Asian Journal of Research in Medical and Pharmaceutical Sciences

10(4): 15-21, 2021; Article no.AJRIMPS.77848
ISSN: 2457-0745

Placebo effect unboxed: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJRIMPS/2021/v10i430172
Editor(s):
(1) Dr. Somdet Srichairatanakool, Chiang Mai University, Thailand.
Reviewers:
(1) Pramudji Hastuti, Universitas Gadjah Mada, Indonesia.
(2) Gilberto Peña Vicuña, Universidad Nacional del Altiplano, Peru.
Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here: https://www.sdiarticle5.com/review-history/77848

Review Article

Received 06 October 2021
Accepted 12 December 2021
Published 13 December 2021

ABSTRACT

As in our body, brain is the most powerful part and our mind could be excellent healing tool when any chance is provided. The idea that our brain can be one of the convincing parts in our body for the fake treatment is the real point this is called as placebo effect [1]. This effect refers to the impact of placebo on any one. However, treatments which are not active also were also demonstrated measurable and positive health response [2]. The ability of placebo effect is reviewed as psychological process [1]. In some cases, placebos can exert an influence powerful enough to mimic the effects of real medical treatments. This effect is more than positive thinking [3]. When this response occurs, many people have no idea they are responding to what is essentially a "sugar pill." Placebos are often utilized in medical research to help doctors and

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scientists discover and better perceive the physiological and mental effects new medications [2] For exactly understanding the placebo effect importance it is crucial to know more about how and why it works. This article explains how this effect is recognized in modern medicine and elements of placebo effect and suggests few conditions under which making utilization of therapeutic potential of this effect could be ethically acceptable, if not warranted.

Keywords: Clinical trials; drug effects; placebo; placebo effect.

1. INTRODUCTION

One of the most successful physicians I have ever known, has assured me, that he used more bread pills, drops of colored water, and powders of hickory ashes, than of all other medicines put together. It was certainly a pious fraud.

Thomas Jefferson (1807)

The mind can have a powerful influence on the body, and in some cases, might help the body heal. [4] The mind can even have capability of tricking you into believing that a fake treatment has real therapeutic results, a phenomenon that is known as the placebo effect. [3] Clinicians and healthcare workers have had revealed that from hundreds of years distinct procedure with unclear mechanism of action or effectuality could still be the result in subjective development of clinical symptoms [5]. Many researchers had attempted to define this effect which results in formation of various framework and models helped in explaining and further exploring these effects and its responses. The placebo effect is anything which in appears like real medical treatment but isn't [6]. Placebo is a medical procedure formed to mislead the participant of clinical experiment. This could be a pill, shot or anything like a fake treatment [5]. What all placebos have in common is that they do not contain an active substance meant to affect health [6]. This treatment is nothing but a positive thought about the treatment will work which creates a good connection in between brain and body and how they work together," says Professor Ted Kaptchuk of Harvard-affiliated Beth Israel Deaconess Medical Center, whose research focuses on the placebo effect. [7] The role of the placebo in modern medicine is poorly defined because of a lack of a common understanding of what the placebo effect is and because of the negative connotations associated with its use. Placebos won't lower your cholesterol or decrease tumor. Rather it works on symptoms regulated through brain like pain. This treatment will results in feel good but it won't cure the problem [8]. It is more effective for conditions like pain management, insomnia and side effects occurred after cancer treatment. Placebos are crucial for designing of reliable clinical trials and one exception in participants had resulted to aim of various studies [9].

1.1 Placebo vs. Placebo Effect

This is essential to differentiate in between placebo and placebo effect are both are distinct things. First one placebo means inactive substance itself, while term placebo effect is any effects of consuming medicine, which could not be attributed towards treatment itself. Whenever a drug is consumed by any individual and given by the person to whom patient believes the capability of positive thoughts and exceptions increases for the benefit of patient. This characteristic of prescribing transaction is called placebo effect. Miserably the utilization of placebo effect often has trivializing connotation in the up- gradation shows simply a placebo effect. We should never disperse what the body could perform autonomously. In this aspect, current perception is way of categorizing effects in us, which we could not elaborate. We should not fall into a trap in which we use the term to minimize or discredit the Placebo process. [10]

1.2 Placebo Effect

The standard of measuring the interventions in persons is "randomized, placebo-controlled" a clinical trial in which volunteer are assigned for testing the group obtaining the experimental interpose or control group obtaining placebo [11]. The comparison of results in two groups shows whether modification in test group occurs by treatment or circumstantially. The placebo effect is advantageous for health outcome leading from a person's expectation, which could help in interventions [12]. The way healthcare workers interact with patient also gives a positive response, which is independent from any particular treatment [10]. Many researchers explored various aspects of this effect. One of the study recognized that a genetic marker which could predict whether someone will relay to

placebo, beside this other investigators supported that placebo response could occur externally to conscious awareness and at last suggestion was placebo could be helpful even if patient were aware about they are receiving placebo [12].

Placebo effect elaborates any physical and mental effect which placebo treatment had on any individual [11]. Investigations on this placebo effect had aimed on relationship between body brain. One commonly known theory of placebo effect is because ofpersons assumption [13].

The organic course of disease and patient partiality could be misinterpreted as response towards placebo [12]. The research regarding placebo effect is therapeutic tumult should be discarded by placebo-controlled trials. Some studies are formed for measuring the placebo response rate directly. Placebos are an intimation of how bit is known about interaction in between mind and body. The placebo effect may be one of the versatile and admonition therapeutic tools at the destruction of physicians [10]. Beside it when people were given the same pills by saying them that these pills will help them to sleep they accomplished the opposite effects.

Many experts also revealed that there is an association between how intensely any individual expects to have results and it occurs or not [14]. As stronger is the feeling more prone person is towards experiencing positive effects of placebo effects. There could be a extreme effect due to interactivity in between patient and healthcare worker [15]. This is also found true regarding negative effects. In addition, if any person anticipates having any consequences like nausea, headache, and drowsiness then there may be more possibility of occurring these reactions [16]. This effect modifies one person to other and its power varies from one disease to other [15]. The cause for the impact of placebo is not understood entirely. As given variation of response, it is more possible that there could be greater than one process at work.

1.2.1 Four factor involved in placebo effect are-

1. Expectation and conditioning
2. The placebo effect and the brain
3. Psycho-neuro-immunology
4. Evolved health regulation

1.3 How Placebos Are Used

Researchers use placebos during studies to help them understand what effect a new drug or some other treatment might have on a particular condition. [15] For illustration few people in a study may be prescribed a new drug for decreasing the cholesterol or even blood sugar. Other could get placebo. Not a single person in a study will know they got placebo or the real treatment. [12] Researchers then compare the effects of the drug and the placebo on the people in the study. That way, they can determine the effectiveness of the new drug and check for side effects. Sometimes a person can experience reaction to placebo. [16] The response can be positive or negative and people symptoms could become better or person could have what appear through side effects of treatment. However, these responses are described as “Placebo Effect”.

The following components have manifested the positive responses for placebo effect.

1.4 Pain

Chronic pain is one of the most debilitating conditions worldwide, and safe pain treatment options are needed. [17] Placebos, by their very nature, are safe. Research also suggests they are effective. A greater understanding of how placebos can be optimized for pain treatment could improve clinical outcomes. [15] The goal of this Research Topic will be to publish both basic and translational work on the overlap of placebo studies with pain or pain treatment. [13] Pharmacological approach towards pain management have initially aimed decreasing ascending neurotransmission and opioid receptor associated treatment. There is very minute knowledge about contribution of endogenous descending modulatory systems to clinical pain outcome and why few patients are affected less and other go through devitalize pain stimulated improper functioning. [18]. The neurological science and placebo effect is a new and frequently exploring aspects which inserts distinct areas for both human and animal neurological science and their complements studies of placebo effects physiology and other outcomes [19]. Placebo and its effects are very problematic to extract from organic course of diseases or actual impact of new drug in a clinical trial. There are strategies for increasing clinical results by modifying expectations and conditioning. Different systems and mechanisms trigger placebo effects, which extremely affect

mechanism of pain, clinical outcome and sense of well-being.

1.5 Depression

The researchers found that the participants reported significant decreases in depression symptoms when they took the active placebo (Placebo give rise to remarkable side effects which convince the individual being treated and received legitimate treatment), compared to when they took the inactive placebo (a tablet capsule or dose form that do not consist active drug components. like sugar, starch containing liquid) [8]. These deductions were associated with elevated μ-opioid receptor brain activity in part of the brain involved in emotion and stress regulation [18]. Remarkably increased activity of μ-opioid receptor stimulates through active placebo was also involved in significantly superior response with further antidepressant treatment. Few people are more amenable towards intention of treating their depression and could do better if treated by psychotherapies or cognitive therapies, which increase the relationship between patient and clinician involved in their case and in antidepressant medications [5].

1.6 Anxiety

Clinical findings suggest that placebo effects can be translated to a real-life setting in the reduction of moderate stress and symptoms of anxiety and depression, at least in the short term. [20] Placebo effects could be converted to a real life in very short duration of reduction in stress, anxiety and symptoms of depression in a non-diseased population. In psychological distress, treatment placebos could be fruitful addition for treating repertoire [16].

1.7 Cough

The true placebo effect means psychological therapeutic effect of treatment and it turns to belief in the efficacy of treatment and attitude of patient as regards to therapist [21]. Parents and physicians needs symptomatic relaxation in cough associated with upper respiratory tract infections. If a placebo is of low cost had no or less adverse effects and could decrease unwanted antibiotic treatment this appears to be a recommended treatment option [20]. Cough medicines work mainly through their sweet tastes and placebo effect. The sweet syrups utilized mostly in counter medicines which may contribute towards the cough resistance and expectorant activity.

1.7.1 Factors contributing to this phenomenon

Why do people experience real changes as a result of fake treatments? While researchers know that the placebo effect is a real effect, they do not yet fully understand how and why this effect occurs. [12] Research is ongoing as to why some people experience changes even when they are only receiving a placebo. Several different factors may contribute to this phenomenon.

- Hormone response
- Conditioning
- Expectations
- Genetics

1.8 Hormone Response

One possible explanation is that taking the placebo triggered a release of endorphins. Endorphins had structure homologues to morphine and opiate painkiller, function as brain's natural painkillers [22,23]. Researchers have been able to exhibit the placebo effect in action of using brain scans, showing that areas that contain many opiate receptors were activated in both the placebo and treatment groups. Naloxone is an antagonist of opioid, which blocks both natural endorphins and opioid drugs. Then after consuming naloxone placebo pain relief was reduced.

1.9 Conditioning

Other possible explanations include classical conditioning, or when anyone forms an association among induction leading to learned response. In few cases, a placebo could be paired with an real treatment until it give rise to the desired effect [14]. Like if any one regularly gives the same arthritis pills for relieving stiff, sore joints one could associate that pill will relief the pain. If you're given a placebo that looks similar to your arthritis pill, you may still believe it provides pain relief because you've been conditioned to do so.

1.10 Expectation

Expectations, or what we believe we will experience, have been found to play a significant role in the placebo effect. [3] People who are

highly motivated and expect the treatment to work may be more likely to experience a placebo effect. Mindsets, which are views or frameworks that orient and direct individuals to develop associations or beliefs regarding situations or experiences, can be shaped by multiple factors, including societal norms, culture, religious doctrines, and social media. [22] Mindsets help create a mental shortcut that simplifies complex inputs to be integrated by neuropsychological processes and that help shape and orient decision-making and related behaviors. [24] Thus, mindsets can strongly influence the effectiveness of treatments or interventions as well as the patient's behaviors within and outside the clinical environment. Mindsets in the context of expectations and expectancies can elicit biological changes related to immune, endocrine, and cardiovascular factors-

Verbal, Behavioral and Social indication could contribute towards expectation of an individual of whether the medication will affect.

1.11 Verbal

Hearing properly to health care workers providing positive thought about treatment.

1.12 Behavioral

The task of intake of pills or injection for improving your condition.

1.13 Social

Encouraging bogy language, eye contact and speech with help of doctor or nurse.

1.14 Genetics

Genes may also influence how people respond to placebo treatments. Some people are genetically predisposed to respond more to placebos. In a study people notice that with a variation of genes which codes for higher level of brain chemical dopamine are more susceptible towards placebo effect than those with less-dopamine version [25]. Individual with high version of dopamine of this gene also tends to have higher level of perception of pain and searching the reward.

1.15 The Nocebo Effect

The negative expectancies participate in occurrence of side effects and influence both clinical outcomes and patient's attachment towards medication [26]. The placebo effect is not mandatory to be positive at all time. For illustration if anyone is said that a pill may result to nausea, they're more prone to experience nausea than someone who had not been told that it may result nausea even pill is a placebo. Few people called it nocebo effect [27]. While placebos could affect the feeling of individual, studies reveled that they do not have significant impact on basic illness. Clinical trials associated with placebos showed that placebos had not major clinical effects on sickness. Beside, this placebo effects have minute influence on patient-reported results mainly approach of nausea and pain [28].

1.16 Is it ethical?

The current debate in medical ethics on placebos focuses mainly on their use in health research. In contrast to these certain an important topic of discussion tends to give over another longstanding but relevant question namely if and how the placebo effect could be employed in clinical practice [29]. Deception in absence of proper amends for giving information about the subjects might notably damage its desire of contributing to important knowledge and have faith in their doctors [30]. Pseudo impression of placebo effects could be formed in various ways [31]. Spontaneous development, distraction of symptoms, regression in mean, additional treatment, conditional switching of placebo treatment, scaling bias, unrelated response variables, answers of courtesy, experimental subordination, conditioned answers, neurological or psychological misjudgment, psychosomatic mechanism, distort etc. [32].

2. CONCLUSION

How placebos work is still not quite understood, but it involves a complicated neurobiological reaction which includes everything from elevation in feel good neurotransmitters like endorphins and dopamine to greater activity in specific part of brain associated to moods, emotional reactions and self-awareness [33]. All of this could consist therapeutic benefit. This placebo effect is a way for our brain to tell that body what it requires for feeling better says Kaptchuk. The certainty that placebo effect is tied to expectations does not make it virtual or fake. Few studies had revealed that there is actual physical modification which occurs with placebo effect [34]. Antidepressant is found to be involved

in treating chemical disproportion, mainly, lack in serotonin or nor-epinephrine in brain. Therefore, data analysis from the article and clinical trial data reveled consistency of advantages from antidepressants in treatment of depression and anxiety because of placebo response and difference in development between drug and placebo is not clinically relevant [35,36]. For illustration few studies have also reported that increase in production of endorphins in body is one of the natural pain relievers. The problem with the placebo effect is that it could be problematic to distinguish from the actual effects of a real drug during a study [37]. Finding ways to distinguish between the placebo effect and the effect of treatment may help improve the treatment and lower the cost of drug testing and more study may also lead to ways to use the power of the placebo effect in treating disease [38]. Placebo and nocebo effects happen instantly and are clinically advantageous but are overlooked in clinical practice [39]. Physicians should be able to identify these phenomena and master tactics on how to manage these effects to enhance the quality of clinical practice [40].

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/77848