

THE PLACEBO EFFECT:

Paradox or Proven? : A Review

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Abstract: Medical science has always worked towards curing mankind. In many of its aspects, it has proved that treating illness is so much more than what just meets the eye. It has always been successful in healing ailments which may be as small as the common cold to even those which require surgical treatments. Every time we pop a painkiller or open the bottle of a cough syrup, we tend to ignore the kind of ingredients and chemicals that have gone into making it. We don't even know the mechanism through which it acts on the targeted organ. All we know is that the capsule or the cap full of syrup will cure our problem. Scientists have found out that the curing of a disease or an ailment does not only rely on the medication that we take, in fact, it is somewhat also dependent on the kind of mind set we have before or after taking the medication. Stating it in other words, as soon as we pop in an aspirin for a common headache, it immediately opens our body's pharmacy to release certain chemical compounds like endorphins which serve as body's own painkillers and tend to relieve pain to a great extent. In the same way, if a person pops a sugar pill which is analogical to an aspirin tablet without knowing about it, he might experience a relief from pain. This is considered as THE PLACEBO EFFECT. A placebo is a substance that looks or mimics the drug but is not the drug in actual, in other words, it is also known as FAKE DRUG or SHAM DRUG. Placebos were used in ancient civilizations to cure diseases and minor cuts and wounds that required immediate treatment. The Mexicans used army ants for stitching wounds and deep rooted cuts in order to prevent blood loss. A placebo could be any inert compound or solution such as sugar pills, saline solutions, gelatine capsules or sugar syrups that have no therapeutic values but are only used for mimicking the medicinal drug. Sham surgeries form an important control in clinical trials because they work as real surgeries without really having any therapeutic goals. Placebos can progress patient-reported complications such as pain and nausea. If used to treat conditions like insomnia and depression, placebos can cause patients to perceive that they are sleeping or feeling better. Placebos are believed to be capable of altering a person's perception of pain as well and have always been an integral commodity of various clinical and pharmacological trials. However, there has always been a conflict regarding the actual effects of placebos on patients and the fact that they are recovering on their own despite the administration of the drug. This review article sheds light on the numerous research works that have been carried out by scientists and researchers across the world on placebos, their effects and their potential in curing ailments.

KEYWORDS- Placebo, illness, treatment, endorphins, mimic, sham surgery, inert.

I. INTRODUCTION

The term PLACEBO in Latin means "I SHALL PLEASE". The American anesthesiologist Henry Beaker became the first person to discover the placebo effect as a medic in World War II. After running out of morphine (a powerful pain-killer), he replaced it with a simple saline solution but continued telling the wounded soldiers that it was morphine in order to calm them. To Beaker's surprise, almost half of the soldiers reported that the saline solution which had no potential pain killing properties actually helped to reduce their pain. He later published a paper in the year 1955 titled: *THE POWERFUL PLACEBO* which shed light on the idea that placebos have quite an importance from their clinical point of view. However, the first scientific demonstration of the placebo effect came in 1799, when John Haygarth, a British physician, set out to test one of the quack remedies on sale at that time. Before the advent of medical science,

Hippocrates, a Greek physician, gave a whole new dimension to medicine and pharmacological studies when he travelled extensively across the globe teaching people the importance of medicine and drugs in curing illness. He also explained that illness and diseases had a rational relation rather than a superstitious belief that they are caused by evil or demonic possessions. In an era, where it was almost impossible to convince people that diseases are caused by biological factors, he became the first person to introduce the concept of medicine and therapeutic treatments among the masses and hence, gradually he came to be known as the FATHER OF WESTERN MEDICINE. Approximately, 250 years later, when Europe started giving birth to learned scholars and scientists, medical science too, started gaining a lot of recognition through the works of various physicians and biologists. Placebos and sham surgeries have been used since then for a lot of clinical trials and studies to estimate the effects of drugs and medications on patients with depression, migraines, pain, insomnia, morning sickness, etc.

Placebo effects do not include methodological factors; rather they include curing ailments with inert substances and sham medicine (*Cally and Stretter, 2010*). The fact that placebos cure patients without actually making them undergo a complex regime of drugs and medications makes it a successful and promising concept in medical science. Clinical trials often involve a lot of data recording and elaborate study materials, in such scenarios placebos help clinicians and doctors establish an easier and statistical relationship between volunteers and their treatment procedures (*McCarthy and Price, 2017*). In a study conducted by the American Medical Association (*Callum and Jovine, 2014*), it was seen that out of 70 healthy volunteers that were chosen for clinical trials of a new analgesic ointment, 40 showed positive response towards the ointment that was not even the actual drug but just a concoction of water, petroleum jelly and boric acid and said that they felt relieved after applying the concoction.

This study proved that the immediate response of the volunteers towards the sham ointment was not because of the fake concoction but because of their in-built response towards pain. Whenever, we injure ourselves or go through a slight discomfort, our body starts synthesizing chemicals that help us cope with the situation. These chemicals include endorphins, dopamine, serotonin and epinephrine (adrenaline). Scientists working on this subject at the University of Texas explained that the ability to endure pain ranges from person to person. Normally, people who are more sensitive towards pain have a tough time coping with it than those who are moderately sensitive (*Greene, Burt, Hilton, 2017*).

The actual intervention that elicits the placebo effect is known as the placebo. The placebo can be any clinical intervention including words, gestures, pills, devices and surgery (*Chaput de Saintonge and Herxheimer, 2011*). Placebo effects contribute towards variability in outcome data from randomized double-fold trials. When patients are given a known drug or medicine in scheduled clinical trials, the effectiveness of the drug is a sum total of the pure placebo effect and the biologically active effect. Certain analgesic placebo responses are also based upon expectations of symptoms change and changes in emotional motivation. They may also have neurobiological influence while having actual effects on the body and brain through neurotransmitters. They are not just response biases. In some cases, classical conditioning and less conscious processes might as well give rise to placebo responses such as immune, hormonal or respiratory activities. The attachment of the placebo theory with routine clinical trials and practices has shed light on some of the most interesting considerations for clinical trial patterns and has paved the way for ethical development of these mechanisms in clinical practice (*Price, Finniss, Benedetti, 2011*). Placebos are chemically identified as inert, which means that they involve the use of those chemical compounds that have no therapeutic or medicinal values. This leaves us with a paradox that if they are inert then what makes them so effective in curing ailments and providing relief to patients who suffer problems like chronic episodes of migraine, arthritis, depression and anxiety (*Oken, 2018*).



Fig: 1- Placebo pills for clinical trials.

(CREDIT- Greene AJ, Burt L, Hilton C. 2017. *The Science of Placebos*. MBJ Medical; 88: 22-30)

Types of placebos:

Placebos are broadly classified into two major categories:

- Pure or active placebo
- Impure or inactive placebo

PURE OR INACTIVE PLACEBOS-

A “pure” or inactive placebo is an inert substance without known pharmacologic effect or therapeutic benefits. These substance comprises inert sugar pills, saline solutions or powders which typically do not have any medicinal properties (*Saljoughiam, 2017*). Pure placebos can trick the patient into believing that they are recovering because of these substances without actually revealing what lies in the drugs.

IMPURE OR ACTIVE PLACEBOS-

An “impure” or active placebo is a prescribed medication that has a known pharmacological effect on some illnesses but not on others. For example, giving vitamin capsules to patients suffering from arthritis without revealing that they are actually vitamins and not some drug meant for curing arthritic pain (*Saljoughiam, 2017*). Impure placebos are quite prevalent in clinical trials and examinations.

II. PLACEBO RESPONSE IN CLINICAL CONDITIONS

There are some conditions in which a placebo can produce positive results even if the person knows that he/she is taking a placebo. Several research studies conducted across the world showed that placebos generally provide effective relief in the following conditions:

1. MIGRAINE:

Migraine is one of the most commonly occurring neurological problems of today’s population. Researchers claim that almost 3-5,000 migraine attacks occur every day for each million of the general population. The condition is marked by severe throbbing headache with nausea and hallucination like symptoms often caused due to stress, hormonal changes, certain food habits and increased sensitivity to light and sound. It is usually self curable and does not require medical attention unless it becomes severe. The throbbing pain is cured by drugs like Acetaminophen and Ibuprofen. However, the placebo effect is just as powerful as a popular pill in relieving migraines. A total of 13 trials (1324 participants in the placebo groups) were included in the analysis. Parallel studies demonstrated a significantly higher placebo response (*Fernandez, Lopez, Marciano, 2018*). The placebo trial groups reported an equal amount of relief from migraine pain as the non-placebo trial groups that were administered with Ibuprofen and other analgesics. Thus, it was concluded that placebos have a very effective response in some patients who suffer from chronic migraine headaches (*Diener, Johnson, Georges, 2018*).

2. DEPRESSION:

Depression is defined as a state of disturbance or disorientation that we normally experience as a result of failures, social insecurity, physical or mental discomfort and even emotional trauma. Depression affects more than 4 million people worldwide every year and in some extreme cases it even leads to suicides or permanent mental lockdown. When a person feels low or upset because of a physical or mental turmoil, he or she goes through a surge of negative thoughts and experiences frequent mood swings. Mild symptoms of depression are usually self curable through the help and support of family, friends and psychologists. However, severe cases in which patients go through uncontrollable trauma and discomfort need special help from medical professionals and doctors. Drugs are prescribed to patients on a regular basis to deal with this condition so that they can recover at a faster rate. These drugs are often meant to stimulate the secretion of serotonin and dopamine- the hormones responsible for triggering the feeling of happiness, pleasure and relaxation. At the University of Michigan, School of Medicine, 35 patients with major depression were enrolled in a study wherein, they were prescribed placebos for a week instead of the actual antidepressant- fluvoxamine.

After seven days, they were asked to complete a questionnaire and also underwent PET CT scan. Their reports showed positive improvements in their mental condition and also in their serotonin levels (*Zubieta, Vencina, Wilman, 2019*).

3. INSOMNIA:

It is a condition in which a person has trouble falling or staying asleep and therefore ends up feeling tired, depressed and disturbed. Insomnia is often related to anxiety, poor sleeping habits, stress, depression and certain medication as well. The good thing about insomnia is that in most cases the person can cure this condition by changing his/her sleep patterns, or through meditation without even turning to sleeping pills. People suffering from bipolar disorder, ADHD and even schizophrenia are at a greater risk of developing insomnia because they are unable to sleep peacefully. 30 patients underwent a clinical trial in which all of them were given inert sugar pills instead of sleeping pills (Halcion and Restoril) for 15 days. After a fortnight, the patients reported that they were feeling better and had shown remarkable improvements in their sleep patterns as well, along with reduced anxiety (*Longfield and Slovonski, 2019*).

4. ARTHRITIS:

An auto immune condition marked by swelling and tenderness of joints and cartilage, there are more than 100 different types of arthritis but the most commonly occurring are rheumatoid and osteoarthritis. It affects both men and women in their mid 40s or 50s but worsens with age. Treatment options include physiotherapy, or sometimes even surgery in severe cases. Since the patient experiences frequent episodes of pain and inflammation in the joints, they are on medications which include NSAIDs like Acetaminophen, Naproxen and Ibuprofen. Placebos also play a significant role in reducing joint pain in arthritic patients (*Fink and Allen, 2019*). In a study conducted on 14 patients who had rheumatoid arthritis, they were given placebo pills instead of the actual NSAIDs for 25 days. After completion of the course, the patients were asked to report a pain score out of 10. Astonishingly, all the 14 patients gave a score report between 3 to 5 which meant that there was a significant dip in the intensity of pain that they experienced before and after the trial (*Van Cristo, 2016*). Thus, it was concluded from the study that although arthritic pain does not have any probable cause or treatment, it can be reduced effectively by increasing the patient's response towards pain and inflammation by triggering the endorphin and serotonin levels in the patient's body.

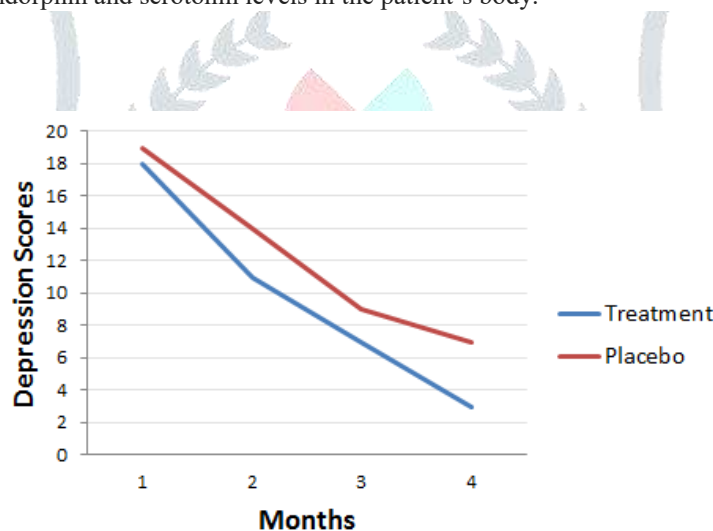


Fig: 2- A graph depicting the effect of drugs v/s placebos in depression patient.

(*CREDIT – Zubieta J, Vencina F, Wilman KA, White E. 2019. Regional μ -opioid receptor regulation of sensory and affective dimensions of pain. Science 293:311–15*)

III. THE MECHANISM OF PLACEBOS

Placebos can work wonders when it comes to curing a medical condition without actually prescribing any actual medication. Several research and clinical studies have been conducted which prove that placebos have always had their own space in medical science when it comes to curing any disorder or disease without actually taking the drug. The placebo effect is a psychobiological phenomenon that can be attributable to different mechanisms, including expectation of clinical improvement and pavlovian conditioning. Overall, the placebo effect appears to be a very good model to understand how a complex mental activity, such as expectancy, interacts with different neuronal systems (*Colloca and Benedetti, 2011*).

The pharmacological approach:

The neurobiology of placebo effect was born in 1978, when it was shown that placebo analgesia could be blocked by the opioid antagonist naloxone (Levine and Collins, 2018). In an experimental model of pain, the placebo response could be blocked by naloxone if it was induced by strong expectation cues, whereas, if the expectation cues were reduced, it was insensitive to naloxone (Amanzio and Benedetti, 2010).

Placebos work by triggering the release of certain chemical compounds in the body known as Endorphins. Endorphins are a group of hormones which are primarily secreted by the pituitary gland and the central nervous system. They act on the opiate receptors of the brain (Mulligan and Turott, 2015). When a person suffers from pain or discomfort, the adrenaline or epinephrine hormone prepares the body to deal with the situation. As a result, a number of chemical messengers like prostaglandins, serotonin, prostacyclins are released to promote inflammation in the form of immune response. Endorphins are released during pain or stress but they are also released when we eat, drink or work out. They, along with serotonin help lessen depression, anxiety, discomfort and pain. Placebos trick our brains into believing that they are the actual drugs with therapeutic benefits and will help us fight the problem and sooner or later we will be able to deal with the discomfort. However, it is these hormones along with our body's defense system that help us deal with the ailment which automatically makes us feel better (Langley and Leavorton, 2012). Placebos may make us feel better but they can't cure us. This has remained a matter of conflict since decades as they won't lower our cholesterol or shrink a tumour. Instead, placebos work on symptoms modulated by the brain, like the perception of pain (Kaptchuk, Welshire, Kumar, 2010).

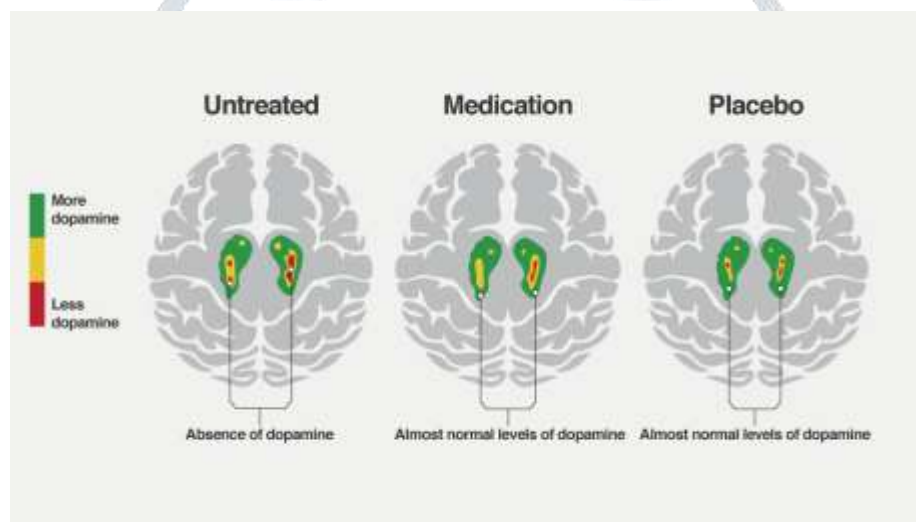


Fig: 3- Comparative analysis of the brain under three different types of treatment measures.

(CREDIT- Levine JD, Collins M. 2018. Influence of the method of drug administration on analgesic response. Nature 312:755–56)

IV. DRUGS ASSOCIATED WITH THEIR CLINICAL CONDITIONS

The following table summarizes the various clinical conditions **in which placebos are given** instead of genuine medications:

Table 1- Commonly used drug molecules which **can be replaced by placebos** to treat their corresponding conditions.

DRUG NAME	CONDITION
Ibuprofen, Aspirin, Acetaminophen, Naproxen	Migraine, muscle spasms, arthritis, other pains
Pyridoxine, Doxylamine	Morning sickness
Diazepam, Alprazolam, Citalopram	Depression and anxiety
Halcion, Restoril, Doxepine	Insomnia

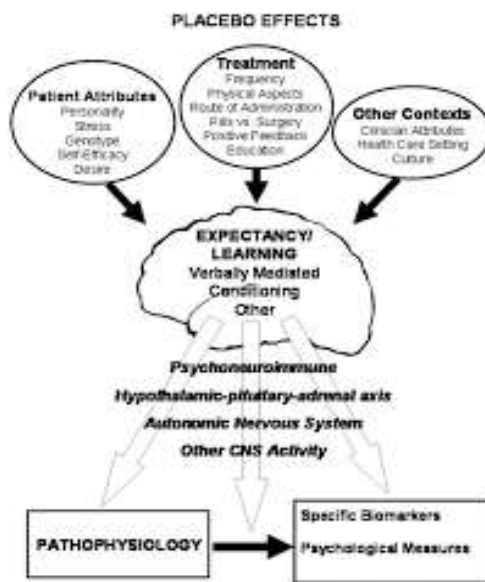


Fig: 4- Theoretical model of how the brain outputs may produce a placebo effect.

(CREDIT – Oken B. 2018. Placebo effects: clinical aspects and neurobiology. *Brain* 131:2812-23)

V. PHYSICAL CHARACTERISTICS OF DRUGS AND THEIR RELATIONSHIP WITH PLACEBOS

The Office of Generic Drugs began to notice that many reports that were being submitted to the FDA for review showed that the tablets and capsules were much larger compared to the reference product. The staff became concerned about the fact that a larger pill would affect a patient's ability to take the prescribed medication because it was well documented that increased pill size can lead to swallowing issues. All the generic drugs available in the market today undergo stringent regulations and guidelines to meet the prerequisites before they are launched. Drug manufacturing companies remain vigilant about the safety, structure, efficacy, physical attributes, purity and stability of the product.

Drugs or medicines which look like tablets instead of pills are better accepted by the patients. Similarly, oral medications are preferred over intravenous injections by those patients who normally do not want to take needle shots on a daily basis. A study conducted by a group of scientists at the Australian University of Medicine and Pharmacology proved that pink or white coloured tablets are visually more appealing and satisfying than blue or yellow coloured ones (Delanois and Harris, 2015). Changes in the physical characteristics of drugs can impact patients' compliance with treatment regimens and also cause medication errors (Peters, 2016). While a lot of speculation surrounds the physical attributes of an oral drug particularly its colour and shape, not much is known about patients' approach towards intravenous shots and solutions since most of them are clear in consistency and resemble water in their physical appearance.

However, when drugs are manufactured in the factories, it is made sure that they meet all the necessary criteria before they are finally packaged and marketed to various chemists and pharmacies across the countries. When patients or volunteers are given these drugs during clinical trials, their vital stats and BMI are carefully assessed in order to deem them fit for the trial while in most cases where placebos are also given to the volunteers, they are informed well in advance about the trials and its stages (Grisham, 2017).

VI. ETHICAL CONCERNS SURROUNDING THE USE OF PLACEBOS IN CLINICAL TRIALS

Volunteers who participate in clinical trials are the sources of essential data and information which is inferred by the researchers and scientists who conduct the trials. Legal and ethical issues form an important component of modern research, related to the subjected and researcher. The ethical and legal matters pertaining to the participation of human volunteers for routine clinical trials had increased the concern of researchers, policy makers, lawyers, health practitioners and scientists. (Yip, Han, Sng, 2019).

The purpose of a clinical trial is to systematically collect and analyze data from which conclusions are drawn, that may be generalisable, so as to improve the clinical practice and benefit the patients in the future (Woods and Joseph, 2012). Therefore, it is important to be familiar with GOOD CLINICAL PRACTICE (GCP), an international quality standard that is provided by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

Based on ICH definition, ‘informed consent is basically a process by which a subject voluntarily ensures his or her willingness to take part in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate (Riley and Ghosh, 2011).

Issues related to the research participants:

Researchers have a duty to ‘protect the life, health, dignity, integrity, right to self-determination, privacy and confidentiality of personal information of research subjects’.

The Belmont Report also provides an additional analytical framework for evaluating research using three ethical principles:

- Respect for volunteers: the requirement to acknowledge and protect the autonomy.
- Beneficence: the welfare of participants is of utmost importance.
- Justice: on both individual as well as societal level.

The past few years have witnessed an incredible growth in the number of clinical trials conducted in India. However, the economical surge in the clinical trial industry has also caused much worries pertaining to the efficiency of the Regulatory Agencies and Ethics Committees (EC). The EC plays an important role in the regulation of clinical research at local level (Kadam and Karandikar, 2015).

There had always been a lot of ethical issues regarding the use of placebos in clinical trials. Doctors and clinicians say that placebos can make the patient feel better in one or more ways but the fact that they can actually cure the ailment does not have any solid evidence (De la Casa, 2019).

It is important for the regulatory bodies to know and understand the possible benefits and harms of exposing volunteers or patients to placebos in clinical trials. In fact, most of the current medications are being replaced by placebos in order to test their efficacy and mechanism of action (Langley and Leavorton, 2012). The safety of withholding active therapy and enrolling patients in trials of new drugs is not an issue if standard treatment is expected to prevent irreversible morbidity or to alter survival, thereby rendering the use of many placebo controls unacceptable (Clark, 2015).

The use of placebos as controls in randomized controlled trials is the subject of considerable ethical debate. The ethical dilemma is particularly apparent in resource-limited settings and infectious diseases where it hinges upon the issue of “double standards” (Cheah, Steinkamp, Price, 2017).

VII. CONCLUSION

The human brain is a very interesting object. It thinks, registers, operates and analyzes things the way we see it; and is the most powerful organ in the human anatomy. Placebos have never aimed at curing us to the best of their abilities however; they have always made us believe that if we think better we feel better (Herbert and Shaw, 2012). The human body is the most complex machinery because it operates on the basis of reception and capabilities. Medical science’s approach towards treating illnesses with placebos rather than conventional pills had shown tremendous spurt in the past few decades but we are still trying to look within, delve deeper in its mysteries and possibilities and perhaps, even trying to strengthen the newly built foundations of pharmaceutical science for better days to come.

VIII. ACKNOWLEDGEMENT

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