REVIEW

Placebo and nocebo effects and their significance in clinical practice

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ABSTRACT

Most people have heard of the placebo effect, while relatively few have heard of nocebo, even within the circles of medical staff. Placebo effect means positive results by treatment via pharmacological inert substances. In contrast to placebo, by nocebo effect, due to negative beliefs and expectations, opposite results are achieved. Said in a more formal manner, what a sick person expects, unfortunately, he/she most often gets.

It is a fact that a high number of medical staff is still uninterested in placebo and nocebo effects, although they would benefit from them. Maybe this is because the treatment would not seem "scientific enough". However, the newest scientific evidence undoubtedly shows that placebo and nocebo effects arise out of very active neurobiological processes intervened by psychological mechanisms such as expectations and conditions. Regardless of whether or not the doctor or the patient are aware of this, placebo and nocebo effects are extremely powerful and represent a significant part of the treatment process, in treatment by methods of ancient cultures, as well as in modern medicine. Of course medicines hold their role, but understanding how the human mind processes information is also very important.

Key words: awareness, medical staff, mental processes, neurobiology, physicians.

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INTRODUCTION

Placebo and nocebo effects are universal phenomena, which follow medical practice from its early beginnings (1). Historically, placebo and nocebo effects have been until recently a result of bias in a subjective display of symptoms and many still consider them as such (2). However, there is growing evidence that these effects are intervened by specific neurobiological mechanisms, since recently this interpretation has been questioned and refused (3).

Considering that placebo and nocebo effects can have deep implications to basic and clinical research, as well as clinical practice, the prevailing stance today is that it is of great importance to better understand neurobiology and psychology of placebo and nocebo effects (3,4). This stance is based on the fact that through basic research we find out more on how psychological processes influence the neurochemistry of the central nervous system (3), as well as how these alternations consequently form the peripheral physiology and functioning of certain organs (5). Growing knowledge of neurobiology of placebo and nocebo reactions increasingly also influence the design of clinical examinations whereby treatment is tested against the placebo (3). In the end, this also influences the healthcare system, not only by initiating discussions within the ethical dimension of treatment by placebo, but rather by increasingly and justifiably forcing us to re-examine the significance of placebo and nocebo in clinical practice (6).

NEUROPHYSIOLOGICAL MECHANISMS OF PLACEBO AND NOCEBO

The phenomenon of placebo and nocebo cannot be explained by one special and unique neurobiological or psychobiological mechanism. These are complicated mechanisms which result in multiple reactions that include psychobiological and neurobiological mediators and reactions (3).

Mechanisms of placebo effect

Today the prevailing opinion is that the placebo effect is intervened by the brain's reward feeling center (4,7). Convincing evidence on the connection between the reward mechanisms with the placebo effects arise out of experimental studies of placebo induced analgesia. In a study in which positron emission tomography and functional magnetic resonance were used, Scott and co. (2007) (8) tested the correlation between responsiveness (lat. responsivus- one that gives an response, responds to something) on the placebo and responsiveness to monetary reward. Using the model of experimental pain with healthy examinees they discovered that responsiveness to placebo is connected to the dopamine activation in the nucleus accumbens which was assessed with the help of in vivo positron emission tomography of connecting receptors to raclopride (agonist on dopamine D2-D3 receptors). The same examinees were subsequently tested with functional magnetic resonance for activation in nucleus accumbens on monetary rewards. A positive correlation was determined between placebo reactions and monetary reactions, i.e. the greater the reactions of nucleus accumbens to monetary rewards, the stronger the placebo reaction. This study suggests that placebo responsiveness depends on functioning and efficiency of the reward system, and this could at least partially explain why some individuals react to placebo and some do not. Those that have a more efficient dopaminergic reward system would also react well to placebo (8).

In the second study of the same group of examinees, Scott et al (2008) (9) studied the endogenic opioid and dopaminergic system in different areas of the brain, including those connected to reward and motivation aspects of behavior. The examinees were subjected to painful stimuli in absence and in presence of placebo with expected analgesic characteristics. For the analysis a positron emission tomography was used (opioid with 11C-carfentanil, dopamine with 11C-raclopride). It was discovered that placebo induces activation of neurotransmission of opioid in the anterior cingulate, orbitofrontal and insular cortex, nucleus accumbens, amygdala and periaqueductal gray matter. The dopaminergic activation was noticed in ventral basal ganglia, including nucleus accumbens. Both dopaminergic and opioid activity was connected also with the expectation and experienced efficiency of placebo. Strong placebo reactions were connected with greater activity of dopamine and opioid in nucleus accumbens. This revelation shows that dopamine

and endogenic opioids that are activated in nucleus accumbens by application of placebo play a key role in modeling of placebo reaction (9).

In clinical practice, this phenomenon can be observed through the expectation of clinical improvement, which probably plays an important role in placebo effect. The findings of research of placebo in patients diagnosed with Parkinson's disease contribute to this (7,10). Based on these findings de la Fuente-Fernandez et al propose the neurobiological placebo mechanism. Once positive verbal suggestion creates a possibility of a reward which in case of placebo application is reflected through therapeutic progress, certain cortical neurons become active, and their activity is tied to the likelihood of a reward. Activated neuron cells send direct excitatory glutamatergic information to the dopaminergic cell bodies together with indirect inhibitory information of gama-amino butyric acid. The combination of these signals arriving to the dopaminergic neurons via direct or indirect connections contributes to the likelihood of tonic activation (11,12). Furthermore, it is stated that neurons in prefrontal cortex, nucleus accumbens, caudatus and putamen show a tonic reaction during the reward expectation (13).

Mechanisms of nocebo effect

In comparison to placebo, a lot less is known about the nocebo effect. This is likely due to the fact that introduction of nocebo reaction represents a stressful procedure for the sick person, so due to ethical reasons its exploration is limited. Term nocebo ("I shall harm") was introduced as an opposite to the term placebo ("I shall please") with a goal to differentiate the pleasing placebo effects from harmful placebo effects (14,15). If the positive psychosocial context typical for placebo effect is reversed then the nocebo effect can be studied. Therefore it is important to emphasize that studies of nocebo effects concern the negative psychosocial context of treatment, and their neurobiological research is an analysis of effects of this negative context on the patient's brain and body.

The basic psychological mechanisms of occurrence of negative expectations, and thereby nocebo reactions are: a) information regarding negative outcomes and expecting these b) previous experience of negative treatment outcomes and c) noticing negative outcomes with other patients (4,16).

Most studies of nocebo effects come from areas of pain processing with healthy examinees. There are two reasons for this. Firstly, because it is easy to give controlled painful stimuli to healthy examinees, and because sophisticated brain imaging techniques are available now (3,17). Following this, within experimental boundaries, it is established that healthy examinees through whose heads fake radio-frequency stimuli are inserted, claimed to electricity experience headache (18). This demonstrates that expectations created discomfort and pain in the head. Even more so, the mental processes can paradoxically modify even the effects of a medicine. Therefore, in one experiment once healthy examinees received incorrect information that they could experience increased pain, the typical analgesic effect of 33% nitric oxide (N_2O), reversed from analgesia to hyperalgesia, i.e. the examinees experienced a low degree of pain as high (19). This indicates that negative verbal information can transform typically painless stimuli into painful and cause nocebo reactions as strong as those caused by direct experience of negative outcomes (4).

These behavioral changes are supported with objective psychopharmacologic results (20) as well as brain imaging results (3,21). On one side, proglumide, the antagonist of cholecystokinin receptor (CCK) type -A/B, blocks the nocebo hyperalgesia reaction after application of placebo together with a verbal suggestion on increased pain, which indicates a specific exclusion of cholecystokinin composition in nocebo hyperalgesia (20). On the other hand, information on increased pain, even if only given once, can disturb the natural flow of pain perception by introducing the hyperactivity of the insular cortex in the duration of between 8 to even 90 days (21). Even more, the discoveries of other studies show that the effects caused by agonist μ-opioid remifentanil can be completely annulled when, during the infusion drug delivery, the examinees are told that the medicine infusion has been stopped, while it has not in fact been stopped. This shows that negative expectation can disturb the pharmacodynamic profile of a medicine (17,22). These observations are also supported with brain imaging studies. Namely, it is determined that during the expectation of pain several areas in the brain are activated like the anterior cingulate cortex

(ACC), prefrontal cortex (PFC) and insula (23-26). These experimental findings in the area of pain are important for patients with chronic pain, and probably in other clinical situations in which mental processes act as the main actor impacting medical outcomes (27).

THE SIGNIFICANCE OF PLACEBO AND NOCEBO EFFECTS IN CLINICAL PRACTICE

It is known in modern medicine that the treatment result of many active interventions is also connected with the active component of the treatment and the components of placebo and nocebo. Current evidence states that placebo and nocebo effects depend on different neurochemical and neurophysiological mechanisms, which can be measured and modified (27). These effects are certainly connected with the treatment context. Namely, all medical treatments are conducted in a certain context. This context includes the doctor's stances, psychological factors, as well as patient's expectations, wishes and hopes. Clinical experience as well as research findings show that in many medical interventions, therapy results can be assigned at least partially to the compatibility between the proposed treatment and the patient's system and beliefs (3,4,27). This part of therapy reaction is normally called placebo, or nocebo effect. A more formal definition of placebo/nocebo effect is that it is the part of the therapy reaction not attributed to the medicine components.

Clinical model of the placebo effect

Placebo therapy effect mechanisms result in multiple reactions, they are complexed and include psychophysical and neurobiological mediators and reactions. Goffaux and co. established a general model of the placebo effect (placebo analgesia), and described modeling of nocebo effects (28). According to this model, the placebo effect includes a complex reaction which begins with introducing the placebo into the therapeutic treatment, and moves via psychophysiological mediators all the way until actualization of the clinical effect (Table 1) (17). The introductory phase of this model includes the presence of an indication, i.e. a condition which benefits from the placebo effects. Content-wise the introductory phase encompasses therapeutic messages, application methods, patient follow up and booster sessions, as well as assessment of side effects during the introduction of placebo. In the introductory phase, in addition to the above mentioned, an assessment of individual characteristics is conducted, such as belief and value systems, personal history, as well as innate predispositions of the sick person and the therapeutic context, including the treatment objectives, therapeutic alliance and socio-cultural factors.

Clinical experience instructs that the significance of the given therapeutic message greatly depends on individual and cultural characteristics of the

Table 1. General model of placebo effect*

INDUCTION ⟶	PSYCHOPHYSIOLOGICAL MEDIATORS ⟶	ACTUALIZATION OF EFFECTS
Introduction or Initiation • Therapeutic message (implicit or explicit) • Method of administration • Follow-up, booster sessions, and assessment of side-effects	**Conditioning** • Environmental cues previously paired with an effective treatment now trigger an analgesic response **Cognition** • Expectations of relief: My pain should subside. **Motivation** • Objectives and desire for relief	**Subjective Experience** • Pain • Emotions • Quality of life • Satisfaction • Relative relief **Behavioral Markers** • Amount of analgesics consumed • Overt pain behaviors
Idiosyncratic Variables • Beliefs and values • Personal history • Innate predispositions	**Emotions** • Reduced anxiety and distress: *There is hope!* ↑ ↓	
Therapeutic Context • Treatment objectives • Therapeutic alliance • Sociocultural factors	**Neurophysiological Mediators** **Neurochemical Responses** • Production of endorphins, dopamine and other various neurotransmitters/neuromodulators **Neurophysiology** • Activation of central modulatory mechanisms, including descending inhibitory circuits	**Physiological Markers** • Physiological nociceptive activity • Objective clinical indicators

*Adapted and modified from: Goffaux P, et al. Placebo analgesia. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH (eds). Pharmacology of Pain. IASP Press, Seattle. 2010;451-73(17).

sick person. Studies, which have examined the importance of such rituals, discovered that the application of the treatment as well as messages concerning the treatment shape the strength of the placebo reaction (28). Basically, an encouraging message like "this treatment is particularly effective and give the relief in most patients" showed positive results.

In contrast to this, uncertainty messages reduce the desirable influence of placebo effects. This is key in conducting randomized two-fold blinded and placebo controlled examinations whereby examinees are informed that they only have a 50% chance to receive active treatment, without positive encouragement (29,30). This certainly decreases the placebo effect or even causes the nocebo effect. Therefore, the same characteristics of the placebo medicine such as color, size and quantity can also contribute to its effectiveness (31,32). In a similar manner, the "generic" placebo is less effective than the placebo carried by a medicine of a well-known name (33). Invasive medical treatment, like intravenous application of medicines and surgical treatments can also cause more pronounced placebo effects than non-invasive treatments like oral medicines (31,32). In the end, follow up of patients through booster sessions or assessment of side effects also contribute to the placebo effect (27).

However, notwithstanding the importance of the therapeutic ritual, the ritual on its own is not sufficient, at least not for an overall placebo effect which also includes other multiple variables. Firstly, the message must be directed to persons with characteristics that make them susceptible to a suggestive message. In addition to this, the history of previous diseases plays an important role, and especially earlier experiences with treatment through which therapeutic messages are often interpreted (28,34). All of the stated factors are of exceptional importance because the placebo effect is more powerful if it is in accordance with the beliefs, values and objectives of the patient (27).

The second phase of the placebo reaction represents a cascade of psychophysiological reactions which begin during or after the introductory phase (Table 1). Psychological mechanisms include previous experiences, i.e. the effects of conditions and expectations from the treatment, as well as the motivation variable, including the wish for relief from suffering and variations in the emotional state (e.g. a decrease in anxiety and distress). These psychological mediators have well-defined neurochemical and neurophysiological intermediators i.e. biological mechanisms which are responsible for the emergence of the placebo effect (28). Once the cascade of physiological reactions occurs, an actualization of effects can be noticed where placebo reactions can be expressed in numerous ways and signals. These effects include a subjective experience such as the change in experiencing pain, emotions, quality of life, pleasure and related relief; behavioral markers with the quantity of consumed medicines e.g., analgesics and behavior during obvious pain as well as physiological markers and objective clinical indicators (Table 1).

Nocebo effect in clinical practice

Possible nocebo reactions are common in clinical testing and practice. Recent laboratory research of nocebo effects, i.e. the harmful effects occurring due to expectations have shown that this is a neurobiological phenomenon which can be manifested through visible bodily changes and can cause harmful health consequences (3). Furthermore, it was noticed that in placebo controlled clinical testing patients that receive placebo often state side effects similar to those experienced by patients subjected to the treatment being studied, i.e. patients which receive pharmacological active substances. These effects can be assigned to the very transfer of information regarding the possibility of harmful effects during the informed consent procedure (35). However, nocebo effects do not include only negative reactions to inert interventions as in placebo controlled testing and laboratory experiments. These effects can also arise in clinical practice due to negative expectations tied to discovering possible side effects of the prescribed treatments. For example, informing the patient regarding the possible side effects of the prescribed medicine can in itself cause the same side effect notwithstanding the pharmacological characteristics of the medicine (4).

Just as interpersonal and environmental dimensions of a clinical encounter have a potentially powerful therapeutic benefit (36), the negative aspects of a clinical encounter can have negative, nocebo effects (4). In daily clinical practice the

nocebo effects can be the result of an interaction between the clinical professionals and patients, and the general psychosocial context in which the patient is found. Harm and negative outcomes can in the same way be connected to the process of discovering serious sickness and prognosis as well as sources of information regarding health (37,38).

Nocebo effects in clinical testing

In clinical testing a considerable proportion of patients in placebo controlled groups, i.e. groups to which, instead of pharmacologically active substances inert substances are given, experience negative side effects which overlap with side effects of actual medicines. Suggestive evidence for this type of nocebo effect is given by meta-analysis of placebo controlled testing of medicines with different side effects. So, for example, Amanzio et al created a systematic overview of harmful effects of a migraine medicine in randomized placebo controlled clinical testing. They found a high rate of harmful events in placebo groups which overlap with those found in specific types of real medicines that were tested (39). The connection between the stated side effects in placebo groups and known side effects of certain medicines suggests real nocebo effects arising during the process of informed consent.

Similar results were obtained for antidepressants as well. Overall meta-analysis of 143 placebo controlled randomized testing of antidepressants including 21 examination of tricyclic antidepressants (TCA) and 122 examinations of selective serotonin reuptake inhibitor (SSRI) showed a higher rate of harmful events in tricyclic testing than in testing of SSRI. This was correct not only for the group receiving the active medicine, but also for the placebo group in tricyclic antidepressants. Symptoms of patients who received the TCA placebo and those who received SSRI looked like this: dry mouth (19.2% versus 6.4%), problems with eyesight (6.9% versus 1.2%); tiredness (17.3% versus 5.5%), and constipation (10.7% versus 4.2%). This demonstrates that information on harmful effects of different types of medicines creates patient's expectations which can influence the experience of side effects and can make the outcomes of clinical testing biased (40).

While the above described examples retrospectively analyzed the appearance of potential nocebo reactions, some experiments were specifically designed to prospectively explore the connection between informing the patients and occurrence of side effects. For example, such a connection between informing and occurrence of side effects was discovered in cases of harmful sexual outcomes with patients with benign prostatic hyperplasia treated with finasteride (41). The study was designed in a way that sexually active patients with benign prostatic hyperplasia who received finasteride (medicine of proved effectiveness for treating hyperplasia) were randomized to two groups with different methods of informing them of the side effects. One group was given information regarding the possible harmful sexual consequences ("...it is not common, but the medicine can cause erectile dysfunction and ejaculation problems, and decrease the libido"), while the other group were not told about these side effects. During the follow up, after 6 and 12 months, it was found that a considerably higher number of patients who were told about the possibility of side effects declared these (43.6%) in comparison to those who were not told about the side effects (15.3%) (41).

Verbal information given during the standard medical procedures can also cause different exacerbation in symptomatic pain. This can be seen in the study on verbal communication with pregnant women. Women at birth that request epidural anesthetic were randomized in two groups: usual description of painful experience during local anesthetics ("You will feel a small sting like a bee sting; that is the worst part of the procedure") or a more assertive description ("We will give you a local anesthetic which shall numb the area and you will be comfortable during the procedure"). Immediately after the injection a neutral observer was called into the room (who was not acquainted with the study's design) to estimate the patient's pain. Those women giving birth who were told to expect pain like a bee sting during the application of the local anesthetic (nocebo group) assessed the pain as considerably stronger than those who received the anesthetic with assertive, positive words (42). Findings of this study show how important is the way of giving information to the patient, even much more important than the fact that information is given.

Besides the harmful effects of informing, exposure to cumulative experiences of pain can also lead

to anticipated pain and conditional nocebo hyperalgesia. An example of conditional hyperalgesia reaction is mentioned in the observational study of hospitalized newborns whose mothers are diabetics. In order to monitor the blood sugar levels, blood samples were taken for these children during the first 24 to 36 hours - by pricking the heel without anesthetics. Newborns of diabetic mothers showed greater pain than newborns of healthy mothers who were subjected to common blood sample taken for control purposes (43). Thereby newborns of diabetic mothers showed their anticipated behavior, i.e. reacted in pain when their skin was only hygienically cleaned prior to the sting. This suggests that the procedure of cleaning the skin connected with taking the blood sample was a conditional stimuli for causing painful reactions in absence of a painful stimuli - which is an example of conditional nocebo reaction.

Nocebo effects are also included in allergic disorders (44) and difficult symptoms such as nausea and vomiting with patients with a malign disease who receive chemotherapy (45). These nocebo effects are in most cases connected with transferred verbal information and negative expectations.

From the above stated, it can be concluded that these harmful effects decrease the quality of life and negatively influence holding on to therapy, which emphasizes the need for a decrease in nocebo reactions to the extent possible.

In conclusion, placebo and nocebo effects arise from very active neurophysiological processes which are intervened by psychological mechanisms like expectations and conditioning. These neurophysiological processes can be measured and modified, which represents the basis for their application in clinical medicine. Namely, it is known in modern medicine that the effect of treatment of many active interventions is connected to the active ingredient of the treatment, but also to the compounds of placebo and nocebo, which have significant clinical implications. Therefore it is advisable that clinical professionals do not attempt to avoid the placebo, but on the contrary, it should be emphasized, while at the same time avoiding or decreasing the nocebo effect.

Managing verbal communication and contextual signals in respect of any medical treatment are important elements of good clinical practice. In general, medical interventions should be accompanied by an assertive, empathetic and supportive communication. Clinical training should include education about placebo and nocebo reactions and strategies for emphasizing the placebo and reducing the nocebo effect, all in accordance with the ethical relationship between the clinical professionals and the patient.

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Placebo i nocebo efekti te njihov značaj u kliničkoj praksi

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SAŽETAK

Većina ljudi čula je za placebo-efekt, dok ih je relativno malo čulo za nocebo, čak i u krugovima medicinskog osoblja. Placebo-efekt podrazumijeva pozitivne rezultate nakon tretmana farmakološki inertnim supstancama. Za razliku od placeba, nocebo-efektom se uslijed negativnog vjerovanja i očekivanja, postižu obrnuti rezultati. Formalnije rečeno, ono što bolesnik očekuje, nažalost, najčešće i dobije.

Činjenica je da je još uvijek veliki broj medicinskog osoblja nezainteresiran za placebo i nocebo efekte, iako im oni idu u korist. Možda je to zato što liječenje ne bi djelovalo „dovoljno znanstveno". Međutim, najnoviji znanstveni dokazi nedvojbeno ukazuju da placebo i nocebo efekti proizlaze iz vrlo aktivnih neurobioloških procesa kojima posreduju psihološki mehanizmi poput očekivanja i uvjetovanja. Bez obzira jesu li ili pak nisu liječnik i pacijent svjesni toga, placebo i nocebo efekti su vrlo moćni i predstavljaju značajni dio liječidbenog procesa, kako u liječenju metodama drevnih kultura, tako i u modernoj medicini. Naravno da lijekovi imaju svoju ulogu, ali razumijevanje kako ljudski um procesira informacije, također je vrlo bitno.

Ključne riječi: svjesnost, medicinsko osoblje, mentalni procesi, neurobiologija, liječnici.