

## May the placebo be the best possible therapy in principle? Is being a doctor not just a science, but an art of relating?

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### ABSTRACT

Placebo drugs are mainly used in clinical studies as a comparison group to the so-called verum. One might therefore think that placebos have no effect at all. However, this is a misconception, as there are a large number of international studies that have been able to demonstrate positive placebo effects. On average, around 35% of patients respond positively. Placebos do not force the organism to do anything, they work together with its self-healing powers. With no side effects and very inexpensive, they could take their rightful place in the healthcare system in the future.

**Key words:** placebo, nocebo, therapies, self-healing powers, healthcare

### INTRODUCTION

In almost all countries, the healthcare system is becoming increasingly expensive and health insurance premiums are rising, even though services and efficiency are not increasing. Smaller hospitals are being closed, the flat countryside has hardly any medical care left. Pharmaceutical companies are no longer offering all existing drugs, but are restricting themselves to new drugs that promise high profits with patent protection. Since the production of biotechnological antibody drugs, prices have exploded once again. It is foreseeable that this system must and will reach its limits.

Naturopaths and complementary medicine practitioners assume that neither a remedy nor a doctor can ultimately heal, but rather the self-healing powers of the organism or the body-mind-spirit unit of the patient. A doctor has therefore already fulfilled part of his mission if he does not stand in the way of the self-healing mechanisms or hinder them.

The question therefore arises as to whether there is a therapy method that can be used at any time and at very low cost, namely the placebo system. A placebo (from the Latin placebo = "I will please") is a drug that does not contain any relevant medicinal substance and therefore has no pharmacologically-describable effect that could be caused by it. In a broader sense, other healing methods are also subsumed under placebo, e.g. aura surgery, sham operations or sham acupuncture.

Placebos are the preferred control substance in clinical research. They are used in placebo-controlled clinical trials in order to quantitatively assess the medical-pharmacological efficacy of various procedures, ideally in randomized double-blind studies. The patient must give their consent. The use of placebos to treat disease symptoms is ethically controversial if it is not based on informed consent (von Uexküll & Langewitz, 2008). However, a doctor can have a general patient contract signed in which the patient accepts the doctor's listed therapy methods, which also include placebos.

The counterpart to the placebo effect is the nocebo effect. These are undesirable effects that occur with apparently harmful substances that do not contain any harmful substance (e.g. an electrosensitive reaction, even if the mobile phone transmitter is switched off).

The effect of placebos is explained by psychosocial and psychosomatic mechanisms. The reported effectiveness of some alternative medical procedures (such as high potency

homeopathic remedies) is also attributed to the placebo effect. However, the effects of "conventional" treatments can also be partly explained by the placebo effect and it is not uncommon for doctors to use them specifically as placebos (Hróbjartsson & Norup, 2003). Meta-analyses by authors who reviewed the existing literature on the placebo effect came to the conclusion that the observed effects with regard to the placebo effect do not meet strict scientific criteria. It was found that the response observed in the placebo group of a clinical trial is often wrongly equated with the placebo effect. However, the observed effects can also be explained by factors that are not related to the administration of the placebo. These include: the natural course of the disease, spontaneous cures, "miracle cures", regression to the mean, additional treatments and other non-specific effects (Kienle & Kiene, 1997; Ernst & Resch, 1995).

### THE HISTORY OF THE PLACEBO

The origin of the word: In Jerome's Psalterium Gallicanum (a Latin translation based on the Greek Septuagint), the verse in Psalm 114:9 reads: "Placebo Domino in Regione Vivorum", = "I will please the Lord in the land of the living"<sup>\*</sup>. The living refers to the souls in the afterlife after earthly death. In the 18th century, placebo became part of the medical vocabulary in its current meaning<sup>†</sup>.

Sick people were treated early on in history by means of discussions and shamanic techniques. Corresponding texts were canonized and partially recorded by priest-physicians in antiquity. The placebo effect was first mentioned in the West not by a doctor, but by the Greek philosopher Plato (427-347 BC). He was of the opinion that words have the power to heal the sick<sup>‡</sup>. He also legitimized medical lies<sup>§</sup>. Accordingly, he considered using words to give a seriously ill patient the feeling that he had a good chance of recovery or that his illness was less serious than he thought. This would be therapy at the level of consciousness.

The example of Hippocrates (460-377 BC) shows that this contradicted the idea of good medical treatment at the time. He founded humoral pathology, according to which the human body contains humors that determine its state of health. The humors were considered to be blood, phlegm, black and yellow bile and water. Another Greek physician named Galenos of Pergamon (129-200) assigned temperaments to the humors and thus added a psychological component. Since ancient times, physicians have repeatedly described the effect of imagination in healing, but without using the term placebo (Jütte, 2010; Jütte, 2019).

The founder of homeopathy, Samuel Hahnemann (1755-1843), used lactose tablets and non-medicinal globules to observe the long-term effects of homeopathic remedies (Jütte, 2014; Stolberg, 1996).

The first documented experiment that was controlled with a type of placebo dates back to 1784 and was carried out by the scientist Benjamin Franklin, among others. At that time, Franz Anton Mesmer claimed that there was a kind of "fluid" in the body that he could influence from the outside. The King of France called together a committee to investigate his work. This committee carried out a series of tests. For example, women were "mesmerized" in a room in the belief that the performer was sitting behind a curtain, whereby the information could be true or false. Franklin succeeded in proving that the success of the treatment only depended on whether the women believed that the mesmerist was there, i.e. imagination as a typical placebo effect<sup>\*\*</sup>.

<sup>\*</sup>Dilexi quoniam exaudiet DNS [= Dominus] voce[m] ora[tionis meae] in Psalm 114,9

<sup>†</sup>Placebo. In: Online Etymology Dictionary

<sup>‡</sup>Plato Charmides 155e

<sup>§</sup>Plato Politeia 389b

<sup>\*\*</sup>Karl Bittel: The famous Mr. Doct. Mesmer. 1734-1815. On his traces at Lake Constance in Thurgau and in the Margraviate of Baden with some new contributions to Mesmer research. Aug. Feyel, Buchdruckerei und

The first controlled clinical trials with "inert" substances were carried out by doctors who either wanted to prove the efficacy of homeopathy or wanted to expose this new healing method as nonsense (Dean, 2006). Placebos as we understand them today were probably used systematically for the first time in 1830 by a Doctor Herrmann under the supervision of a Doctor Gigler in a military hospital in the Russian city of St. Petersburg. The aim was to investigate whether a homeopathic treatment was effective. This study not only compared the then new homeopathic treatment with the usual medical treatment of the time, but was also the first to systematically introduce a non-treatment group that was treated with placebos in the form of pseudo-pills. It turned out that the placebo group had the best results.

Many doctors in the 19th and 20th centuries still produced their own medicines, so the dispensing of placebos went unnoticed. Since the "lie in medicine" legitimized by Plato was considered an ethical principle, they had no problem with it.

## STUDIES

It took until the middle of the 20th century for placebo-controlled studies to become the standard in clinical research. It was not until the 1970s, however, that double-blind, randomized, placebo-controlled trials became the standard in scientific studies of drug efficacy, following the recommendation of the Food and Drug Administration (FDA) (Merrill, 2009).

In 1955, the Journal of the American Medical Association published an article by anesthesiologist Henry Knowles Beecher (1904-1976) entitled "The Powerful Placebo". Beecher evaluated 15 different placebo studies on the treatment of headaches, nausea or pain after operations and came to the conclusion that of the 1082 patients who took part in these studies, an average of 35% responded to placebos - a percentage that was frequently quoted afterwards (Beecher, 1955). This was the first time that the placebo effect had been quantified and scientifically documented on a relatively broad basis.

At the end of the 1970s, another topic was added to placebo research after the discovery of endorphins (German Medical Association on the recommendation of its Scientific Advisory Board, 2011). An American research group proved that it was possible to achieve an endorphin release with placebos and thus switch off pain receptors (Levine et al., 1978). This convinced them that they had discovered a mechanism of action of the placebo effect.

The fact that placebos have a bad image is probably due to their mode of action, which for a long time could only be explained with the help of psychological factors. Nevertheless, anonymous surveys of doctors and nurses have shown that a large proportion of them have already consciously used placebo effects (Hróbjartsson & Norup, 2003). It is estimated that between 20 % and 80 % of the effect of even effective drugs is due to placebo effects (Binsack et al., 2012).

A new study from Dresden/Germany shows clear placebo effects (Bschor et al., 2024): a meta-analytical study was carried out to determine for which psychiatric diagnoses the placebo is most effective. The subjective symptom severity was significantly reduced in all disorders. Patients with depression benefited the most, followed by anxiety disorders, ADHD, post-traumatic stress disorder, social phobia, mania and compulsions. Schizophrenia showed the smallest effect.

A study on patients with irritable bowel syndrome who received three placebo treatments of different intensity shows how effective placebo effects can be in psychosomatic illnesses. The first group was only examined, the second received sham acupuncture and the last sham acupuncture in combination with empathic, attentive, trusting conversations. In the

group with sham acupuncture, the symptoms improved significantly compared to the untreated group and in the group with sham acupuncture and additional conversations, the improvement in symptoms was once again significantly greater than in the group that was only treated with sham acupuncture (Kaptchuk et al., 2008).

The placebo effect therefore plays a more or less important role in every successful treatment. Pure or complementary placebo therapies are also often used in clinical practice (Bernateck et al., 2009). Especially in pain therapy, placebo effects can positively support the treatment (German Pain Congress, 2007).

The placebo effect does not work for every patient. Every person has their own psycho-neuro-endocrino-immunology. Placebo effects can be triggered by evoking expectations or by a conditioned stimulus. The triggered neuronal activations in the brain (especially receptors for morphine, endorphins, cannabis, etc.) can influence the metabolism and thus cause physical reactions.

### EXPECTATIONS

Many placebo researchers consider positive expectations of a treatment to be the most important prerequisite for a placebo effect to occur. Doubts hinder the effect. A practitioner who takes time for the patient, responds empathetically to the patient and is convinced of their treatment strengthens the patient's expectations. Classical conditioning states that a new, conditioned reflex can be added to the natural, usually innate reflexes. In a complex series of experiments, Amanzio and Benedetti were able to demonstrate in detail that a pain-reducing placebo effect can be triggered both by a cognitively induced expectation and by classical conditioning (Amanzio & Benedetti, 1999).

### PLACEBO EFFECTS OF INVASIVE MEASURES

Not only medication, but also operations have a placebo effect. In an experiment in Houston, Texas, 120 patients with knee osteoarthritis underwent surgery, 60 of whom received superficial incisions on the skin. After two years, 90 percent of patients in both groups were satisfied with the operation. The only difference was that the non-operated patients felt less pain than their control group (Moseley et al., 2002).

The fact that studies in surgery can be meaningful has been proven in the past. A classic example is a study from 1959: in patients with angina pectoris, doctors either performed a left-sided ligation of the thoracic artery or only sham blocked the blood flow. Symptoms improved in 80 percent of patients, both in the verum and placebo groups. The effects of transmyocardial laser revascularization in patients with refractory coronary ischemia are also apparently due to a placebo effect, as a study from the year 2000 showed (Sham surgery, 2008). A randomized, double-blind, placebo-controlled study also found a placebo effect in the use of stents for stable angina with regard to the relief of symptoms (Al-Lamee et al., 2018).

### EFFECTS OF OPEN PLACEBO TREATMENT

There are indications that "open-label placebo therapy or nonblind placebo therapy", which takes place with full patient information and the patient's conscious consent, could also be effective (Kaptchuk et al., 2008; Park & Covi, 1965). In the study published in 2010, the 80 participants suffering from irritable bowel syndrome were previously informed in detail about the placebo effect, and possible positive effects of placebos were mentioned. One of the

authors of the study, psychologist Irving Kirsch, hypothesized that one possible mechanism of action was the activation of the patient's self-healing powers as a form of self-regulation<sup>††</sup>.

### MECHANISMS OF ACTION

Opioids have been among the most widely used painkillers for centuries. Opioids bind to opioid receptors, which are found on cells in various areas of the nervous system. This binding reduces the perception of pain in the brain, and in some cases also the transmission of pain to the brain. There are at least five different types of endorphins and three different types of endorphin receptors. It can be assumed that endorphins are involved in the pain relief provided by placebos (Meissner et al., 2011). There is also increasing evidence in the recent literature that the reduction of negative emotions plays a role in the pain-relieving effect of placebos (Ter Riet et al., 1998). A number of older studies show that placebos work best in people who come to the doctor with a little anxiety and high esteem, i.e. who are in a state of stress. This theory believes that the placebo effect works particularly well by reducing stress (Oken, 2008).

### ETHICAL ASPECTS OF THE ADMINISTRATION OF PLACEBOS

For legal and ethical reasons, placebos may only be used in the treatment of complaints after informing the patient and with the patient's conscious consent (Scientific Advisory Board of the German Medical Association, 2010). On the other hand, placebos show reduced effects after the patient has been fully informed. In the past, these contradictory facts have repeatedly led to discussions about the extent to which circumventing the legal provisions and ethical principles is justifiable for the benefit of the patient, for example if there is a fear that long-term administration of painkillers could lead to side effects (Lichtenberg, 2008; German Medical Association on the recommendation of its Scientific Advisory Board, 2011).

### THE WORLD MEDICAL ASSOCIATION

The General Assembly of the World Medical Association (WMA) in Seoul in 2008 called for a more limited use of placebos in clinical trials for ethical reasons in a revised version of the guidelines. The use of placebos is only justifiable if there is no other effective treatment. Exceptions are permitted if there are compelling and scientifically conclusive methodological reasons and if serious or irreversible harm to patients is ruled out. In a second amendment to the declaration, the World Medical Association demands that patients must not only be informed of the study results, but must also receive the treatment under investigation if it offers advantages over another treatment (Meyer, 2008; Charlesworth et al., 2017; Wiesing & Parsa-Parsi, 2015).

### CONCLUSIONS

The declarations of Helsinki and Seoul are understandable when it comes to clinical trials of serious diseases in which a patient in the placebo group may face death and chance decides whether he or she survives. For this reason, clinical trials are often discontinued if the placebo group clearly shows poor results. However, this requires unblinding and reduces the value of the study. The declarations do not affect the treatment methods of a doctor whom the patient has decided to consult of his own free will and in full knowledge of his abilities, i.e. whom he trusts.

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<sup>††</sup>I. Kirsch: "We have the capacity for healing physical conditions through psychological means. First, we have to accept that. Studies of placebo effects are great demonstrations of it. You might think of this healing capacity as a self-regulatory mechanism." Meet the Ethical Placebo: A Story that Heals. Irving Kirsch in Interview with Steven Silberman, Plos Blogs.

What can such a doctor do? He can explain the findings, the diagnoses and their background to the patient. He should identify the errors in the lifestyle and recommend improvements: what to stop doing and what to do instead. He can use methods and remedies that are in harmony with the self-healing powers and do not block them. These include side-effect-free orthomolecular, nature-identical endogenous substances that compensate for deficits in the body. Conventional medicine is familiar with this when thyroid hormones are substituted in the event of a deficiency. Surprisingly, this is not used for a variety of other deficiencies, e.g. when the prohormones DHEA or pregnenolone could be used for a deficit of sex hormones. Substitution with artificial, chemically synthesized, non-natural sex hormones, on the other hand, increases the probability of cancer development. A peculiar situation.

The reflex-like approach of a doctor in the sense of: Symptom - diagnosis - medication without considering the causes and background can be better carried out by artificial intelligence (AI) in the future anyway. Doctors who stick to this approach will make themselves superfluous.

Orthomolecular treatment is not an actual placebo therapy. However, much would be gained if medicine - whenever possible - switched to endogenous, nature-identical and side-effect-free remedies. If these are no longer available, the time has come for the placebo. On the other hand, the instruction leaflet on the packaging of chemical products has negative effects. It creates doubt and fear, the opposite of what a placebo needs. The doctor is thus forced to use highly effective remedies to overcome the patient's psychological defenses, or to force the patient into a passive role - without free will - with a white coat and the title of professor by exercising authority.

A practitioner who takes time for the patient, responds empathetically to the patient and is convinced of their treatment strengthens the patient's positive expectations. Let's take Jesus the Christ as an example: He did not say that he had helped the patient or even performed a miracle, but rather: "Your faith has helped you". Faith here certainly does not mean assuming, accepting or simply believing, but a firm and certain conviction or strong belief. It is the basis of a meaningful use of placebo as the crown of the medical art, provided that one takes the "primum nihil nocere" (Hippocrates) seriously.

What should the doctor do? He should reduce his rationality in favour of his empathy, he should recognize whether the patient is ready for a treatment that takes place via the activation of his self-healing powers. One could also say: whether the patient has the inner maturity to actively deal with the causes of his illness, to clear them up as far as possible and to trust the doctor and the means used without any doubt. If the patient is unable or unwilling to do this, an informative discussion can be held with them. Finally, as a last resort, symptom-repressing medication remains.

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