

Original contribution

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Abstract

The far-reaching meaning of placebo and nocebo are often undervalued or ignored in clinical practice. Presently the term placebo is either used: (1) in the context of randomized controlled trials, (2) to describe a sham treatment in various nuances, (3) to describe effects often attributed to healers. This diverges from “no treatment” which has entirely different implications. Even less accepted is the term nocebo, which literally means “will harm”. As placebo this term can be ambiguous and can appear in many concealed ways. Research in the past years has been based on experiments and elaborated studies and on imaging studies. This both placebo and nocebo also have an empirical and scientific background. Also, ethical aspects concern placebo and nocebo issues, in particular in regard to changing relations of the physician- patient relationship, which affects both terms. Based on this knowledge, increasingly physicians and patients are aware of these phenomena, and it will be important to raise awareness not only in physicians, but also the health care personal involved in the treatment of patients.

Resumen

El significado de gran alcance de los efectos placebo y nocebo a menudo se subestiman o son ignorados en la práctica clínica. Actualmente, el término placebo se usa: (1) en el contexto de ensayos clínicos controlados aleatorizados (RCTs, por sus siglas en inglés); (2) para describir un tratamiento simulado en varios matices y (3) describe los efectos a menudo atribuidos a los curanderos. Esto difiere del “no tratamiento”, que tiene implicaciones completamente diferentes. Aún menos aceptado es el término nocebo, que literalmente significa “que dañará”. Como placebo, este término puede ser ambiguo y puede aparecer de muchas maneras ocultas. La investigación en los últimos años se ha basado en experimentos, estudios elaborados y en estudios de imágenes. El placebo y nocebo también tienen antecedentes empíricos y científicos. Además, aspectos éticos conciernen a los conceptos placebo y nocebo, en particular con respecto a las relaciones cambiantes de la relación médico-paciente, que afecta a ambos términos. Con base en dicho conocimiento, cada vez más médicos y pacientes son conscientes de estos fenómenos, y será importante concientizar no solo a los médicos, sino también al personal de atención médica involucrado en el tratamiento de los pacientes.

Palabras clave

*placebo, nocebo, ningún
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Introduction

The meaning and importance of placebo and nocebo are often undervalued or ignored in clinical practice and by Health Care Practitioner (HCP).

Presently the term placebo is either used in the context of Randomized Controlled Trials (RTC), or describing a “fake” or sham treatment, in different circumstances.

This is different from “no treatment” which has different implications, and also will be discussed in the paper, in particular as this can occur with or without consent of patients.

There is less awareness for the term nocebo, which means “I will harm” and is often considered a “bad prediction”. Like placebo also nocebo can appear many concealed ways.

The knowledge and the appreciation of the placebo effect is still in need of more dissemination, both in regard to physicians, medical personal and patients.

The scientific basis and evidence for placebo has dramatically increased in the past years based on sophisticated studies, the effects of placebo effects calculated in studies and imaging studies¹ placebo and health,² meaning;² and psychiatric conditions³ It is important to acknowledge, that all drugs do have a placebo effects to some extent.⁴

In addition to the need to raise awareness on placebo and nocebo in clinical practice, also ethical consideration and contextualization (“Zeitgeist”) are important. As an example, the meaning of placebo is presently different, than in the first half of the last century.

History

Medicine until the beginning of the 20th century to some extent has a history of placebo (P) (as the term is used now), as seen from contemporary medicine

as standardizes pharmacological therapies were not available.⁵

The effects of both P and nocebo (N) have been observed in ancient cultures. However, also the present distribution of health resources suggest that in 80 % of the world population medicine is not available, but persons are treated by traditional methods, herbs and healers, as demonstrated in a review on epilepsy.⁶

In the middle ages the term of “Placebo” was reserved for professional mourners and had a continuous development until today. Well known are examples as Mesmerism and Perinism, (around 1700)⁷ which were at the time investigated and clearly demonstrated, effects which we would now term “Placebo”.

During the last century the meaning of P has undergone changes: until the second world war the application of P drugs, without the knowledge of patients, was accepted. The major change in doctor patient relationship has changed since.

At the same time the term of the term P has become an essential part of RTCs. Thus, the meaning of the term has shifted to a technical expression. It is also interesting, that the “meaning/value” of P is perceived differently by different professional groups.

Presumably basic researchers and scientists may have a low opinion on P, contrary to physicians and some HCPs.

What is a placebo?

Placebo is a term which needs further clarification and will be explained below:

1) Placebo is considered an inert therapy or “sugar pill”. The term “sham” refers to a similar effect but is usually combined with an intervention (eg. knee operations). A positive effect of the intervention is considered a placebo effect.

2) In an RTC, which is considered the state of art, in clinical studies, the placebo effect is always determined in the verum group and the placebo group; the difference is the therapeutic effect.

3) Placebo also refers to the relation of physicians and patients. This is not only the personal interaction, but also other circumstances of interaction and treatment. These circumstances are often defined as “rituals”.

4) The placebo effect is not only person dependent, but also depends on the disease: for example, diseases with natural fluctuations (eg. Migraine, seizures), are associated with different placebo effects than a chronic progressive disease as PD or dementia. These are fundamental differences, which make the comparison of the placebo effects difficult.

d) It is unacceptable to exclude patients from drugs, if a medication is available for the purpose of a study.⁹

In RTCs usually a treatment group and a placebo group are compared. Presumably, also a “no treatment group” would be needed to exclude the interaction of the patient with the study team, when serving as an observer. It must be assumed, that even the information that this group will receive no treatment, might be a bias.

Examples of no treatment groups can be historical patient groups (for example the natural history of a disease before adequate treatment was available), patients not treated for other reasons or patients refusing treatment. There are also examples of patients which were deliberately excluded from already available therapies for the sake of investigation. An example of such a practice is are investigations on the natural course of syphilis.⁹ This is an example of no treatment, and there are many ethical concerns involved.

Table 1. Placebo effect and factors to be considered.

Natural course of the disease

“Regression to the mean”

Fluctuations

Doctor and patient bias

The “Hawthorne effect” *⁸

Observer bias- patient bias

Patient learning and “unlearning”

* Hawthorne effect: the “Hawthorne effect” describes changes in behavioral pattern, in persons being observed.

“No treatment” group

The “No treatment” is not the same as placebo also there is some discrimination of the terms is necessary:

- Is the patient informed that he receives no treatment?
- is he in a controlled study group?
- Is it a historic comparison group

Is there a placebo patient?

The identification of a “placebo patient” is seen controversially and is aimed to identify patients in regard to their inclination to have a placebo response.¹⁰ This discussion is controversial, and also touches genetic aspects.¹¹

The potential response towards placebo could also be depending on the type of the disease. As examples depressive disorders seem to have a high placebo response than other diseases (see below).

Cultural influences also need to be considered and are important in dealing with patients, who have another cultural background. In particular pain and pain tolerance vary in different cultures. Issues of migrants are becoming increasingly important as the individual spectrum may vary.

Inherent factors influencing the placebo effect:

The P effect has several components. Expectation, conditioning, and observational learning are important key words in placebo, which will be discussed below.

a. Expectations

Expectation is an important and essential part/dimension of/in placebo. The expectation of an event can be very powerful and can exert a main influence on the placebo effect. Additionally, age, social, observational and cultural aspects also seem to have an influence.

A daily life example is “wine tasting” by experts, where the expectation of the wine tasters can be influenced by factors stimulating their expectation. Two groups who were served expensive and cheap wine following the announcement of the quality of the wine were not able to distinguish between the two types.

In a similar experiment 2 groups been given regular and decaffeinated coffee. After several interchanges between the two groups also in this case accurate distinctions could not be made.

b. Conditioning

Conditioning is best explained by Pavlov’s dog experiments. Upon the ringing of the bell hypersalivation sets in. In a similar way/pattern, medical procedures and rituals may condition for upcoming experiences. The type of effect of the same procedure in different patient population could be related both to expectations and conditioning.

The perception can be influenced by prior experience, fear and anxiety, reward expectations, motivation, the wish for improvement or amelioration, as well as cure in both the placebo and the serum drug/procedure.¹²

c. Observational learning

Means that patients and relatives learn from one another. This means that positive effects as placebo

or the reverse can be elicited. A famous term is the “Hawthorne effect”. This observation was made in an industrial environment; however, it can be compared to the patient- physician relationship.

Are there scientific results explaining the placebo effect?

There is increasing evidence and literature,^{13,14,15} for biological effects of placebo. Some mechanisms are summarized on [Table 2](#).

Important issues in the P and N effect are functional MR investigations, which help to identify neuronal networks. Investigations demonstrate functional MR changes occurring during placebo effects.^{16,17}

The issue of similarities between “verum” drug treatment and placebo was described in studies.¹³

Another interesting question is whether the knowledge that the study contains placebo arm, also influences the result of the study.¹⁸

There are many other questions and topics related to placebo, which have been summarized in published works.^{13,14,15}

The mechanisms of placebo effects are also subject to several items relating from psychological effects towards biochemical and receptor-based assumptions: The P effect was also studied in regard to learning frames and behavioral patterns¹⁹ and whether the awareness of possibly receiving a placebo also influences the study.¹⁸

Table 2.

Psychologic phenomena
The endogenous opioid system
The endogenous cannabinoid system
The cholecystokinergic system
The dopaminergic system

The placebo effects vary in different diseases:

Placebo effects appear in different shapes and manifestations in different diseases. This can be explained by the characteristics of the disease. Episodic diseases must be compared with chronic progressive diseases, where the placebo effect has different dimensions. Also fluctuations, spontaneous remissions and “regression to the mean” and the effect of the physician patient relations are important.²⁰ For neurological diseases, the placebo effects will have distinct and varying patterns in migraine, neuralgia and chronic progressive diseases as Parkinson syndrome.

For several diseases as endocrine dysfunctions, gastrointestinal disorders, long and respiration disorders, autoimmune diseases, chronic pain syndromes investigations to determine the P effect have been made. In particular in cardiovascular diseases many studies are available.^{21,22}

Placebo is not exclusively connected with drug treatment, but is inherent to other interventions as knee surgery, the well examined operation of internal mammaria artery, and in regard to the disputable sham surgery.

Placebo controlled studies can be difficult in vulnerable populations as children, psychiatric patients, geriatric patients and dependents for other reasons.

The physician and HCP as a placebo

The relation of patients with physicians and HCP are important factors and contribute to the P and N effect. It is important that, independent of the acknowledgement of P and N, any relation between patients, therapists and carers implicitly contain a placebo or nocebo effect. It is important to raise the awareness of the issue among the HCP.

The unique relations between patients and HCP for both placebo and nocebo effects are important to disclose. Bedside manners, engagement, empathy and enthusiasm to treat patients are factors for increased success in the treatment of patients. In the same line are rituals. These rituals either overt or hidden determine the interactions between patients and therapists.

The ritual of the admission of the patient by studying the patient’s history, previous findings and the somatic examination is an important part of therapy. The role of the mindful and attentive physician, who pays attention to language, mood, and presentation of the patient is crucial.

Other important parts of the doctor–patient-relationship are trust and several other “soft” factors determined by human relations. Language, prosody, appreciation wording are important elements. Haptic contacts are often regarded controversially and require a bilateral intuitive perception. Although it may sound trivial, the appearance of the HCP, both optic, haptic and regard to smell, may play a role.

Empathy and “compassion”

The terms empathy and compassion are often used in a similar context. Empathy describes the ability to be able to affectively deal with emotional aspects. Further distinctions are made between verbal and cognitive empathy.²³ Empathic behavior can also be observed in the prescription behavior of drugs.²⁴

The term Compassion describes the “co-suffering” which also animates to provide emotional help. “Compassion fatigue” is usually considered a sign of exhaustion²⁵ and may be similar to what is considered a “burn out” syndrome,²⁶ which is an ambiguous and multi-contextual term which many be traced to Graham Greene’s book “A burnt out case”.²⁷

Other terms, which have closely related meanings, such as sympathy, an emotional reaction towards the misfortune of others, especially those who may suffer “unfairly”,²⁸ and “passion”²⁹ are used to describe attitudes and relations with patients.

“Grooming”

Grooming which defines the care for one’s appearance, is used as auto- or also allogrooming and employed in the nursing literature. It describes a social behavior, including intensive social contacts, consisting of empathy, compassion, eye contact and haptic sensations. The grooming of the patient by the HCP and, in particular, the physician can also provide a reciprocal reward for the HCP and is infrequently mentioned.³⁰

“Trust”

Trust is a cornerstone of the relation between HCP and patients. In addition to psychological explanations, also the circuit of the amygdala and the effects of oxytocin seem to play an eminent part. Interpersonal factors, as relationship, the appreciation of the HCPs work or often admiration for physician’s work play an important role and may enhance trust.

The Nocebo effect

Conversely to placebo, the meaning of the term nocebo is practically less commonly used, however, it may be of equal importance. Translated its meaning, the term suggest: “I will harm”, which is probably not always the intention.

The intentional use of nocebo is rare, but not impossible. However, one can assume that usually the attitude of physicians and HCP rather strives for a placebo effect. Sometimes a nocebo effect can be interwoven in the placebo response.^{31,32} Examples are Placebo controlled trials, where persons on placebo develop side effects of the verum group, which cannot be expected from the inert placebo

and are presumably induced by studying the description of the possible side effects.

Fear, worry and anxiety can predispose to negative expectations. The phenomenon of the negative prediction has also been observed as a cultural phenomenon in the “Voodoo” acts.³³

More trivial, but important in a large number, are possible negative predictions contained in manufacturer’s instructions for medications.^{34,35} The information is often unweighted and not listed according to frequency and the impact of the side effect. Often patients are then distracted from the main effect of the drug, and experience the nocebo effect as side effects.^{36,37}

Nocebo can also be induced by negative comments or non-appreciative behavior of the medical personal towards the patient as well as carers. Disrespect, negatively formulated statements, lack of attention and mindfulness are examples.

Placebo-Nocebo: Hope or euphemism?

The present concept of patient relation is based on autonomy and partnership. Compared with the prior paternalistic concept of physician – patient relations, the confrontation of severely sick patients has been avoiding prognosis and the discussion of death.

The physician is often confronted with hope and euphemisms. Hope for the sick patient is not always the hope for cure, but the amelioration of symptoms, reduction of pain, disappearance of nausea, or some personal issues, as meeting members of his family³⁸ as well as settling important personal issues.

The doctor/nurse as a patient?

Mostly, the self-experience of disease in the HCP is lacking. This is particularly relevant in the case

Table 3. Examples of nocebo in patient contacts.

Examples of nocebo in patient contacts	
Uncertainty when discussing a therapy	“the drug might help”
Using medical jargon	“we cut you up, we wire you ...”
Ambiguously	Emphasizing the negative
Unjustified	trivialization

of large age differences between the medical personnel and the elderly patients. The concept of understanding and immersion into the relevant age and circumstances of life needs skill and empathy. The only medical field which systematically trains self-experience is psychiatry and depending on the psychiatric school, trainees and young psychiatric often have to undergo a self-analytic process.

Ethical aspects:

Ethical attitudes and opinions are subject to time changes and contextualization. Until the 1960s the prescriptions of inert drugs as placebo were tolerated and at times even encouraged. This has changed and presently there are severe concerns that this practice would be considered as a deliberate deception of the patient.^{39,40,41}

However, in addition to this rather clear defined aspect, there are some sliding and more vague aspects regarding placebo, for example, prescribing a drug in a lower dose, using an off-label drug, as well as lacking adequate knowledge on the drug effects which were described.

Self-responsibility also includes increased self-medication. This depends on the region of the world and to the access of drugs. The literature search for this problem was not revealing significant work on this focused problem, except in psychiatric disorder and addiction.⁴²

The “golden standard” is often discussed in the debates of ethic boards, i.e. “The best or most successful diagnostic or therapeutic modality for a condition, against which new tests or results and protocols are compared”. However, the

study results are based often on a small margin between the effect of the therapy and the placebo effect. Frequently, statistical finesse is needed to substantiate this effect.

No treatment seems be unambiguous. However, “no treatment” can be done with consent of the patient and is not acceptable for study reasons, if some kind of treatment is already available and is, thus, denied to the patient. The example of the Tusagee event,⁹ where penicillin was denied to patients to study the natural course of the syphilis disease is deplorable.

Can placebos be used with the knowledge of the patient that he is receiving a placebo? Yes, this can occur and has been practiced under the term “undisguised placebo”. A good example is the sale of OBECALP (which is the reverse spelling of Placebo). (<https://blogs.webmd.com/all-ears/2012/07/placebos.html>). In this case, the patients and carers are informed that the prescribed drug is inert.

Another similar example comes from a psychiatric scenario where a patient with a depression received a placebo during a study and improved. After the study the result was revealed to the patient, and the prescription of the verum was offered. He refused on the ground that the drug he had received was successful.

In RTCs, the P treatment is part of the current concept; however, this procedure might be subjected to critique.⁴³ Nevertheless, the RTC can be considered to a legitimate and approved method, also defined according to the Helsinki criteria.⁴⁴

From the previous considerations, it is worthwhile to consider that placebo is an inert substance;

however, the large number of possibly associated circumstances as procedures, rituals and interaction, and possibly even the shape and color of the drug play an important role.

In summary, it is not easy to define the ethical aspects of P, however it seems easier to define concerning the N effects. Statements can include negative predictions: as an example, the medical information often distracts the patient from the aim of the prescription. However, there is also a small slope which is between a realistic and truthful disclosure, and a euphemistic information, which may spare the patient from the negative prediction, but may not be truthful.

The expectation of a patient in need is improvement or cure of his condition. This expectation is usually combined with hope.

Several investigations discriminate between placebo effects in different conditions. As an example, cancer pain in a progressive metastatic state will not have the same type of hope for healing. A transient disease, as headache⁴⁵ or migraine may have completely different placebo effects, than a chronic progressive disease. In particular, periodically recurring diseases, despite severe and often debilitating symptoms, leave the hope for the patient for complete remission and improvement. Increasingly also alternative therapies are considered.⁴⁶⁻⁴⁷ Although still scarcely reported, also the placebo effect may play a role in advanced disease, and also palliative situations.⁴⁸

As P and N mirror the interaction of the patient with the HCPs, in particular the patient/physician relation, the effect is ubiquitous and not avoidable, and has to be taken into account in any interaction.

In practice the adherence of patients to autonomy and self-responsibility, may still include several uncertainties. True content can be transmitted in several ways: true content with emphasis of the negative aspects, a more weighted content trying to describe the content and the advantages and disadvantages, or a euphemistic approach. All three possibilities are "truth"-based but may have

different effects ranging from nocebo to placebo or even deliberate deception. None of these three approaches is completely right or wrong. Often the wishes and needs of the individuals are not sufficiently considered.

Strictly speaking also therapies as alternative methods as AP may fall in the category of placebo and often these methods such as massage, physical therapies etc. are used and prescribed, however their effect is not proven in the conventional settings.

Vulnerable patient groups:

Some patient groups are vulnerable, meaning that they are, for some reason, unable to understand or give consent or are in some kind of dependency. These are children, psychiatric, geriatric patients and dependents such as members of organizations (eg. army) or prisoners, who for other reasons might not be able to give consent. This also has throwbacks as necessary studies in the vulnerable groups cannot be made. Possibly, new designs and comparisons of other parameters which were formerly used in the RTC, will help to enable investigations, and at the same time adhere to ethical principles.⁴⁴

Summary

This short review outlines the importance of placebo and nocebo in medicine. It also points out, that placebo has several meanings, from the study group in an RTC towards many other aspects of interaction of patients, carers and HCP. Contrary to placebo, the term nocebo is not well known, but of equal importance, yet the awareness is still less, and the theoretical background is also less explored. In addition to P and N also the meaning of “no treatment group” is important as it also includes a spectrum of different possibilities.

The changes in patient – physician relationship also has an influence on changes of the term and content of placebo. Yet, despite evidence based medicine, autonomy and self-responsibility of patients, placebo and nocebo are inherent parts of therapy.

The aim of this paper is to raise awareness for the manifold appearance of P, and also the awareness of N. This is important as both effects are continuously contained in our interactions.

Apart from the well formulated P effect in RTC, the ubiquitous P and N effects are a permanent part of our work.

Conflicts of interest

We declare that this research has no conflicts of interest.

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