Editorial

THE PLACEBO EFFECT

The word "placebo" comes from the Latin translation, which means "I shall please". It is a substance that was believed to have no therapeutic effect, and therefore, was used as a control in drug trials in evaluating the efficacy of new drugs. In clinical trials, the placebo is a comparator from a methodological point of view and validates a new treatment, be it pharmacological or non-pharmacological.

Placebos have been recognized and studied for the past half a century, and for a long time it was found useful in placebo controlled double bind studies (RCTs). This became a gold standard till about twenty years back, when a new observation hitherto not reported, was made. More and more recent studies found that the difference between the two groups was at best modest, and in many studies, placebos were found superior to the active drug. The pharmaceutical companies were particularly shocked by this finding.

This is interesting, and there are studies going on examining the biological and psychological mechanisms at play, and the importance of the social context in which placebos work. The question that is most intriguing is "what has happened in the past 20-30 years?" that has increased the effect size of placebos and decreased the effect size of active drugs. Many explanations have been offered for this question and some of them will be discussed in detail.

The psychosocial context of the treatment is important. The placebo effect is partly produced by the communication, both verbal and nonverbal, of health workers, inducing positive expectations of clinical improvement and therapeutic benefit.

Usually, there is improvement in quality of life and the severity of symptoms like pain, motor performance, anxiety and depression. There is no scientific evidence of a real effect on the time course of the disease itself. This is seen in drug trials of a new anti-parkinsonian agent, where a placebo is used. A placebo is therefore, "the entire ritual of the therapeutic act". The ritual could be sugar pills, injection, sham surgery (which has a powerful psychological effect), acupuncture etc.[1] Both pharmacological and non-pharmacological treatments have a very important placebo component, means; they have an important psychological component. The greater the psychological component, the more powerful the placebo response, whether used for pain, anxiety, depression or any other symptom.

Neuroscientists are interested in understanding the underlying neurophysiological and neurochemical pathways involved in the mechanism of placebo action, ruling out spontaneous remission and "regression to the mean". In statistics, regression toward the mean is the phenomenon that if a variable is extreme on its first measurement, it will tend to be closer to the average on its second measurement, and if it is extreme on its second measurement, it will tend to be closer to the average on its first measurement.[2] The psychobiological component becomes clear on eliminating spontaneous remission and regression to the mean.

Studies have shown evidence of the following systems in placebo action:

- The endo-opioid system–pre-conditioning with an opioid drug like morphine activates this system.[3,4]
- The endo-cannabinoid system–pre-conditioning with a non-opioid drug like ketorolac activates this system.
- The prostaglandins (PG) - particularly PGE2–where there is a reduction in the overactivity of PGE2, both by placebo and by aspirin.
- The dopaminergic system–placebos cause activation of the reward system by release of dopamine in the nucleus accumbens.[3,4]

In drug trials, the placebo balanced trial is presently considered the best. In this trial, four groups of patients are studied.

Group I: Patients receive a placebo and are told that they are receiving a placebo.
Group II: Patients receive a placebo and are told that they are receiving the active drug.
Group III: Patients receive the active drug and are told that they are receiving a placebo.
Group IV: Patients receive the active drug and are told that they are receiving the active drug.

The placebo balanced trial is expensive and needs more patients, and therefore, is seldom used.[5]

There are two mechanisms of placebo response:

- Conscious placebo response, which includes positive expectation, belief in doctors and the therapy.[6]
- Unconscious placebo response, which includes the psychosocial aspects are often related to classical conditioning like the shape, size of the pill and its color, which can affect the response.

The nocebo effect is the antonym of the placebo effect. The nocebo effect is when a negative expectation of a phenomenon causes it to have a more negative effect than it otherwise would. A nocebo effect causes the perception that the phenomenon will have a negative outcome to actively influence the result. Mental states such as beliefs, expectations and anticipation can strongly influence the outcome of disease, experience of pain, and even the success of surgery. Both placebo and nocebo effects are presumably psychogenic but also produce measurable physiological changes as well as changes in the brain, the body and behavior. For example, when a patient anticipates a side effect of a treatment, he/she can suffer them even if the medication provided is an inert substance. One article that reviewed 31 studies on nocebo effects reported a wide range of symptoms that could manifest as nocebo effects including nausea, stomach pains, itching, bloating, depression, sleep problems, loss of appetite, sexual dysfunction and severe hypotension.[7,8]

Clinical trials form the basis for therapeutic decisions by all physicians. To maximize the likelihood that useful information for therapeutics emerges from the trials, the selection of controls is important. The sine qua non of any clinical trial is its controls. Many different types of controls can be used, and selection of a proper control group is critical. In drug trials, the randomized, double-blind placebo control trial is the most common design used all over the world. It is not necessarily the optimum design for all studies. The balanced placebo trial, in many situations is a better study design. The placebo effects are validated by inclusion of larger number of patients–particularly those that involve subjective responses. This is evident in research of pain, anxiety and depression.

Hawthorne Effect: This is a major component of the placebo effect. This is also referred to as 'the observer effect', and is a type of reactivity, in which, individuals modify their behavior in response to the awareness of being observed. This was first described, when factory workers were studied for their productivity. They were divided into two groups; one group of workers was put in an area which was dimly lit and the other group worked in a brightly lit area. The aim of the study was to find out, if lighting in the work area had an effect on the productivity. Surprisingly, the productivity went up considerably, in both the groups studied. This was, at that time, difficult to explain. This became to be known as the "Hawthorne Effect". The leading suspected cause in the placebo effect, is the participants' false belief in the material efficacy of the intervention. The leading suspected cause in the Hawthorne Effect, is the participants' response, to being studied i.e. to the human attention.[9]

Placebo Effect and the Brain

Functional neuro-imaging upon placebo-induced pain reduction shows activation and increased functional correlation between this activation in the anterior cingulate gyrus, prefrontal, orbitofrontal, and insular cortices. The nucleus accumbens, amygdala, the brainstem periaqueductal gray matter[10,11] and the spinal cord[12,13,14,15] are also linked.

Change in the Magnitude of the Placebo Effect Over Time

A review published in Journal of American Medical Association (JAMA) Psychiatry found that, in trials of antipsychotic medications, the change in response to receiving a placebo had increased significantly between 1960 and 2013. The authors of this review identified several factors that could be responsible for this change, the most important factors being inflation of baseline scores and enrollment of fewer severely-ill patients.[16] Another analysis found that placebo response in clinical trials of neuropathic pain had increased between 1990 and 2013. The researchers suggested that such trials have "increased in study size and length", during this time period.[17] All these 3 factors described as culprits, are in a sense, the result of flaws in research methodology. There can be only two reasons for this. One could be an unintentional flaw. This is unlikely given the fact, that there is a paradoxical increase in false positive results in drug trials that pharmaceutical companies would not mind.

The other possible reason could be a bias among doctors conducting drug trials to increase the likelihood of getting positive results by tweaking research methodology.

The ongoing research on placebo effect will answer many of the questions raised, sooner than later, considering the pace at which research in this field is going on.

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