



The Importance of the Placebo Effect in the Treatment of Different Diseases: A Vision From General Medicine



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Submission: January 30, 2019; **Published:** February 07, 2019

Abstract

Although there is currently no comprehensive list of placebo effectiveness for all major diseases, the clinician should be aware of the placebo effect in the intervention on clinical conditions where psychological factors are prominent, especially in acute, and postoperative pain, mental illnesses, functional digestive diseases, Parkinson's disease, migraine, osteoarthritis, symptoms secondary to chemotherapy, asthma, systemic hypertension, angina pectoris, silent myocardial ischemia, congestive heart failure and tachyarrhythmias. Since the effects of placebo contribute to the responses of the active drugs, it is feasible to increase the patients' benefits of the treatments by increasing the additional placebo effect. There are several possibilities to use the effects of placebo in the consultation:

- a) A positive environment of communication and doctor-patient relationship;
- b) Stimulate positive expectations and minimize patient's negative expectations; and
- c) In addition to focusing on a "personalized" choice of drugs based on biomarkers or genes, it is the doctor-patient communication that must be adapted. Physicians should remain aware of the strength and meaning of both placebo and nocebo responses and why and how patients actually respond to health problem management strategies

Keywords: Placebo effect; Nocebo; Treatment effectiveness; Disease; Motivation; Physician-Patient relations

Introduction

Placebos are substitutes for medications or active interventions that can improve symptoms in patients when they are prescribed or performed by a doctor and for a patient and their effect cannot be explained by the medication itself or by the intervention itself. In research studies and, presumably, also in clinical routine, placebo effects contribute substantially to the efficacy of medications. Although this is a field whose evidence is still in development, current knowledge grows in approximately 10,000 publications per year in placebo-controlled studies, and in almost 100 articles on the placebo effect itself [1].

A definition of what the placebos are and how they act would be: "any therapeutic procedure (or a component of the therapeutic procedure) that is deliberately given to have an effect, or that unknowingly has an effect on the patient's symptoms or illness, but which objectively it does not have a specific activity for the treated condition." The placebo effect is defined as the changes produced by placebos [2,3]. And in contrast, the nocebo effect is defined as the worsening of the symptoms induced by any negative attitude of the non-pharmacological therapeutic intervention, both active

and inactive therapies. When a patient anticipates a negative effect associated with an intervention, medication or change in medication, they may experience an increase in this effect or experience it initially [4]. That is, simplifying, placebo is defined as an inert substance that provokes perceived benefits, whereas the term nocebo is used when an inert substance causes harm [5].

In this context, it is also important that the patient have a sense of control over the disease and actively participate in the administration of the treatment, as this will increase the likelihood of a favorable effect. In addition, greater placebo effects are obtained when patients are safely given a firm diagnosis, they are given diagnostic tests, they are told to use a new utility procedure, and they are encouraged to improve [6]. Consequently, the placebo effect that confirms the mind-brain-body interaction acts through different mechanisms such as reward, conditioning, social learning, etc. [7]. Likewise, it can be said that, in evolutionary terms, nocebo and placebo effects coexist to favor perceptual mechanisms that anticipate dangerous threats and events (nocebo effects) and promote safety behaviors (placebo effects) [8]. Recent developments in brain imaging allow a better understanding of the

neurobiological mechanisms underlying the effects of placebo, of which the opioid and dopaminergic systems are the most reliably documented [6].

However, the placebo effect is a complex phenomenon that occurs in a wide variety of clinical conditions. Although there has been much placebo research in diseases such as depression, chronic pain and irritable bowel syndrome [9], the possible practical conclusions remain unclear. It is often stated that placebo interventions substantially improve the results reported by patients and by observers in many clinical conditions, but most reports on the effects of placebos are based on studies that did not randomly assign patients to placebo or the no treatment group. The reviews carried out on the subject show that there are results data available in hundreds of clinical trials, and that they are directed to the investigation of at least 60 clinical conditions. These reviews do not find that placebo interventions have significant clinical effects in general. However, in certain settings, placebo interventions can influence patient-reported outcomes, especially pain and nausea, although there are often many potential sources of bias (mainly variations in the way the trials were conducted and in the way in which patients were informed), and it is difficult to distinguish placebo effects reported by the patient from other causes. On the other hand, even in studies with low risk of bias, the effects can vary from being insignificant to clinically important [10].

What is clear, however, is that the placebo effect is not verified in the same way in all pathologies and therapies. In some conditions the placebo effect is enormous and demonstrates the importance of the psychological component of the problem, as in the case of pain, whereas in other conditions the placebo effect is insignificant or goes unnoticed, as in strictly biological or anatomical problems (an infection or an anatomical malformation, for example); that is, the placebo effect has limits [7].

On the other hand, among the multiple factors that can interfere in the placebo effect, it is known that one of the main factors is the doctor-patient relationship, especially in general medicine where there is a continued attention over time that favors relational links between patient and doctor. The results of the treatments are more dependent on the personality of the therapist and the doctor-patient relationship created in the consultation, than on the pharmacological effect or the technique used. There is evidence that health professionals can influence patients about the way they think and feel about their illnesses or their treatment. Therefore, the "how" of prescribing is than important as "what" we prescribe [3]. In this complex scenario, little emphasis has been placed on differentiating diseases or clinical conditions more or less susceptible to the placebo effect. Thus, this article aims to reflect on the different placebo effect according to different diseases, and their implications for clinical practice.

Discussion

At present, a complete list of the effectiveness of placebo for all major diseases is still lacking [11], although as a general rule it has been reported that the effect of drugs and placebos is more

intense in acute stressful situations, such as postsurgical pain, headache or anxiety [2,3]. One of the reasons for this relative lack of differential information on the placebo effect in different diseases can be attributed to the existence of numerous psychosocial factors affecting the diseases themselves, modifying experiences and emotions, and consequently modifying the doctor-patient relationship and the effect placebo. These psychosocial factors of the diseases include, among others, feelings of anguish, guilt, punishment, fear of death, stress, low self-esteem, etc. And different types of them are present in diseases such as, cardiovascular diseases, bronchial asthma, rheumatoid arthritis, digestive functional disorders, migraine, Parkinson's, psychiatric diseases, AIDS, hepatitis C, cancer, etc. [12]. On the other hand, the symptoms perceived and communicated by patients, especially in general medicine can be expressions of biochemical alterations, symbols for the patient, expressions of the group context, or ways of coping with a situation [13]. In addition, representations of health and illness are dependent on the cultural context, even though there are commonalities; there are also perceptions of different psychosocial aspects according to cultures [14], which make it more difficult to generalize results of the placebo effect. In any case, among the pathologies that are clearly affected by the placebo phenomenon, pain deserves special consideration, followed by Parkinson's disease and mental illnesses, all of them health problems where the interaction of pharmacological effect and psychological effect is huge.

Pain

Pain is the condition where the placebo effect - which is essentially a psychological or psychosocial effect - has been studied more, clinically and experimentally, from postoperative pain, musculoskeletal pain or headache, due to the fact that it is a psychologically influenced symptom. Placebo induces significant analgesia, on average, in 35% of patients with pain, with some variations depending on the pathology studied and the modalities of therapy. Almost the same percentage (36%) of the patients is the one that responds to treatment with morphine in medium doses. This placebo effect is especially influenced by the expectations and beliefs of the patient, the doctor, the environment and the quality of the doctor-patient relationship. As with a real psychogenic analgesia, this effect could in part cause a release of endogenous opioid substances. Through a good relationship with your patient and a treatment that corresponds to your expectations and beliefs, the doctor induces a powerful placebo effect that increases the specific effects of your analgesic treatment [15,16].

But it has even been reported that in pain, the response to placebo is usually very high, approaching 100% of cases, equaling the pharmacological effect. However, it is also possible that the placebo effect goes in the opposite direction producing a nocebo effect and increasing the perception of pain. Giving the patient a negative diagnosis, such as cancer with a poor prognosis, produces a negative expectation and an aggravation of pain in the patient. On the contrary, an expectation of therapeutic benefit and clinical improvement is a crucial factor of the placebo effect in pain. In this

situation, certain stratum of the brain produces certain biochemical processes, activating and releasing various neurotransmitters such as endorphins and endocannabinoids that inhibit pain. On the contrary, it occurs when the expectation is of clinical worsening, producing a nocebo effect, and activating neurotransmitters such as cyclooxygenase that have a pain-amplifying effect [2,7].

Placebo responses, both acute pain and chronic pain, are generally high in pain treatment settings and the history of treatment modulates this effect. Different mechanisms can be the basis of placebo responses to acute and chronic pain. Consequently, a basic implication for the physician is the need to consider the responses to the placebo and the history of interventions in the treatment of chronic pain [17]. The investigation of the placebo effect in recent years has improved our understanding of how placebo treatments reduce the patient's symptoms. The expectation of improvement of symptoms is the main factor underlying the placebo effect. These expectations are shaped by past experiences, contextual cues, and biological traits, which ultimately modulate the degree of a person's response to a placebo. The body of evidence describing the physiology of the placebo effect has been derived from studies primarily restricted to pain. The findings of imaging studies support the role of endogenous opioid and dopaminergic networks in placebo analgesia in both healthy patients and patients with painful medical conditions [18].

The effects of placebo and nocebo are currently in the focus of clinical and experimental pain research. Neurophysiological and psychophysiological mechanisms could play an important role. The effects of placebo and nocebo can be mediated via the descending inhibitory pain pathway through endogenous opioids. Apart from that, three different psychological mechanisms could be relevant for the placebo and nocebo effects: classic conditioning, social learning and pain expectation. An open analgesic application, detailed patient information on the efficacy and possible adverse events (without an extensive focus on it) of drugs and analgesic interventions and active patient participation in pain therapy (for example, through the use of analgesia controlled by the patient) could improve the treatment of acute pain through an additive placebo effect (which could be around 30%) [19].

In musculoskeletal diseases as in osteoarthritis, pain, stiffness, self-reported functional limitation, and the overall evaluation of the physician, they clearly improve in response to placebo. The determinants of the magnitude of the placebo response include patient-physician interaction, expectation of response to treatment, knowledge of the treatment, personality traits of the patient and specific factors of the placebo, such as route and frequency of administration, the brand and the treatment costs. Therefore, contextual factors that improve the response to treatment should be used in the treatment of chronic painful diseases, such as osteoarthritis, where the available treatments are only modestly effective [20].

Mental illness

In patients with psychiatric illnesses, such as anxiety disorders or depression, a large overlap is observed in clinical changes in

patients who respond to medications and in those who respond to placebo, which supports the role of serotonergic networks in the response to the placebo. The serotonergic system appears to be involved in the effects of placebo observed in depressive patients, as demonstrated by a study using Positron-Emission Tomography to compare changes in brain glucose metabolism induced by placebo versus fluoxetine [6]. Molecular techniques have been relatively underutilized in the understanding of the placebo effect until recently. It may be thought that in the future there will be a general description of the phenotypes responding to placebo and the genetic markers that have been associated with the placebo effect in schizophrenia, anxiety disorders and depression (as well as in pain) [18]. It has been reported that some genetic variants correlate with the placebo response. In social anxiety, for example, carriers of a certain genetic variant of the transport of serotonin and tryptophan hydroxylase respond well to placebo, whereas non-carriers of the variant do not. Similar situations seem to occur in major depression and irritable bowel [7].

In the depressive disorder it is accepted that the antidepressant pharmacological effect supposes 25%, the placebo effect 50%, and the remaining 25% is attributable to spontaneous remissions of depressive symptoms. In addition, the placebo effect in the depression-anxiety problems is probably increasing, given the tendency to prescribe more psychotropic drugs, which increases the placebo effect of the psychological expectation of the active treatment drug. It is evident that in the psychiatric field and in general medicine, in health problems such as the abuse of substances such as drugs, alcohol, or tobacco, the placebo effect plays an important role. In general, it can be affirmed that the expectation of receiving one of these substances reinforces the pharmacological effect and induces greater pleasure. Expectation plays an important role in drug dependence.

For example, the prescription of an amphetamine to a dependent patient, saying it is an amphetamine, greatly reinforces its effect compared to if the patient is told that it is a placebo: in the first case the patient "expects an effect", in the second, not [7]. In short, with respect to psychiatry, the placebo effect plays an important role in most psychiatric disorders, such as depression, anxiety, addictions and, contrary to what might be expected, also in schizophrenia. In the same way, the nocebo effect should not be neglected, to identify the factors that cause it, and to try to prevent it [21].

Gastrointestinal diseases

The analgesia with placebo is an effect of psychosocial context that is rarely studied in visceral pain. Patients with irritable bowel syndrome exhibit visceral hyperalgesia and increased activation of the affective / cognitive brain region during visceral stimuli. The psychological factors alter the pain and the pattern of cerebral activation, and these changes are more pronounced in patients with irritable bowel syndrome. Here too, expectation constitutes the main neuropsychological mechanism in the placebo effect. [22]. Chronic abdominal pain (as in irritable bowel syndrome) is very frequent, with a damaging individual and socio-economic impact and limited and ineffective treatment options. At the same time, these

patients, as in irritable bowel syndrome, show high rates of placebo response in clinical trials and benefit from placebo interventions. In randomized controlled clinical trials, a positive response has been reported in 20% to 40% of patients with irritable bowel syndrome in the “placebo control group.” On the other hand, there is no specific treatment that has been shown to be effective for digestive functional disorders. Diet, lifestyle, antidiarrheals, laxatives and psychoactive treatments are of marginal benefit in irritable bowel syndrome. For digestive functional disorders, the strongest therapy is provided by the therapeutic relationship. Psychological factors, including emotions and cognitions in the context of visceral pain, have been related to the pathophysiology of the as in irritable bowel syndrome and other conditions characterized by somatic symptoms without medical explanation [23].

In other words, randomized controlled trials have shown similar short- and long-term placebo response rates in the digestive system compared to other medical diagnoses. Most mediators and moderators of the effects of placebo in gastrointestinal diseases are also of a similar type and size to other medical diagnoses and are not specific to gastrointestinal diagnoses. Experimental studies with placebo and nocebo underline the “power” of expectations and conditioning processes in the configuration of gastrointestinal symptoms [24]. Consequently, the physician must make an early and firm diagnosis, provide the patient with the expected diet and lifestyle advice, use the known data on the natural history of digestive functional disorders (for example, irritable bowel syndrome) to reassure the patient and convince them about that cancer is not the cause of their symptoms. And then, doctor should strive to mobilize the placebo effect through the ancient healing elements of empathy, explanation, tranquility and a positive approach [25].

Neurological diseases

A complete understanding of the placebo effect must include both its psychological mechanisms and the underlying neurobiology. In contrast to other types of conditions, neurological disorders could provide specific clues to understanding the effect of placebo, since the pathogenic mechanisms of different diseases could interfere with the neural circuits involved in the perception of the symptoms of the disease. However, there are ethical considerations that dictate the limits of the use of placebo. In any case, the placebo effect is of importance in several neurological conditions, such as Parkinson’s disease, neuropathic pain, headache, multiple sclerosis, and epilepsy. [6,26]. In the neurological field, one of the pathologies that shows a greater placebo effect is Parkinson’s disease. It is perhaps the second condition, after pain, most studied in relation to the placebo effect. Parkinson’s disease mainly affects the motor system, and its main symptoms are tremor, muscle rigidity and slowness in the execution of movements. Drug treatment is fundamentally based on the replacement of missing dopamine. In this condition, the administration of a placebo activates the dopamine in the striatum that controls movement and correlates with clinical improvement with decreased tremor and muscle stiffness. The

activation of dopaminergic system when giving placebo has been documented by using Positron-Emission tomography [6].

The response of acute migraine to the placebo effect is important, and the response to its prophylaxis, even though it is less, is not negligible. In a systematic review of 11 placebo-controlled trials that investigated the treatment of acute migraine with analgesics, pain relief was obtained in approximately 30% and cessation of pain after 2 hours in 9% of patients treated with placebo. A meta-analysis that included studies, comparing triptans with placebo, revealed an average rate of 30% of responders with placebo when the endpoint was pain relief and, from 4 to 9% when the endpoint was no pain status. Another meta-analysis conducted in 98 studies on migraine attacks yielded a rate of 30% of patients who experienced pain improvement after 2h, and 9% of patients who were released from pain after receiving placebo. The response to placebo is lower in the prophylaxis of migraine: a meta-analysis, which included trials comparing propranolol with placebo, 14% of patients achieved a reduction of more than 50% in the frequency of migraine. In another study from a meta-analysis of 32 studies that investigated migraine prophylaxis, the combined response and placebo rate was 21% [6].

Heart diseases

In cardiology, the effect of placebo on the clinical course of, syncope, systemic hypertension, angina pectoris, silent myocardial ischemia, congestive heart failure and ventricular tachyarrhythmias is well documented. In the prevention of myocardial infarction, there seems to be a direct relationship between compliance with placebo treatment and favorable clinical outcomes. The safety of short-term placebo-controlled trials has now been well documented in drug studies [27,28].

Many patients who are included in controlled clinical trials of new drugs for the treatment of heart failure show hemodynamic and clinical responses favorable to placebo treatment. This placebo effect is due both to the creation of a supportive therapeutic environment and to the spontaneous improvement that is often observed when measurements of symptoms and cardiac function recur frequently over long intervals of time. Three months of treatment with a placebo produces a reduction in symptoms in 25% to 35% of patients, an increase in cardiac output and a decrease in pulmonary wedge pressure, and an increase in exercise tolerance up to 90 to 120 seconds. Physicians generally seek to maximize the placebo effect, since the goal of treatment in the clinical setting is to improve the patient’s quality of life. On the other hand, clinical researchers seek to minimize the placebo effect, since the objective of a research study is to test the hypothesis that the new drug is superior to a placebo [29]. Both goals should be included in general medicine.

Respiratory diseases

A prominent placebo effect has been observed in respiratory diseases. Asthma has been proposed as a useful model because of its

easily measured objective outcomes. Studies examining the placebo response in asthma have not only contributed to the understanding of the mechanisms behind the placebo response but also shed an interesting light on the current treatment and diagnosis of asthma [30]. So, in the case of bronchial asthma there is experimental evidence that a placebo, accompanied by the verbal suggestion that it is a potent anti-asthmatic, reduces bronchoconstriction. There is also an important placebo effect on cough, which can account for 85% of the total effect of the treatment [7].

Surgery

Surgery has a strong emotional component, and thus is subject to the placebo effect, which has been described since the 1950s. [7].

Cancer

There is currently no evidence that the administration of a placebo has any effect on the growth of a tumor. However, in the oncological field the placebo and nocebo effect are evident in the symptoms such as pain, nausea or vomiting. Here, we must highlight the nocebo effect as an anticipatory response to chemotherapy, which is important in medical practice. It is a learning mechanism by pharmacological conditioning [7].

Conclusion

There is no complete list of the effectiveness of placebo for all major diseases, but it is known that this effect is important, at least, in acute, and postoperative pain, mental illnesses, functional digestive diseases, Parkinson's disease, migraine, bronchial asthma and osteoarthritis. Since the effects of placebo contribute to the responses of the active drugs, it is feasible to increase the patients' benefits of the treatments by increasing the additional placebo effect. There are several possibilities to use the effects of placebo through the configuration and adaptation of information about medication and the association of medication intake with a positive context:

a. A positive communication environment and doctor-patient relationship is very important to generate clinically significant placebo effects;

b. Stimulate positive expectations and minimize patient's negative expectations, which may pave the way for a practical and ethically sound use of placebo knowledge in daily practice;

Instead of focusing on a "personalized" choice of drugs based on biomarkers or genes, it may be the doctor-patient communication that must be adapted. Physicians should remain aware of the strength and meaning of both placebo and nocebo responses in their own practices and the biopsychosocial complexity of why and how patients actually respond to health management strategies.

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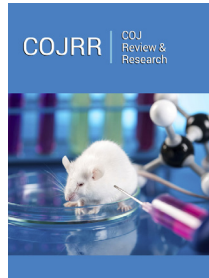
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