Review Article

Placebo Response in Clinical Trials: Taming the Human Brain

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Abstract

The use of placebo in comparative clinical trials has exposed another lesser known side of the placebo, i.e., the placebo response. The placebo response is now being increasingly discussed, not only to adjust for the true clinical efficacy of a drug but also to understand the basis of psychological therapy, and benefits in therapeutic areas such as neurological disorders, especially pain. The mechanism of placebo action is multifaceted and works on the levels of brain and biochemical signaling, stimulated by priming and expectations. The imaging data show that certain areas of the brain are hyperactive while some are hypoactive during the placebo-mediated response, and trigger a biochemical pathway that relieves the symptoms. The data also suggest that the extent of benefit, i.e., the effect size of placebo response is directly proportional to positive expectations associated with the treatment, trust on the treating doctor, and certain beliefs associated with previous treatment. Although placebos incite a positive response, these might compromise or artifact the true efficacy of the drugs, thereby necessitating the need of addressing or minimizing the placebo response. Furthermore, it is important to identify the factors that modulate the placebo response, such as severity and natural burning out of the disease. Therefore, it is important to take a two-pronged approach-first, placebo as a treatment, for example, in neurological diseases, and second, adequately designed studies that minimize the placebo response. In this article, we discuss the placebo response, the mechanism behind it, its implications in clinical trials, and how to address the same.

Keywords: Clinical trials, implications, mechanism, placebo response

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Introduction

Clinical trials for long have embraced the use of placebo in almost all the trials, so much so that the use has become an epitome of evidence supporting efficacy and safety of tested interventions. The use of placebo takes its glory from the study designs that control for the biasing factors, thereby mandating the use of a comparator that allows evaluating the active treatment versus a situation when no intervention was given (placebo). This trend is increasingly evident now and can be attributed to a harmony between patients and the treating physicians. Interestingly, the placebo response is more pronounced in active comparator trials as patients have a surety of receiving treatment.[1,2]

As a so-called "inert-treatment," placebo is supposed to provide an insight into the true efficacy and safety of the intervention. However, time and again the cumulative data suggest that it has something more than its "inert" nature. The data show that such positive effect is evident even when the truth is disclosed to the recipients.[3] Placebo response may be stronger in pediatric patients,[4] and up to 41% of children showed benefit in an abdominal pain-related functional gastrointestinal disorders trial.[5]

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This psychological priming, rather taming, of the human brain makes it believe that the body is being treated, and it is going to show a benefit. This essentially outlines the need to understand this powerful interaction between human body and brain. Besides, this aspect is being now increasingly explored to understand the complex mind-body interaction, and how certain mind games and behavior can impact the human body in either direction.

The emerging data from physiological, psychological, immune-neuroendocrinology studies suggest that this interaction can be utilized in a number of ways to benefit the human beings in health and disease.

The Mechanism of Placebo Effect

The earliest evidence supporting this interaction between brain and body dates back to Pavlov, where a conditioning effect was

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seen on hunger. This reflects into many of our daily activities, and we think that this is just a habit. However, these habits are nothing, but how we have primed ourselves or tamed our brain/thinking. Despite having witnessed this daily "placebo" effect, we remain unaware of the mechanism of this placebo effect or priming.

The conceptual thought around placebo effect can be attributed to the severity of the disease, positive thinking/expectations, conditioning/priming, harmonious relations with treating doctors, and compassionate support from paramedical staff and family/friends. This in turn triggers a positive response leading to neurotransmitters and releasing endogenous opioids, and neuromodulation [Figure 1].

The key players that modulate these effects are patients' understanding of the disease and their expectations from the treatment, severity and impact of the disease, patient–doctor relationship, patients' state of mind, and social and environmental factors. When the treatment is administered, whether active or placebo, it is administered with a trust that it will bring an improvement in the clinical symptoms.[6] However, the effect size of placebo response is variable, and different individuals respond differently.[7] In a recent pilot study, the benefit was directly related to hope of healing and indicates self-healing as the core of this benefit.[8] The three key fields spanning the understanding so far have been described here.

Priming and expectation

In layperson's language, placebo works by priming the brain, where brain believes that a particular intervention will benefit the body. The simplest example from the day-to-day life is where just a peck from the mother on child's hurt hand takes away the pain. Another example is where doctor assures patient that there will be a benefit and as a miracle patient experiences benefit/relief.[9] This expectation for the positive outcome seems to play a key role in placebo-related benefit, along with other factors such as optimism and social conditioning and may produce a medium-sized benefit.[10] Positive expectations may also enhance the treatment response, and the extent of benefit seems to be related to the strength of belief/expectation.[11,12] Such benefit of positive impact is apparent even when the treatment remains unchanged when only the expectation with the "so-called" new treatment is changed.

The data also show that lower is the expectation of receiving active treatment, for example, in multi-treatment arms, lower is the placebo response,[13,14] and vice-versa.[15] Placebo effects may be exaggerated by having positive discussions with the patients. The data show that patients have better learning experiences in clinical set-up versus healthy people. Similar is the case with preconditioning, which tends to deliver maximum benefit out of placebos. In either situation, the previous impact has a large influence on the overall outcome.

Effects on brain

The imaging data show that on receiving treatment for pain, the regional blood flow reduces in the left basomedial/basolateral and right ventrolateral amygdala, including amygdala-frontal projections to dorsolateral prefrontal cortex (DLPFC), rostral anterior cingulate cortices (rACC), anterior insular cortex (AIC), and subcortical areas hypothalamus, thalamus, amygdala, and periaqueductal.[16-19] Similar results were noted in another study, where DLPFC, insula, and nucleus accumbens correlated with placebo analgesia.[20] These findings indicate a specific functional connectivity that clearly suggests that cognition and expectation, essentially a function of DLPFC, play an important role in the placebo effect. The expectation related to pain and its treatment has been evaluated quite extensively. One study shows that the magnitude of expectation was dependent on the functional connectivity between right frontoparietal network and rACC, and associated pain relief was dependent on the functional connectivity between the somatosensory areas and the cerebellum.[21] Another study shows that the functional connectivity between the dorsomedial prefrontal cortex and insula predicted the magnitude and probability of pain relief with placebo.[22] Similar results were observed in a meta-analysis using data from 11 imaging studies, where left

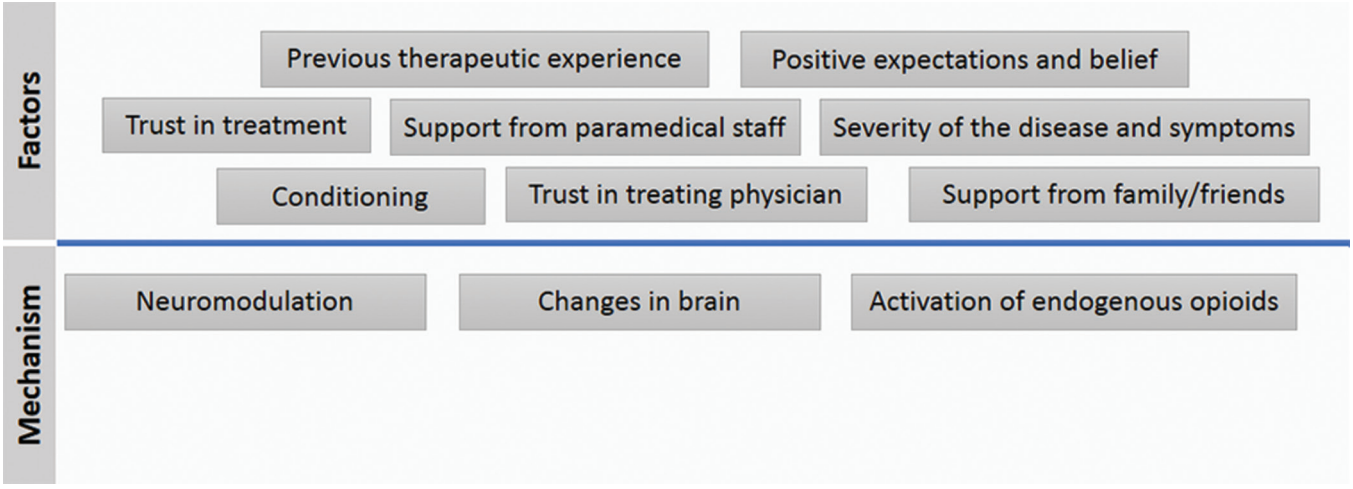

Figure 1: Conceptual framework for placebo response

anterior cingulate, right precentral and lateral prefrontal cortex, and the left periaqueductal gray were particularly active during expectation phase.[23] Significant placebo response was noted for placebo analgesia in experimental conditions, where pain processing was lowered in the thalamus, AIC, and anterior cingulate cortex, and was proportional in nature.[17]

Having discussed the mechanism of placebo response in detail, it is should also be noted that the size of the placebo effect varies largely. This seems to be driven by the expectation and optimism that a patient has had associated with the treatment.[24,25] Therefore, when the patient knows that treatment is being given, the benefit is higher versus when the patient is unaware of the fact that treatment is given.[26,27]

Biochemical trail

The above findings clearly suggest that cortical regions play a key role in managing placebo effect and triggering the pain relief through inhibition of pain regulating pathways. Endogenous neuropeptides such as opioids, oxytocin, cholecystokinin (CCK), and cannabinoids are known to regulate the pain pathways.[28-30] There could be non-opioid pathways engaged as well.

The evidence for placebo working through the opioid-CKK systems comes to the studies where opioid antagonist seemed to prevent while CCK antagonists seem to increase the analgesic effects of placebo.[31,32] This works through activation of μ-opioid neurotransmission in the brain including DLPFC, the anterior cingulate cortex, the insula, and the nucleus accumbens.[33] The alterations in opioidergic neurotransmission are also associated with changes in dopamine levels, and endogenous opioids work together with dopamine in eliciting placebo effect.[34] The proof came from disruption of placebo analgesia following naloxone administration that disrupts the endogenous opioid release.[32]

The data show that nonopioid mechanism may also work in the background of placebo analgesia, largely by conditioning. This is mediated by the endogenous cannabinoids,[28] and oxytocin, which works through oxytocinergic pathway.[30] The difference between opioid and nonopioid mechanisms can be demonstrated using previous exposure to naloxone and rimonabant, i.e., opioid- and cannabinoid-mediated placebo responses, respectively.

Imaging studies also suggest that dopamine release following activation of nucleus accumbens, which is involved in reward mechanisms, seems to modulate the placebo effect.[35] This also means that placebo response may enhance the reward learning in healthy individuals.[36] It is believed that the placebo works through a neuroimmune pathway, and therefore such pathways are now being increasingly studied, especially due to technology advancement.

The possible mechanism of placebo response was first proposed by Fuente-Fernandez while studying patients with Parkinson's disease.[37] There were two-blinded treatment scenarios-patients received an apomorphine versus placebo and an apomorphine only. Results demonstrated that the placebo response was achieved by endogenous dopamine release across the parts of striatum using the positron emission tomography (PET) scan of the brain using raclopride. This benefit directly correlated with the extent of endogenous dopamine release; however, there was a large variability in the response across the study population. The extension study supported these findings and suggested that for some patients, the magnitude of benefit with placebo can be as strong as the active treatment. Another study showed that placebo activates the dopamine receptors in the brain (ventral and dorsal striatum, both),[38] which could be due to the altered firing rate of neurons specific brain regions.[39,40]

When it is and When it is Not

Patients may often show benefit due to natural burning out of the disease (e.g., chronic pancreatitis), spontaneous remission (e.g., inflammatory bowel disease), incorrectly defined or inadequate efficacy measures (e.g., less stringent clinically meaningful important difference), less severe or very severe disease, methodological complexities and shortcomings, and unknown factors.[41,42] Importantly, these factors may impact patients differently, and often may bias the results even when a proper randomization was done since many of these factors work in the background.

One very common finding in clinical trials is that more is the severity of the symptoms, more is the treatment benefit. In such cases, placebo response can be attributed to the increased severity of the disease/symptoms at baseline, and such biases can be addressed using regression analysis. This is, however, not the placebo response.

Sometimes, the benefit is extended by natural burning out of the disease, which is not the placebo response but actually the natural "dying out" of the disease. To rule out any confusion, the natural history of the disease should be taken into consideration. A meta-analysis showed that at half of the time, the placebo response could be explained by spontaneous remission or natural burning out of the disease or variation.[43]

Therefore, it is important to understand that drugs and placebos act differently, even though the result is same. In this context, one should understand that the benefit extended by the drugs is longer lasting versus placebo, mainly by addressing the root cause of the problem or relieving the symptoms by blocking/enhancing certain pathways. In addition, increasing the dose increase may also help differentiate between a drug and a placebo. This also means that placebos may be especially helpful in psychological disorders.

Besides psychological disorders, placebo has shown efficacy in other diseases as well, for example, irritable bowel syndrome, where a psychological intervention showed a positive effect.[44]

Clinical Implications

The placebo effect may sometimes, therefore, compromise/enhance the efficacy of the drug in clinical trials, especially

when patients are not sure if they are or are not getting an active drug.[45,46] At times, there could be no difference observed between placebo and active treatment.[47] However, in real-world they are always sure that they are getting an active treatment, thereby increasing the effect size versus that observed in clinical trials. This effect has been observed with sham surgeries for pain, as well.[48]

Patients may have a response or maybe the better clinical outcome(s), which sometimes may apparently reduce the cost of the treatment. Interestingly, the higher the patient perceived price of the treatment was, greater was the benefit.[49-51]

There have been suggestions to elicit placebo response such as speaking positively about treatments, cultivating encouragement, trust, reassurance, support, respect uniqueness, exploring values, and "creating ceremony."[52] It is believed that such practice would induce a positivity in the patients and help them heal better.[53,54] However, the use of placebo for additional benefit to the patients should be ethical and should complement their active treatment in clinical practice.

On the other hand, the data from antipsychotic trials indicate that placebo response grossly affects the efficacy data, and could pose a major challenge.[55] There could be specific patient and disease characteristics that manipulate the placebo response size. These factors should be considered while conceptualizing a study, and planning the biostatistical analyses.

Quick Fix

Placebo effect size can vary largely and can be as high as up to 60% in sleep trials[56] and 40% psychiatric trials.[13] In general double-blind, randomized controlled trials will address the placebo effect since both the groups receive a blinded drug, and the effect would be the same in the treatment groups. This ensures that active treatment yields a treatment benefit over and above the placebo, and hence can be used to effectively treat a disease. However, some thoughts contradict this proposal. This is because the expectation is that subtracting the placebo effect from the drug should yield the true effect size and give a true estimate of drug's efficacy. This also has implication in power calculation and should be taken into consideration.[57] In a meta-analysis of fibromyalgia trials, the placebo effect size for pain, and other outcomes were estimated. Placebo effect size increased with increasing strength of the active drug and was also impacted by age, gender, and disease duration.[58]

Carefully and thoughtfully designed clinical trials may limit the biases to a large extent, and address or minimize the "placebo" response size.[59,60] A recent study shared the perspective on identify placebo response and responder predictors.[61] Another precaution is a careful and thorough study of the natural history of the disease. Furthermore, objective endpoints should be preferred over subjective ones to avoid biased results. For example, a run-in period may help to identify the limiting factors and fix these accordingly. The data show a lot of focus is now directed toward innovative trial designs to not only rule out the placebo effect[59] but also harness some benefit out of this.[62] Researchers have been brain-storming to minimize placebo effect by introducing newer clinical trials designs, especially where psychological outcome(s) are being measured.[63] In addition, there have been suggestions to assess patients' expectations in clinical trials, which may help to understand and address such biases.[64]

Having said this, it is of clinical importance that placebo response is maintained below the clinical threshold to minimize the possible interference with the clinical effect of the tested drug.[65]

Interventions Where Core Efficacy Depends on the Placebo Response

We have been struggling for long to find out the placebo arms for lifestyle interventions, especially those active interventions that seem to influence beliefs and mind, for example, counseling, yoga, and meditation, also referred to as mindfulness-based stress reduction or cognitive therapy (MBSR or MBCT). The data show that MBSR-based interventions could have a different mechanism of action versus placebo, and activates higher-order brain regions, possibly orbitofrontal and cingulate cortices while placebo may decrease pain-related brain activation.[66] Seemingly, yoga and meditation positively impact the body, and it is imperative that mastering such technique take a good amount of time, during which the brain becomes conditioned and produce (placebo) response. This could be a reason that higher-order brain regions are activated in MBSR-based interventions. PET imaging of novices versus experienced meditators mat help us in understanding the impact on the brain in a better way. An interesting article published over a decade back raised a very interesting question-yoga is a better treatment or better placebo.[67] In a comment to a paper published by Raina *et al*.,[68] the author questioned if better expectation with yoga led to better effect in yoga group versus exercise group in a study including alcoholic patients. This seems plausible as now we know that response has to do a lot with the expectation. Therefore, it is increasingly difficult to segregate the benefit of psychological interventions such as yoga-meditation/MBSR and counseling versus placebo response, where the outcome is derived based on psychological impact.

Similar is the case with psychological interventions, which seem to work on the basis of psychoneuroimmunology,[69] although there is no significant data published around it.

Conclusion

Personally, we all, at one or the other point in time, rather many times, have experienced the placebo response even if we have believed it or not. Truly speaking, it has generally a positive side associated and has helped many patients to achieve a clinical benefit despite a difficult to treat disease. Therefore, it is of utmost importance to harness the power

of placebo response by a positive approach, yet segregating it wisely from the ailments where an active pharmacological intervention is needed. How the placebo works may have deeper than visible roots as human brain and mind are complex and the mechanism of action of placebo unraveled so far may be just the tip of the iceberg.

In summary, more answers to this question might be available with continued research and insights into the human brain, particularly with advancing technology.

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Conflicts of interest

There are no conflicts of interest.

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