatment usually look for procedures outside the study protocol more often than patients in the placebo group. This bias may underestimate the placebo response; (c) *biases for patient withdrawal*: usually, withdrawal affects more patients who belong to the group without intervention; (d) *biases produced by the informed consent*: a cross-over trial was designed to determine whether the informed consent can modify the analgesic effect of naproxen and placebo. The difference in therapeutic activity between naproxen and placebo was moderately higher in uninformed patients. Information can increase both the apparent efficacy of the drug and that of placebo, and decrease the perceived difference between the two,[11] and (e) the *publication bias* studies with significant results are more frequently published than studies with no differences between groups.[12] Clinical trials with positive results are published more often and more rapidly than clinical trials with negative results.[13]

At present, the placebo effect has staunch advocates, granting it, in many diseases or conditions, an impact similar to the effect of active ingredients. But some authors, led by the Danish author Hróbjartsson, believe that the placebo effect is overrated and that creative and rigorous clinical trials are needed to reduce bias. Studies should compare a placebo intervention group to a non-intervention group. These studies would demonstrate the true effect of placebo interventions and investigate the elements involved in the placebo response.[1] In Figs. 1–3, we can see how the design of a clinical trial may overestimate the placebo effect or the results due to treatment.

Context and placebo effect

Research in neuroscience has shown that the placebo effect is a real biological phenomenon, due to the psychosocial context present in every therapeutic encounter.