



On the History of the Placebo Effect: A Brief Outline

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Short Communication

The placebo effect (and maybe still more the nocebo effect) is one of the greatest challenges for academic medicine. There are numerous examples for their effectiveness regarding the literature of medical history. Let us consider the most extreme situations: Patients suffering from a disease with an infest prognosis may recover unexpectedly due to the placebo effect of a special manipulation or belief sometimes called 'miraculous healing' (of course, academic medicine must not rely on it), on the other hand, healthy people may be killed by the nocebo effect of a frightening imagination e.g. a voodoo spell well-known in ethnology.

There are some leading questions at the beginning:

- How far, to which extent, is the placebo effect important for medical practice?
- Traditionally spoken: Is "magic" a general trait of medical practice?
- What can medical historiography reveal regarding a rather mysterious legacy?
- In the scope of global health: What may traditional (oriental and occidental) medicine teach modern Western biomedicine regarding the placebo problem?

The placebo concept was introduced in medical terminology in the 1950s signaling a novel methodology of clinical research, especially in the field of pharmacology. For the first time, meta-analyses were performed. They showed that roughly one third of the test subjects felt a remarkable recovery of their state of health because of the placebo effect, which was the stronger the more they suffered from anxiousness and stress [1].

It became more and more relevant since the 1990's, when the evidence-based medicine (EBM) was established. But it is well-known throughout the history of medicine that in all forms of medical treatment, there is an inherent healing factor, which can hardly be quantified exactly. The natural healing movement (German: Naturheilkundebewegung) of the 19th and 20th centuries tried to stimulate the "healing power of nature" by different methods (hydrotherapy, dietetics, Kneipp cure, magnetopathy etc.). In the 1880s, the "suggestion therapy" was introduced by the university professor of internal medicine Hippolyte Bernheim (1840-1919) in Nancy, which became the basis for modern psychotherapy including psychoanalysis. It originated from the concept of hypnosis or "hypnotism" coined by the Scottish surgeon James Braid (1795-1860) in the 1840s, who thought to be able to introduce a "nervous sleep" by his method of "eye fixation" (i.e. visual fixation on a small object held closely in front of the forehead).

Braid, who was very impressed by the phenomena of animal magnetism or mesmerism, wanted to overcome the respective speculations about the "magnetic fluid" and its alleged transfer by

"magnetizing" or "mesmerizing" propagated first by Franz Anton Mesmer (1734-1815), a medical doctor in Vienna in the 1770s. The "magnetic sleep" induced by the medical doctor should produce a "beneficial crisis" supporting the healing power of nature and restoring the disturbed harmony within the body.

Such an approach was based on the early modern natural philosophy of the 16th and 17th centuries admiring Nature (Latin: natura) as a divine (female) power, the mysteries of which should be revealed by physicians and natural scientists for the benefit of mankind. Insofar, "natural magic" (Latin: magia naturalis) signified a process of serious research in contrast to "black magic". Religious medicine, e.g. spiritual healing, belief healing, exorcism, cult of the saints etc., was of great importance during the Middle Ages, but this tradition is long-lasting until today. All the above-mentioned concepts are more or less indicative of a mysterious healing factor called "placebo" nowadays.

"Placebo" is Latin and means "I shall please". The "placebo effect" stands for a healing factor independent from the effective substance (drug) or the medical treatment as such. The personal doctor-patient-relationship respectively the circumstances of a medical treatment per se influence the healing process. Consequently, the psychoanalyst Michael Balint (1896-1970) spoke of the "drug 'doctor'" [2].

The "nocebo effect" acts as opponent. "Nocebo" is Latin and means "I shall harm". Accordingly, the "nocebo effect" means a harming factor of a medical treatment despite of its healing intention, especially when a medical doctor influences the patient in a negative way producing eventually even an "iatrogenic illness". It is really remarkable that in contrast to the placebo research the nocebo effect is widely ignored by scientific medicine. So, the database PubMed of the National Library of Medicine shows about 200 times more hits for "placebo effect" than for "nocebo effect".

There is a well-established placebo formula of the pharmaceutical research. The effect of the "verum preparation", i.e. the preparation of a specific drug, minus the effect of the placebo preparation without the specific drug equals the "true" or "real" efficacy of the specific drug. This approach of pharmaceutical research became the model of the so-called Evidence-based Medicine (EbM). Its target is to detect the real efficacy of a medical drug by excluding the placebo effect. Its methodology created the "gold standard" of scientific biomedicine: the double-blind randomized controlled trial (RCT). But there is a crucial problem: What is about the personal individuality of doctors and patients, their cultural codes, attitudes, and speculations influencing the outcome of medical treatment? What is the "true remedy" and what is just due to the "placebo"? And how far is it possible to evaluate healing concepts, which do not fit into the frame of the EBM (e. g. psychotherapy, homeopathy, naturopathy, "alternative" healing methods)?

The term “placebo effect” emerged in the middle of the 20th century. Nevertheless, the respective phenomena are well-known throughout medical history. The placebo effect was always more or less deliberately used to support the medical treatment in all medical cultures worldwide, one may suppose. The idea to exclude it systematically as far as possible from medical practice is quite recent and due to the natural scientific foundation of medicine during the last 150 years and particularly the biostatistical (IT based) methods of EbM, developed during the last decades.

One must not forget the impact of the nocebo effect in medical practice. It is at least as important as the placebo effect and concerns one of the most important principles of medical ethics going back to the Hippocratic oath: “Do not harm” (Latin: *nil nocere*). As said above: The “evil twin” of the placebo effect is still widely underestimated and it is time to view it as a fundamental challenge especially for clinical research.

There were diverse concepts in medical history implying phenomena of what we call now “placebo effect”. A most important doctrine was the “hypnotism” offering a theory and practice, which was compatible with the academic medicine based on natural science and biology in the second half of the 19th century. The founder of this concept James Braid was fascinated by the “power of the mind over the body”, which he explained with neuro-physiological processes in the individual nerve system refusing all magic or “magnetic” speculations claimed by the followers of animal magnetism or mesmerism [3]. Hypnotic procedures fascinated medical doctors in particular.

They thought to get an efficient method regarding not only pain management and anesthesia (ether anesthesia was just established in 1846), but also numerous (foremost somatic) disorders. Hypnotism stimulated many physicians and dentists to apply it to their patients. One of them was Hippolyte Bernheim, who introduced the concept of “suggestion” and “autosuggestion”, a purely psychodynamic model operating with “resistance” and “transference” – terms of central importance for Sigmund Freud (1856-1939) later on. Suggestion therapy became the very foundation of modern psychotherapy.

Going back to the early modern period, the basic concept of “natural magic” (Latin: *magia naturalis*) included obviously moments of the placebo respectively nocebo effect. It is not possible to display the idea of the “magic of nature” (i.e. nature as a magician) here [4]. The microcosm-macrocosm analogy, the doctrine of signatures, the simile principle, the far distance (quasi telepathic) effect of sympathy, and so on. The idea of imagination (Latin: *imaginatio*) is highly significant: It indicates the incorporation of an external *imago* or visual thing into the organism influencing and modifying its vital processes. In this context, a sort of nocebo effect could harm the integrity of the body.

The most cited paradigm was the alleged malformation of the fetus, when the pregnant woman was horrified by a sudden event (e.g. by a hare causing a harelip). This theory shows a radical psychosomatic model: The mind was supposed to have the power to rebuild even the body. One of the most prominent early modern medical authors, who stressed the concept of “*imaginatio*”, was Paracelsus (i.e. Theophrastus Bombast von Hohenheim, 1493/94-1541), the alchemistic natural philosopher and controversial forerunner of medical chemistry. He addressed intensively the relevance of *imaginatio* and “belief” (German: *Glauben*) for health and disease. Obviously, he was aware of the placebo-nocebo problem and viewed the doctor as a potential healing factor.

But probably the most original conception in medical history was demonology including the concepts of possession and exorcism, going back to antiquity, notably the Babylonians. We should be aware that demonology was more or less well-regarded throughout history. Today, exorcism is still practiced in some Christian churches and certain esoteric circles. In general, the scope of religious healing is remarkable occurring globally. Even in advanced West European countries like Germany or the UK a lot of religious (respectively “magical”) healing methods are practiced today outside academic medicine: laying on of hands, prayer healing, spiritual healing, exorcism, pilgrimage, cult of the saints etc. In this sphere, the effectiveness of a placebo could be investigated spectacularly and also enlighten the psychodynamic processes provoked by psychotherapeutic procedures.

The fundamental polarity of placebo and nocebo, of beneficial and harmful factors, is crucial for demonology. Possession by spirits is ambivalent, too: “good” versus “evil spirits”. On the hand, divine powers may possess an individual. Socrates, apart from other Greek philosophers, used the term “*eudaimonia*” (literally “good spirit”). In the Christian tradition, the term “enthusiasm” (literally “possessed by God”) is important in regard to the martyrs and saints. A famous event in the New Testament is the outpouring of the Holy Spirit on Pentecost. On the other hand, evil spirits producing misery, disorder, and disease challenged all sorts of healers, especially sorcerers, shamans, priest-doctors, or clergymen. “Devil’s possession” played an important role in early modern times, when the witch-hunt had its heyday. In spite of the fact that since the Age of Enlightenment demonology was overcome by anthropological and psychological theories and integrated in medical psychology and psychiatry, it is still alive. So, exorcism is practiced even in some regions of Europe, i.e. in Roman-Catholic communities in Italy.

The manifestations of magic or religious suppositions are a global phenomenon of everyday life and essential for the healing arts. Academic medicine should know about the alternative health market, where popular traditions and rituals are attractive for all classes of population. Paradigmatically, one can study the offers of innumerable amulets against all possible ailments. Insofar, placebo therapy is booming. Regarding diverse conceptions of “alternative” or “complementary medicine” – among others traditional Asian medicine(s), naturopathy, homeopathy, herbal medicine – Western academic medicine (biomedicine) tends to explain their effectiveness mainly with the impact of the placebo effect.

They would produce pure placebo phenomena – in contrast to the “true” remedies of biomedicine effective without placebo. So, two important realms of pre- or unscientific placebo therapy were identified by a representative of the scientific placebo research addressing the “ocean” of the placebo effect: The historical concepts of pre-modern, non-scientific medicine (like humoral pathology), and the contemporary concepts of alternative medicine [5]. But according to the self-understanding of traditional/alternative healing methods, their effectiveness is claimed to be the consequence of “real” material or natural processes, rejecting all placebo hypotheses.

The problem for the academic Western medicine is the fact that all of its applications are also more or less contaminated with the placebo effect and that it is very difficult and often impossible to subtract it from the (“real”) effectiveness of a medical intervention.

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