Journal of Biological Engineering Research and Review, 2020; 7(2): 19-23
ISSN: 2349-3232 Online
Available online at www.biologicalengineering.in/Archive

Mini Review Article

Placebo: An Effective Investigational New Drug Over an Investigational Product and Associated Ethical Implications

Gaurav Dabas, Vansh Maheshwari, Kaushalendra Kumar*

Department of Clinical Research, School of Biosciences and Biomedical Engineering, Galgotias University, Greater Noida, Uttar Pradesh, India

***Corresponding author. E-mail: kaushalendra.kumar@galgotiasuniversity.edu.in (K Kumar)**

ARTICLE INFO:

Article History:
Received: 21/07/2020
Revised: 01/11/2020
Accepted: 05/12/2020
Published: 24/12/2020

Keywords:
Placebo; Clinical Trials; FDA; IND; Ethical issues

Abstract: There is always a bright side behind the use of placebo as a controlled treatment in the clinical trials. The aim of this work was to define the beneficial impact of the placebo rather than of investigational products in certain health conditions and its need to be proceeded for prescription after approval by the Food and Drugs Administration (FDA) above negligible ethical implications. Neurobiological, psychological or perceived effects of placebo came out as some advanced mechanistic responses seen in varying trials. Exponential decrease in the graph of new drugs approval by the FDA, placebo being the major factor behind the phase 3 failures and drop out of drugs from the pipeline. Researchers made the application of use of placebo in cancer trials despite earlier ethical issues. Advanced mechanistic responses and efficacy of placebos as seen in Phase 3 trials led to dropping out the Investigational Product (IP) and to process the placebo as an Investigational New Drug (IND) Application.

Citation: Dabas G, Maheshwari V, Kumar K. Placebo: An Effective Investigational New Drug Over an Investigational Product and Associated Ethical Implications. Journal of Biological Engineering Research and Review. 2020, 7(2), 19-23.

INTRODUCTION

Since the beginning of the Clinical Trials, effectiveness has always been the essential component in the journey of a drug from Bench side-To-Bedside. Placebo refers to "a sham treatment or an inert medication intervening the psychological or the pharmacological response during a treatment. If a placebo is found to be promising in conditions such as stress, panic disorder, etc. over an active treatment, it has the right to be approved as an IND over the IP being investigated. Before the introduction of placebo-controlled clinical trials, physicians judged the efficacy of medicines solely on the basis that the treatments made their patients better [1]. This was a problem! Ethical concerns and comparative analysis as comparators in presence of effective treatment are the basic two reasons behind the limited use of placebo over the past years.

IND refers to any substance (drug, vaccine, biological product) for which FDA approval is being sought while Investigational Product as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial [2]. After a successful pre-clinical phase an IND application is filed to seek an approval from concerned regulatory authority for further proceedings in humans. Following the clinical phases where different trial designs are implemented according to suitability of study, blinding and randomization are two common words that play a specific role in the description of the design. Blinding refers to the masking of concerned components of the study from the treatment they are allotted and randomization means the random allocation of the treatments to the subjects removing the chances of biases such as in terms of active treatment and placebo [3].

In 2002, the Merck's research-initiated study with an antidepressant codenamed MK-869 failed to pass the phase-3 due to complained side effects such as hopelessness and anxiety while the placebo group reported drastic improvement in condition [4].

According to psychological considerations, a variety of mechanisms contribute to placebo effect. These include expectations, conditioning, learning, memory, motivation, somatic focus, reward and reduction of anxiety [5,6].

Scans of patients taking a placebo show that their brains switched on parts that can help control stress and pain. Neurobiological viewpoint to placebo has addressed placebo analgesia, and so, the neurobiology of placebo effect is considered in terms of opioid and non-opioid mechanisms [7,8]. A thing which normally prevails is that if an effective cure is present then why one should be confronted to an inert substance. The use of placebos in clinical trials has been challenged by the World Medical Association (WMA). It has been proposed by WMA in the revised Declaration of Helsinki that placebo treatments should not be allowed in trials when an effective medicine exists to which the test medicine can be compared [1]. This recommendation by the WMA was criticized by those involved in clinical trials, and the WMA accepted an amendment to allow use of placebos

at the Washington, DC, meeting in 2002 [1]. In 2003, AstraZeneca's sucrosa became the first FDA approved placebo available to physicians for prescription in Random Occasional Non-Specific Pain and Discomfort Disorder [9].

This review discusses the effectiveness of a placebo comparative to the active treatments in recent times which becomes responsible for many active treatment failures over today's debatable ethical considerations for its use.

HISTORICAL REVIEW

It was observed that a person's willingness to recover from the brutal phase, is what makes inert medication successful too. This is defined as "any change in a patient's symptoms due to the therapeutic intent and not due to the specific physicochemical nature of medical intervention" [3]. In 1753, the advocacy of placebo controls took place. Following world war II, recognition of placebo effect in research protocols which are designed that promote efficacy and safety of pharmacologic therapies took place. A wounded soldier was assisted by an army nurse who was provided with a syringe containing only normal salt water when the morphine supply ran low by assuring that he was getting a potent painkiller. Amazingly, that bogus injection proved to be beneficial [10]. In 1946, full recognition of placebo and their role in controlled clinical trials profounded after a therapy session on placebo and double blinded methodologies in Cornell Conference. Double-blind technique where both physician and subject are unknown of the treatment subjects admitted to ensure that both expectation and beliefs are excluded and a report in 1955, where 15 studies of which included 1082 subjects were analyzed from which on an average 35% of subjects benefitted from placebo therapy [11].

Among all the ethical implications at the end of 19th century, WMA (World Medical association) set up international guidelines for clinical trials and proposed that placebo should not be used in clinical trials if an effective alternative treatment is available in the revised Declaration of Helsinki (Edinburgh,2000) [1]. Later this was reconsidered after the personnel involved in clinical trials who showed up their concerns and WMA accepted the amendment at the Washington DC meeting, in 2002. The WMA concern was, confronting the subjects to the risks by using placebo as a comparator to test the efficacy of test medicine in presence of effective treatments [12]. The amendment was based on the assessment of the poorly designed and low standard trials which may not meet the quality of trials when there would be no significant evidence of efficacy of test medicine against the currently available effective medicine [12]. In 2002, the National Depressive and Manic-Depressive Association, United States produced a consensus statement which concluded that placebo-controlled trials have a major role in treatment studies in affective disorders. It also mentioned that, equivalence between the new drug and standard treatment is not evident of efficacy till the superiority of the new drug is not established against the placebo [13,14].

In another study, where the efficacy of an antidepressant drug was compared only to the standard treatment available rather than placebo [15]. Similar studies led to the acceptance of ineffective treatments thereby narrowing the range of treatment options because of compromised use of placebos [15].

WHY CAN'T PLACEBO BE AN EFFECTIVE TREATMENT?

In recent times, double-blinding, randomization and placebo-controlled trial designs are some measures which aid in assessing the efficacy of an active treatment group with that of a placebo or a standard treatment. The pharmaceutical companies are adopting these strategies to compete with the rising demands in the healthcare sector continuously. In compliance with the FDA requirement for the approval of a drug, the superiority of the pharmaceutical active drug components is the major consideration against the already existing treatments available in the market, so the use of placebo-arms has increased dramatically over the past few years [16]. A report suggesting that exponential increase in phase 3 failures is due to the unexpected placebo response [16]. For diseases with high placebo response (e.g., pain), failures are more common. For example, in 2011, clinicaltrials.gov listed 4,152 trials in progress for the treatment of pain, yet from 2008-2011, the only new drug approvals were given for new formulations or new dosage forms of existing drugs [16].

Patient expectancy is one of the major factors along with number of treatment arms, no. of therapeutic encounters, the patient's genetics and clinical trial's duration contributing towards the placebo response. In 2011, a study for the evaluation of lung function randomly assigned asthma patients to three different groups: first group receives an inhaler with albuterol (this drug opens the airways), second group provided with an inhaler with a placebo, "sham" acupuncture received by the third group (in which needles were withdrawn before they touched the skin) and fourth one got nothing (Fig 01). Evaluation of the lung function is done by two criteria: self-reporting by patients for their asthma symptoms and an objective measure of lung functioning [17]. Analyzing the first criteria, the following illustration compliments the equal effectiveness of albuterol, placebo & sham acupuncture [17].

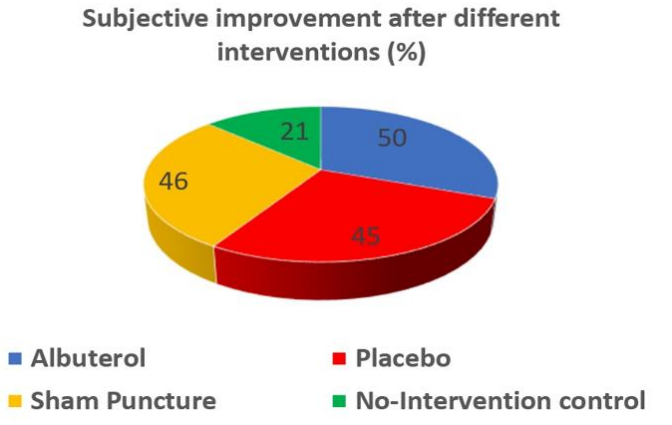


Fig. 1: Study data of subjective improvements after administering Albuterol, Placebo, Sham Acupuncture and a No- Intervention control group [17]

Similarly, across various trials no difference is met between verum (where needles are inserted up to certain depths, at certain points to control pain) and sham acupuncture along with greater minimization of symptoms as reported from placebo treatment as compared to no- treatment and usual care-control groups. Placebo effect is expected to affect the psychology of the subject rather than pathophysiology of the disease thus determining the greater efficacy in the treatments over the time.

Near around 2002, where a greater lag was seen in pharmaceutical industry in terms of sales by the Merck's Research against companies like Pfizer and GlaxoSmithKline, As told by the Merck's director to Forbes, they aimed to target the "Central Nervous System". An antidepressant codenamed MK-869 in the early phases sets out to be innovative molecule with minimal side effects promoting feeling of well-being. Later, subjects complained that their hopelessness and anxiety lifts. But parallelly subjects who took a placebo (an inert substance) for the comparison to the real medication showed the improvement in health drastically, hence the drug failed. In the period of 2001-2006, failure rate for phase 2 rose by 20% and those for phase 3 elevated by 11% mainly due to poor results against placebo [4]. A report at that time suggested that about half of the drugs at that time drop out due to their inefficiency to beat placebo [4].

PLACEBO RESPONSE IN ANTI-HYPERGLYCEMIC & ANTI-EPILEPTIC AGENTS CLINICAL TRIALS

An analysis of data obtained from US-FDA in oral anti-hyperglycemic agents' clinical trials revealed a trend in placebo response over the past few years. Placebo response-defined by decrease in HBA1c levels increased by 0.035 every year while drug response elevated by 0.017 every year following 1999 [18] (Fig 2A). Also, placebo response increased significantly over time without impacting efficacy outcomes. The FDA reviewed and source verified data of Anti-epileptic Clinical Trials showed that placebo response is increasing over time nearly quadrupling in magnitude. Placebo response (percent reduction in seizure frequency) increased by 0.7% seizure reduction following 1996, growing from 5% to nearly 20% in most recent trials (Fig 2B). On a similar note, drug response grew only about 5% in seizure reduction effect over nearly 20 years [19].

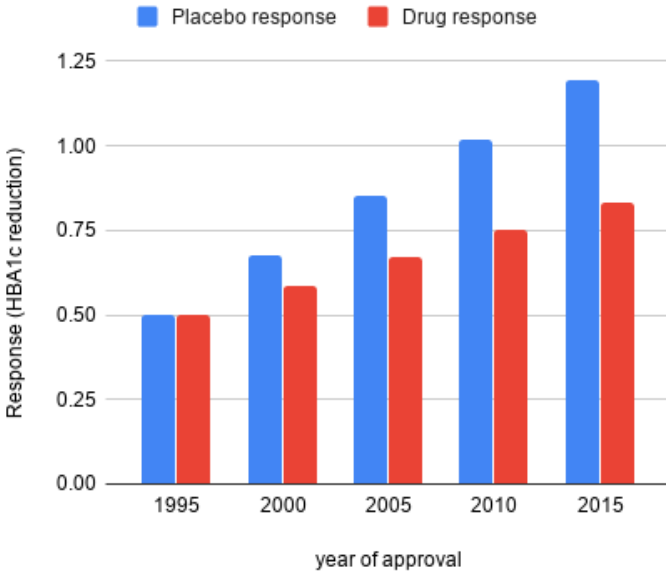


Fig 2A: Plot of Placebo response Versus Oral Anti-Hypertensive agent over the years [18]

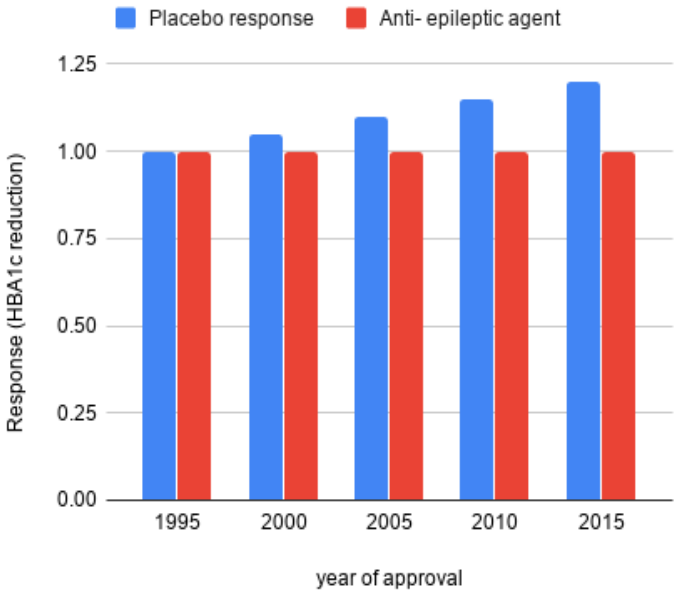


Fig 2B: Plot of Placebo response Versus Anti- epileptic agent over 20 years [19]

PLACEBO IN CANCER TRIALS

Earlier, Cancer studies seemed to be an inappropriate field for the inclusion of a placebo arm due to several ethical and clinical complications. One of the reasons for the same was chemotherapy treatments that caused tumor shrinkage and striking, severe side effects which is not possible by "sugar pill" [20]. Recent targeted drugs made the stabilization of the tumor growth rather than shrinkage of the tumor. To demonstrate the effects of these new drugs, a control group has to be implied to study to assess whether the stabilization is the drug's effect or natural recovery process. Continuous application of previous known treatments makes it difficult for the newer drugs to mark their effectiveness in clinical testing which make the use of placebo for the comparison and determine good and bad effects [20].

PLACEBO'S MECHANISTIC APPROACH

Patient-Physician relation

Medication performance is overshadowed by the intent with which it is prescribed along with the patient's psychological response towards the mechanism of action of the treatment. Physicians attentive approach during a treatment may compliments the effectiveness of the active treatment being provided which favors the placebo response i.e., active treatment minus the natural recovery of the disease. Expectations and beliefs of patients & physicians respectively are the core behind the implementation of any kind of treatment. In a study to demonstrate the belief of the patients regarding the color perception of the tablets, students are sorted into four groups and provided with one or two tablets of red and blue color respectively and asked to rate the sedative or stimulant effects accordingly (Fig. 3). As the tablets were inert to their medication pharmacology, unknown to the students who reported more stimulant effects in case of red pills and those taking blue tablets scored greater sedative effects [21]. In general, red color demonstrates aggression/danger while blue color calm/quietness. Students also reported more severe effects in two doses rather than one.

Fig. 3: Pill Color and its Placebo effects [10].

Perceived placebo effect

Accurately described in two sections: Non-specific effect & true placebo effect.

***Non-specific effect*:** Natural healing or spontaneous recovery of the condition implies the non-specificity of any of the expected responses. Patients recruited in an anti-acne study with the inclusion criteria of severity of the acne i.e., those individuals having severe or troublesome acne are screened ruling out the inclusion of mild ones. This engraved the possibility that acne severity will decrease due to natural recovery, hence measure of the symptom severity will decrease during the course of the trial, this referred to as "regression to mean" [22].

True placebo effect: It's been very difficult to measure the true placebo effect as no-treatment group is used in clinical trials rarely, hence the chances of natural recovery always persist. If a no-treatment group is used in a clinical trial, a direct comparison of the placebo effect is possible between the placebo treatment group and no-treatment group, this is deemed as the true placebo effect. Control of spontaneous recovery is not possible in the controlled placebo trials in which both active treatment and placebo control is used [23].

PLACEBO IN FDA'S LIST

If a placebo were submitted to the FDA for approval, they would no doubt be impressed with its efficacy, but would probably not approve it due to its frequent side effects [10]. A placebo named sucrosa was manufactured by Astrazeneca for the treatment of Random Occasional Non-specific Pain and Discomfort Disorder. GlaxoSmithKline manufactured Appeaser and Inertra to treat Erectile Dysfunction and Lower Back Pain respectively. Similarly, Pacifex, a placebo by Eli Lilly was manufactured for the treatment of Post-traumatic Stress Disorder. A very long course of advancements since the inception of Clinical Trials in pharmaceutics, there was no one till 2003 who evidently said that let's roll out with the placebo which can be a promising candidate for prescription to the patients in certain conditions. In 2003, sucrosa, a white crystalline substance of sandy consistency obtained from evaporated juice of Saccharum Officinarum plant approved by FDA as a placebo. Astrazeneca's sucrosa is approved for prescription in doses ranging from 1 to 40,000 mg in pill and liquid forms. Placebo's effectiveness in Random Occasional Non-specific Pain and Discomfort Disorder was reported along with treatment of lower-back pain, erectile dysfunction to nausea. On a similar scale, research also proves placebo to be effective in post-traumatic stress disorder, panic disorder, depression, bipolar disorder.

Following Astrazeneca's sucrosa, GlaxoSmithKline comes with two versions of placebo; Appeaser & Inertra, former being prescribed to patients 55 & over while the latter designed for middle-aged women respectively in liquid form. Eli Lilly's Pacifex hits the shelves later on, which was green in color and shaped like a triangle. Despite the several side effects concerns, negligible side effects related to the above medications that come under limelight which was a slight elevation in blood- glucose levels. A desperate need is way far ahead looking towards the benefits reported [9].

CONCLUSION

Currently, a drug's effectiveness is considered as the difference between the responses of placebo and drug groups. The placebo is more than a control medicine in a clinical trial. Research shows that the difference in effectiveness of real drugs and fake ones has narrowed. For the Clinical Improvement, placebo must be addressed for prescription on a broader scale as the placebo effect is one of the greatest components of any treatment and this challenge should be accepted by modern medicine to harness the placebo effect for the benefit of patients. Subjective clinical improvements in clinical studies has affixed a complimentary aspect to the advancement of placebo use in the market above the negligible ethical complications.

ETHICAL STATEMENT

No ethical issue to be declared

CONFLICT OF INTEREST

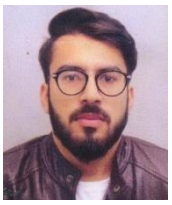
Authors declare that no competing interests exist.

REFERENCES

1. Eccles R. The power of the placebo. Current allergy and asthma reports. 2007 Mar 1;7(2):100-4.
2. Guideline IH. Integrated addendum to ICH E6 (R1): guideline for good clinical practice E6 (R2). Current Step. 2015; 2:1-60.
3. Byerly H. Explaining and exploiting placebo effects. Perspectives in biology and medicine. 1976;19(3):423-37.
4. Silberman S. Placebos are getting more effective. Drugmakers are desperate to know why. Wired Magazine. 2009 Aug; 17:1-8.
5. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu. Rev. Psychol. 2008 Jan 10; 59:565-90.
6. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. Journal of Neuroscience. 1999 Jan 1;19(1):484-94.

7. Kirsch I. Response expectancy as a determinant of experience and behavior. American Psychologist. 1985 Nov;40(11):1189.
8. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain. 1999 Nov 1;83(2):147-56.
9. FDA Approves Sale Of Prescription Placebo, viewed 04 May 2020, <https://www.theonion.com/fda-approves-sale-of-prescription-placebo-1819567087>
10. Glasser P. Essentials of clinical research. Glasser SP, editor. Springer; 2008 Jul 20.
11. Beecher HK. The powerful placebo. Journal of the American Medical Association. 1955 Dec 24;159(17):1602-6.
12. World Medical Association. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization. 2001;79(4):373.
13. Charney DS, Nemeroff CB, Lewis L, Laden SK, Gorman JM, Laska EM, Borenstein M, Bowden CL, Caplan A, Emslie GJ, Evans DL. National Depressive and Manic-Depressive Association consensus statement on the use of placebo in clinical trials of mood disorders. Archives of General Psychiatry. 2002 Mar 1;59(3):262-70.
14. Kupfer DJ, Frank E. Placebo in clinical trials for depression: complexity and necessity. Jama. 2002 Apr 10;287(14):1853-4.
15. Khan A, Khan S, Brown WA. Are placebo controls necessary to test new antidepressants and anxiolytics? International Journal of Neuropsychopharmacology. 2002 Sep 1;5(3):193-7.
16. Dumitrescu TP, McCune J, Schmith V. Is Placebo Response Responsible for Many Phase III Failures? Clinical Pharmacology & Therapeutics. 2019 Dec;106(6):1151-4.
17. Resnick B. The weird power of the placebo effect, explained. Vox. 2017.
18. Khan A, Mar KF, Schilling J, Brown WA. Magnitude and Pattern of Placebo Response in Clinical Trials of Oral Antihyperglycemic Agents: Data From the US Food and Drug Administration, 1999–2015. Diabetes Care. 2018 May 1;41(5):994-1000.
19. Khan A, Mar KF, Schilling J, Brown WA. Magnitude and pattern of placebo response in clinical trials of antiepileptic medications: Data from the Food and Drug Administration 1996–2016. Contemporary clinical trials. 2018 Jan 1; 64:95-100.
20. Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. Journal of clinical oncology. 2008 Mar 10;26(8):1371-8.
21. Blackwell B, Bloomfield S, Buncher CR. Demonstration to medical students of placebo responses and non-drug factors. The Lancet. 1972 Jun 10;299(7763):1279-82.
22. Kienle GS, Kiene H. Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. Alternative Therapies in Health and Medicine. 1996 Nov 1;2(6):39-54.
23. Ernst E, Resch KL. Concept of true and perceived placebo effects. Bmj. 1995 Aug 26;311(7004):551-3.
24. Michelle Hancock, Placebo or Platitude? 2005 Jan, viewed 12 May 2020, <https://www.alive.com/health/placebo-or-platitude/ >

About Authors



Mr. Gaurav Dabas is currently pursuing Bachelor's degree In Clinical Research domain from Galgotias University, Greater Noida and working as a Trainee Clinical Trial Assistant at CIDP - Centre International de Développement Pharmaceutique, New Delhi. His area of interests are Clinical Data Management and Clinical Trial studies.

Mr. Vansh Maheshwari is pursuing B. Sc. Healthcare & Clinical Research from School of Biosciences & Biomedical Engineering, Galgotias University, Greater Noida, Uttar Pradesh. From his high school days, he has a keen interest in science and research activities. His curious nature always motivates him to gather scientific facts and is responsible for his academic interests. He dreams to excel in a career in the clinical research industry and contribute to the field of medical sciences.

Mr. Kaushalendra Kumar is currently working as Assistant Professor in Department of Clinical Research, School of Biosciences & Biomedical Engineering, Galgotias University, Greater Noida. Also, he is currently pursuing his Ph.D. Studies from Galgotias University, Greater Noida. He received M.Sc. degree from Jamia Hamdard, New Delhi. His areas of interest are Clinical Operations, Regulatory affairs, Clinical Data Mangement.