THE POWER OF PLACEBO. BETWEEN MYTH AND FACT

Ecaterina MUNTEANU[1], Ludmila FRIPTU [1*], Maria COLȚA[1]

[1]Department of Software Engineering and Automation, group FAF-223, Faculty of Computers, Informatics, and Microelectronics, Technical University of Moldova, Chișinău, Republic of Moldova

*Corresponding author: Ludmila Friptu, ludmila.friptu@isa.utm.md

Abstract: *The placebo effect has been studied for a long time and it became a subject for debate for various reasons: its efficacy, existence and practicality. Researchers managed to infer some possible explanations for what actually happens in people's minds that causes this effect, and how medicine uses the placebo effect in different treatments and practices.*

Key words*: cancer, homeopathy, hormonal response, nocebo, placebo.*

Introduction

The placebo effect occurs when individuals receive an inactive substance or treatment that resembles a real one, resulting in a perceived improvement in their condition. This fake treatment, known as a placebo, doesn't have any actual therapeutic properties and can be a pill, injection, or liquid that is consumed [1].

Typically, the individual receiving the placebo treatment is unaware that it is inactive and thinks they have received the actual treatment. The placebo is made to look like the real treatment, but it doesn't have any actual impact on the condition being treated [1].

The first scientific demonstration of this effect came in 1799; John Haygarth tested an expensive metal rod named Perkins tractors, a quack remedy that claimed to draw disease from the body. He found that 4 out of 5 patients with rheumatism reported pain improvement, demonstrating the placebo effect. Haygarth did not employ the phrase "placebo effect" to describe his observations, despite the word "placebo" having been utilized in other contexts previously. The term "placebo effect" was coined in a 1920 article in The Lancet, but it was not widely used until several decades later. Henry K. Beecher, an American anesthesiologist, observed during World War II that some wounded soldiers healed well without morphine, which led to increased interest in the placebo effect. Studies have shown that placebo effects can be powerful in situations where perceptions are important, such as in pain, anxiety, and depression [1].

Placebo and Homeopathy

Homeopathy is considered to be a part of alternative medicine and it is based on two main theses: "Like cures like" and "Law of minimal dose". The first one assumes that an illness can be treated by a substance that produces similar symptoms in healthy people and the second one assumes that the more we dilute a certain substance that has medical properties, the more potent the substance becomes. Both of these axioms beat the purpose of science and if they were true, we would have to rethink everything related to physics and chemistry. We are interested specifically in the second statement because it assumes that the lower the concentration of the initial drug, the greater the effect of this drug. This declaration is based on the belief that normal concentration damages our body and that the water "memorizes" the substance which is diluted in it [2].

But why do some people feel that the homeopathic pill (which already doesn't have any molecule of the initial substance) helped them? There are more than 200 clinical studies done on homeopathy and even though their results are not entirely uniform, one thing is for sure: placebo plays a big role in the success of homeopathy. Patients who consult homeopaths do get better, and observational studies have shown this ad nauseam, and thats mainly because of the placebo effect and the lengthy consultation with a compassionate clinician that manages to instill some kind of psychological comfort in their patient, resulting in self healing [3].

Placebo and Cancer

The National Cancer Institute in the United States has confirmed that cancer clinical trials occasionally use placebos. Patients in these trials receive the standard treatment for their specific cancer as well as the placebo. To minimize the possibility of receiving a placebo, clinical trials can be designed in a way that restricts the use of placebos. Using placebos in cancer clinical trials was uncommon in the past as most chemotherapies had apparent effects. However, many modern cancer treatments have less visible effects, and researchers need to compare the new drug or treatment to something to determine its impact. Using a placebo can help researchers determine whether a new drug is truly effective in treating cancer and its effects, especially in volunteers who have already undergone all known effective treatments. In such cases, volunteers may be assigned to either the placebo or experimental group. If a patient's cancer worsens during the trial, they will be switched to the experimental group to receive the study drug or treatment [4].

According to a clinical trial realised by the American Society of Clinical Oncolgy, placebos may be appropriate in with illnesses or treatments when:

- If we compare it to a new treatment, it helps researchers learn whether the new treatment works better or not;
- Different types of cancer that are studied tend to get better and then worse, or signs of disease go away at times (called remission);
- The known treatments do not work well or cause serious side effects;
- There is no known effective treatment [4].

The placebo effect refers to a situation where some individuals experience a positive outcome after being given a substance or treatment that resembles an actual medication. This placebo, which can come in the form of a pill (such as a sugar pill), injection (like saline solution), or liquid, has no scientifically proven medical properties. In most cases, the recipient is unaware that they are being administered a placebo and instead believe they are receiving a genuine treatment. Even though the placebo has no actual impact on the condition it purports to cure, it is designed to look and feel like the real thing. While the placebo effect is not simply a result of positive thinking, many people who experience it are unaware that they are responding to a substance with no medical value. Medical researchers frequently use placebos to examine and comprehend the physiological and psychological effects of new medications [4].

Placebo in medical trials

1. Asthma and Placebo

In the results of a study on asthma, presented in Fig. 1, patients showed that those who received the real drug Albuterol reported a 50% improvement in their symptoms, while those who received a placebo reported a 45% improvement. Patients who received sham acupuncture reported a 46% improvement, while those who received no intervention reported only a 21% improvement. These findings suggest that in this particular study, placebos were only slightly less effective than the real drug, with a difference of only four to five percentage points in terms of subjective improvement. Alternatively, the real drug was only slightly more effective than the placebos, with a difference of four to five percentage points [5].

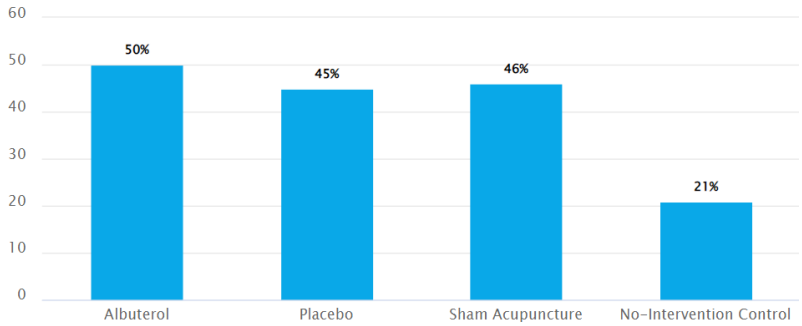

Figure 1. Subjective Improvement from Different Interventions (Albuterol vs Placebos in Asthma Treatment)[5]

2. Mental health and placebo

Mental health treatments can be affected by the placebo effect, making it difficult to isolate the effectiveness of interventions. Some mental health professionals believe that the placebo effect can be beneficial, but there are also potential dangers.

- Anticipation of therapeutic benefit can cause a significant dopamine release, as shown in studies where patients had a 75% chance of receiving medication;
- In a study on depression and placebos, there was no significant difference in response rate between medication and placebos for completers, but patients with experience using antidepressants had higher response rates to medication;
- Clinical improvements were higher for patients with prior antidepressant use who received medication compared to those who received placebos;
- Patients who had never taken antidepressants before the study showed a higher rate of clinical improvement with both medication and placebos [5].

The data shown in Fig. 2 suggests that placebos may be more effective for people without experience using medication, while patients with prior antidepressant use had better clinical improvements with medication compared to placebos [5].

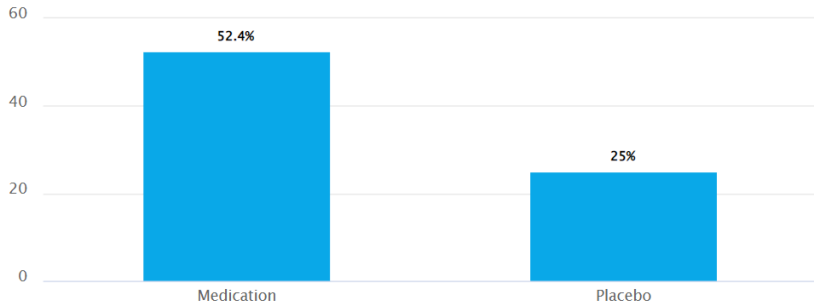

Figure 2. Response Rates of Antidepressant-Experienced People on Medicines and Placebos [5]

Causes of the Placebo Effect

Although researchers have acknowledged the placebo effect, its underlying mechanisms, and causes remain unclear. Several elements could play a role in this phenomenon [6].

- Hormonal Response

A potential explanation is that taking a placebo triggers a discharge of endorphins, which have a structure close to morphine and other opiate painkillers and act as the brain's own natural painkillers [6].

By conducting brain scans, researchers have shown that the placebo effect can be observed in action, as areas containing numerous opiate receptors were activated in both the placebo and treatment groups. Moreover, the use of naloxone, an opioid antagonist that hinders natural endorphins and opioid medications, resulted in diminished pain relief from the placebo for participants [6].

- Conditioning

Additional possible explanations for the placebo effect include classical conditioning, in which an association between two stimuli is formed, leading to a learned response. In some instances, a placebo can be coupled with a genuine treatment until it brings about the desired effect. For instance, if an individual is frequently given the same arthritis pill to ease stiff and sore joints, they may begin to link that pill with pain relief. If they are given a placebo resembling their arthritis pill, they may still believe it provides pain relief due to the conditioning effect [6].

- Expectation

Studies indicate that expectations, or our anticipations about the outcomes we will experience, play a crucial role in the placebo effect. Individuals who are highly motivated and anticipate favorable results are more likely to experience a placebo effect. Furthermore, a doctor's enthusiasm for

treatment can affect a patient's response. If a physician expresses optimism about a treatment's efficacy, a patient may be more likely to perceive benefits from taking the medication. This illustrates that the placebo effect can occur even when a patient is using actual medications to manage an ailment. Moreover, a person's expectations of whether a medication will be effective can be influenced by verbal, behavioral, and social cues. For instance, the act of taking a pill or receiving an injection to improve one's condition can serve as a behavioral cue. Reassuring body language, eye contact, and speech from a doctor or nurse can act as social cues, and listening to a healthcare provider talk positively about treatment is an example of a verbal cue [6].

- Genetics

There is evidence suggesting that genes can play a role in determining how individuals respond to placebo treatments. Some individuals may be genetically inclined to be more receptive to the placebo effect. A study found that people carrying a gene variant that produces elevated levels of the neurotransmitter dopamine are more likely to experience the placebo effect compared to those with the low-dopamine version of the gene. Moreover, individuals with the high-dopamine version of the gene tend to have higher levels of pain perception and a propensity for seeking rewards [6].

- The Nocebo Effect

The nocebo effect is the complete opposite of the placebo effect and occurs when a negative outcome is expected due to a belief that an intervention will cause harm. This effect can lead to physically experienced adverse effects, which are often clinically diagnosable. Negative perceptions are formed faster than positive ones and can be influenced by media reports, leading to an increase in the number of adverse reaction reports. This effect can also play a role in patients' experiences with generic medicines, as pre-existing skepticism around generics can cause side effects when switching from branded to generic products. A quarter of patients discontinued a biosimilar due to a perceived loss of efficacy or an increase in side effects. The perception of cost can also enhance the nocebo effect, and this has been observed in New Zealand funding situations [7].

Conclusions

After studying different sources concerning the placebo effect, it can be stated that it is not a myth for certain, but as all unorthodox methods of treatement placebo should not be the only treatment a patient should rely on, because of its inconsistency (meaning that a patient can benefit from placebo today, but tomorrow its efficacy is not guaranteed) and lack of further clinical studies. Placebo should be considered only in mild cases of desease, because a serious condition would require real medication. It can also be stated that placebo is not only a substance, but also a free bonus that comes when administrating a patient with empathy and compassion, making them more determined to fight with their illness.

References

1. MESTEL, R. “The imagination effect: A history of placebo power.” *Knowable Magazine*, 25 October 2017, [online] [accessed: 19.02.2023]. Available: https://knowablemagazine.org/article/mind/2017/imagination-effect-history-placebo-power.
2. TEIXEIRA, MARCUS Z., et al. “The placebo effect and homeopathy.”*PubMed*, [online] [Accessed: 6.02.2023], Available: https://pubmed.ncbi.nlm.nih.gov/20471615/.
3. ERNST, E. “Why I changed my mind about homeopathy | Placebo effect.” *The Guardian*, 3 April 2012, [online], [accessed: 5.03.2023.], Available: https://www.theguardian.com/science/blog/2012/apr/03/homeopathy-why-i-changed-my-mind.
4. ASCO.org. “Placebos in Cancer Clinical Trials.” *Cancer.Net*, 10 02 2022, [online].[Accessed: 19.02.2023], Available: https://www.cancer.net/research-and-advocacy/clinical-trials/placebos-cancer-clinical-trials.
5. ZUCKERMAN, A. “46 Placebo Effect Statistics: 2020/2021 Data, Examples & Implications.”*CompareCamp*, 27 May 2020, [online]. [accessed: 6.03.2023], Available: https://comparecamp.com/placebo-effect-statistics/.

6. CHERRY, K. "Placebo Effect: Meaning, Examples, and Impact." [online] *Verywell Mind*, 12.09.2022, [accessed: 19.02.2023], Available: https://www.verywellmind.com/what-is-the-placebo-effect-2795466.
7. MEDSAFE (New Zealand Medicines and Medical Devices Safety Authority). "The nocebo effect." *Medsafe*, 7 March 2019, [online]. [accessed: 19 February 2023]. Available: https://medsafe.govt.nz/profs/PUArticles/March2019/The%20nocebo%20effect.htm#references