



Ethical Concerns of Placebos in Clinical Trials - Review Article

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ABSTRACT

Placebo is a medicine or procedure prescribed for the psychological benefit of the patient rather than any physiological effect. The use of a placebo in clinical research continues to be a topic of debate in the medical community. Some argue that the use of placebos is often unethical because alternative study designs would produce similar results with less risk to individual research participants. In any medical study every patient including those of control group should be assured to the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain. In randomized clinical trials for conditions having no effective treatment the control regimen with which the new treatment is compared is warranted to establish the evidence. But still there are team of health care providers who takes care safety of subjects receiving placebos i.e IDMC with the help rescue medication. Because the blinded study designs are also proven one of the best design to avoid bias. Thus use of placebo is ethical and safe in clinical trial.

Keywords: Placebo, randomized clinical trials, regimen, IDMC.

INTRODUCTION

A placebo is an inert substance that is designed to have no therapeutic value which is prescribed for psychological benefit to the patient rather than physiological benefit which used as a control in new drugs. Placebo is made up of substances like sugar and starch without any active ingredient that looks exactly like a real drug. A placebo may be a pill, injection, or a surgery (sham surgery). Placebo effect is when an improvement of symptoms is observed despite of using a non-active treatment. For many years, placebos have been conceptualized by their inert content and their use as controls in clinical trials and treatments in clinical practice. Recent research demonstrates that placebo effects are genuine psychobiological phenomena attributable to the overall therapeutic context, and that placebo effects can be robust in both laboratory and clinical setting. Evidence has also emerged that placebo effects can exist in clinical practice, even if no placebo is given.¹

The use of the word 'placebo' in a medical context, meaning innocuous treatment to make a patient comfortable, dates back to at least the end of the 18th century.² The interest in placebo effects only began with the widespread adoption of the randomized controlled trial (RCT) after world war II. Since then several trials using placebo as a control group have been carried out. However, its use in certain clinical trials remains one of the debated elements.

History of Placebo Study

Sometimes "Power of mind influences the body" where the placebo effect history was started in 1799. There are many trials conducted by John Haygarth are successful but never mentioned it as placebo. Thus, placebo came into light in 1920. Later placebo entered clinical vernacular by American anaesthesiologist Beechu observed the use of morphine for wounded men in battle fields of world war-II. From then with the urge of Beechu, placebos were put into scientific era as GOLD-STANDARD, DOUBLE-BLIND clinical trials to pull out the true effect of medicine.

Prior to 1906, when the Pure Food and Drug Act passed, there were no regulations regarding the ethical use of human subjects in research. There were no consumer regulations, no Food and Drug Administration (FDA), no Common Rule, and no Institutional Review Board (IRB). What follows is a brief discussion of why federal rules and regulations were established and why the IRB became a necessity.

The Effect of Placebo

As we know that placebo is not a real drug and it doesn't show any effect on disease but it has effect on how they feel, sometimes these are helpful in relieving symptoms and makes subject feel better. This is called placebo effect. In contrast the effect goes in other way and gives more signs and symptoms which include headache, nervousness, nausea, constipation. This type of effect with placebo is called NOCEBO EFFECT.



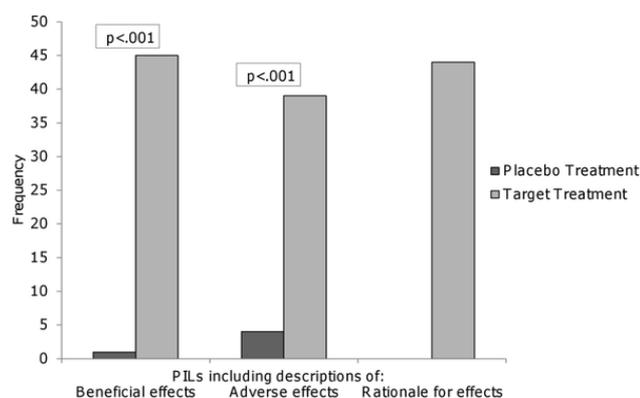


Figure 1: Image representing the statistical representation of placebo and treatment drug results (as example)

STUDY DESIGN OF PLACEBO IN CLINICAL TRIALS

When a new drug is undergoing discovery process for any particular disease or symptom the test drug is compared with the Gold standard drug studied in the lab and if it works then it is tested in animals followed by human beings but the test drug is always compared in humans as a reference.

If there is no approved treatment for a disease then placebo is given in some subjects and test drug in some subjects. Main reason to have placebo group is to make sure that all the effects in the subject is only due to test drug but not any other factors.

As we already studied that placebo effect depends on mindset the subject. This study is always a controversy that if patient thinks that he/she is receiving placebo that there are any benefits or not. To avoid this type of bias placebos are used the study designs like blinded studies, double blinded studies and randomised studies are preferred over open label studies where subject and investigator does not know which subjects are receiving test drug and placebo.

CONSIDERATION OF STUDY DESIGN IN PLACEBO STUDIES

Blinding

Blinding is the with-holding of information from participants which may influence them in some way until after the experiment is complete. Good blinding may reduce or eliminate experimental biases such as confirmation bias, the placebo effect, the observer effect, and others. A blind can be imposed on any participant of an experiment, including subjects, researchers, technicians, data analysts, and evaluators. In some cases, while blinding would be useful, it is impossible or unethical. For example, is not possible to blind a patient to their treatment in a physical therapy intervention. A good clinical protocol ensures that blinding is as effective as possible within ethical and practical constraints.

During the course of an experiment, a participant becomes unblinded if they deduce or otherwise obtain information that has been masked to them. Unblinding that occurs before the conclusion of a study is a source of experimental error, as the bias that was eliminated by

blinding is re-introduced. Unblinding is common in blinding experiments, and must be measured and reported.

Natural history groups

The practice of using an additional natural history group as the so-called "third arm" has emerged; and trials are conducted using three randomly selected equally matched trial groups. Reilly wrote: "... it is necessary to remember the adjective 'random' [in the term 'random sample'] should apply to the method of drawing the sample and not to the sample itself."

The Active drug group (A): who receive the active test drug?

The Placebo drug group (P): who receive a placebo drug that simulates the active drug?

The Natural history group (NH): who receive no treatment of any kind (and whose condition, therefore, is allowed to run its natural course).

The outcomes within each group are observed, and compared with each other, allowing us to measure:

The efficacy of the active drug's treatment

The difference between A and NH (i.e., A-NH). The efficacy of the active drug's active ingredient: the difference between A and P (i.e., A-P). The magnitude of the placebo response: the difference between P and NH (i.e., P-NH).

It is a matter of interpretation whether the value of P-NH indicates the efficacy of the entire treatment process or the magnitude of the "placebo response". The results of these comparisons then determine whether or not a particular drug is considered efficacious.

Natural-History groups yield useful information when separate groups of subjects are used in a parallel or longitudinal study design. In crossover studies, however, where each subject undergoes both treatments in succession, the natural history of the chronic condition under investigation (e.g., progression) is well understood, with the study's duration being chosen such that the condition's intensity will be more or less stable over that duration. In these circumstances, a natural history group is not expected to yield useful information.

Indexing

In certain clinical trials of particular drugs, it may happen that the level of the "placebo responses" manifested by the trial's subjects are either considerably higher or lower (in relation to the "active" drug's effects) than one would expect from other trials of similar drugs. In these cases, with all other things being equal, it is reasonable to conclude that:

The degree to which there is a considerably higher level of "placebo response" than one would expect is an index of the degree to which the drug's active ingredient is not efficacious.

The degree to which there is a considerably lower level of "placebo response" than one would expect is an index of the degree to which, in some particular way, the placebo is not simulating the active drug in an appropriate way.

However, in particular cases such as the use of CIMETIDINE to treat ulcers, a significant level of placebo response can also prove to be an index of how much the treatment has been directed at a wrong target.

Mechanism of Action of Placebo in Clinical Trials

Generally, a placebo is seen as an inert substance or procedure and the placebo effect (or response) is something that follows the administration of a placebo. The difficulty in this statement lies with the fact that if something 'inert' by definition should be unable to elicit an effect and therefore placebos cannot elicit effects. This can be further confused with terminology such as 'active', 'true', and 'perceived' placebos³⁻⁶ these mechanisms can be broadly discussed from psychological and neurobiological viewpoints.

Physiological mechanisms

From the psychological viewpoint, a multitude of mechanisms contribute to placebo effects. These include expectations, conditioning, learning, memory, motivation, somatic focus, reward and reduction of anxiety.⁷⁻⁸

Neurobiological mechanisms

Research into the neurobiology of responsiveness to placebo has addressed placebo analgesia; accordingly, the neurobiology of placebo effects is commonly considered in terms of opioid and non-opioid mechanisms.⁹⁻¹⁰ Several studies have demonstrated that placebo effects can be completely or partially reversed by the opioid antagonist naloxone, supporting the involvement of endogenous opioids in some analgesic effects of placebo.¹¹⁻¹⁴ Furthermore, analgesic effects of placebo are likely to be inhibited by the peptide cholecystokinin (CCK) for they are potentiated when a CCK antagonist is administered. Considered together, these studies demonstrate that some mechanisms of placebo operate by altering the activity of both CCK and endogenous opioids.^{12, 15, 16}

Guidelines for the Use of Placebo in Clinical Trials

The use of placebos is always a controversy in clinical trials when it outweighs risks over benefits. Thus, there are separate guidelines to be followed with the use of placebos which are updated time to time situations faced in trials. In 2008, FDA declared that foreign clinical trial of NDA should follow the ICH- GCP rather than declaration of Helsinki but was not followed as GCP's changes without FDA approval. Thus FDA can follow on its own and make agenda about placebo control studies. In 2018, there are few guidelines banned on the basis of adverse events especially in oncology patients. The PCT, RCT trials for therapies to treat oncologic disease, the FDA recommends that it should be conducted only in the selected circumstances which surveillance is the major standard of

care or with specific trial design features like patient support on degree of subjectivity outcomes. When the placebo control is considered the sponsor should provide statistical analysis of subjects in blinding and unblinding in the protocol. If the disease reoccurs or progresses or a suspected adverse event occurs then ICF should specify the risks and potential disadvantages of this approach and justification for potential and should un-blind subject to ensure optimal patient management with one or more drug products with substantial toxicity or invasive procedures is being considered. But in this unblinding subject should not be terminated from trial.

Use of Placebo in Clinical Trials

The placebo is a pharmaceutically inert substance (typically a sugar pill) is the clinical researcher's analogue to the scientist's control experiment. To prove a new treatment effective above and beyond the psychological results of a simple belief in the ability of the drug to cure, a researcher compares the results of the experimental treatment for an illness with those obtained from the placebo. The placebo-controlled trial is widely regarded as the gold standard for testing the efficacy of new treatments.¹⁷ Interest in placebo effects began only with the widespread adoption of the placebo-controlled clinical trials after World War II. The randomized clinical trial was a major methodological breakthrough in medicine and the best evidence for new treatment came from randomized placebo-controlled (RCT) double-blind studies. It was noticed that patients improved, sometimes dramatically, in placebo control arms. Henry Beecher popularized this observation in his famous proto-meta-analysis which claimed that about 35% of the patients responded positively to placebo treatment.^{18,19}

Ethical Concerns in Placebo Studies

The use of a placebo in clinical research continues to be a topic of debate in the medical community in recent times. Some argue that the use of placebos is often unethical because alternative study designs would produce similar results with less risk to individual research participants. Others argue that the use of placebos is essential to protect the society from the harm that could result from the widespread use of ineffective medical treatments. In randomized clinical trials, for conditions having no effective treatment, the control regimen with which the new treatment is compared, is warranted to establish the evidence. However, when an effective treatment already exists, it is unethical to create a placebo group that will receive no treatment. In other words, patients are deprived from an already existing effective therapy. The objective of testing such drugs to establish whether the new drug is better in efficacy or safety when compared to the existing drug/s placebo-controlled trial considered unethical. The association of placebo effects with RCTs has caused confusion because the response in the placebo arm is not necessarily a genuine psychosocial response to the simulation of treatment. In fact, the observed response to placebo in RCTs may reflect the natural course of the



disease, fluctuations in symptoms, regression to the mean, response bias with respect to the patient's reporting of subjective symptoms and other concurrent treatments.^{3,4} Use of placebo is a tradition followed from many decades though ethics are highly contrasted, to avoid bias. Placebos in blinded study designs are always successful studies. As clinical trials main objective is safety of subject. In many studies two groups of subjects in oncology and psychological studies there are many proofs that placebo worked always better i.e almost 77% of patients had a positive response in treatment but still when it is compared with oncology there is a big controversy because oncology is different from psychological treatment as clinical conditions in cancer need symptomatic treatment. It is always discussed that if there is use of placebo in cancer subjects the worsening of symptoms is observed because of no proper treatment. The ethical challenges of using a placebo in randomized controlled clinical trials for therapies to treat hematologic malignancy and oncologic disease, the US Food and Drug Administration (FDA) recommends that a sponsor use a placebo-controlled design only in selected circumstances, according to new draft guidance released Thursday. Such circumstances include "where surveillance is standard of care," or with specific trial "design features (e.g. if the trial uses an add-on design, when the endpoint intended to support a labelling claim has a high degree of subjectivity, such as patient reported outcomes)." When considering the use of a placebo control, FDA says sponsors should provide a rationale for the trial design and a detailed description in the protocol and statistical analysis plan of the proposal for blinding and unblinding. "If a sponsor intends to maintain the treatment blind when disease recurs or progresses or a suspected adverse event occurs, the informed consent document should specify the risks and potential disadvantages of this approach, and the protocol should include justification for the potential added risk." FDA also recommends that sponsors un-blind a patient "at the time of documented disease recurrence or progression to ensure optimal patient management." Continued blinding at the time of disease progression or occurrence of serious adverse events presents additional challenges, FDA says. "For example, in a blinded immunotherapy trial, a patient who develops adverse events on the control arm may receive unnecessary treatments (e.g., immunosuppressive drug products including a high dose of glucocorticoids, cyclophosphamide, interleukin-6 antagonist, or infliximab) for management of adverse events incorrectly attributed to the investigational drug product." Maintaining the blind after disease progression could also affect a patient's subsequent therapy. FDA also recommends unblinding the patient and investigator "when the patient has an adverse event suspected to be related to the investigational drug product and for which management of the adverse event with one or more drug products with substantial toxicity or invasive procedures is being considered. In such cases of unblinding, the patient should not be removed from the trial." In terms of the practical and ethical concerns related

to using placebos in some oncology trials, FDA notes that in many cases, because of the toxicity of the active treatment, patients and investigators may know if they are receiving a placebo treatment. As we know that subject's safety is the primary motto there are always special teams to take care of subjects at each and every moment in clinical trial period. To avoid this type of worsening conditions the independent data monitoring committee who will be monitoring the subjects regularly in different intervals in the whole trial period. As we know that subject's safety is the primary motto there are always special teams to take care of subjects at each and every moment in clinical trial period. To avoid these types of worsening conditions the independent data monitoring committee (**IDMC**) who will be monitoring the subjects regularly in different intervals in the whole trial period. Rescue medication is the treatment given to the subjects who were given placebo as a symptomatic treatment when they find a change in the clinical symptoms in this point of view placebos are always an ethical to use in trials for blinded design studies.

Effect of Placebo in Oncology Trials

For cancer patients, placebo effects are recognized when treatment is given for relief of symptoms. Placebos are regarded as essential in trials of antiemetic, but effective control of chemotherapy-induced nausea and vomiting does not exceed 15% in placebo groups and cannot be attributed specifically to placebo. Moertel et al. performed a review of four double-blinded, placebo-controlled, randomized trials of analgesic medication for cancer pain. They concluded that 113 (39%) of the 288 patients who received placebo experienced 50% or greater relief of pain. However, in these studies, the evaluation of pain was not based on a prospective comparison of validated scales that assessed the level of pain before and after treatment but on patients' estimates of percentage of pain relief. Such estimates depend on the memory of the previous state and might lead to an inflated estimate of benefit. In a more recent study, Boureau et al. used validated scales (the visual analog scale and the French version of the McGill Pain Questionnaire) to assess pain in a double-blinded, placebo-controlled, randomized trial for cancer patients with bone metastases. The placebo effect provided no details of the active treatment or of its efficacy. Many treatments, some with substantial toxicity, are given to patients with cancer. For patients with metastatic disease, it is rare that such treatments lead to improved survival, but they may lead to tumor response and/or improve symptoms and quality of life. All or part of these effects might also be due to placebo effects. If this were the case, it would be prudent to select nontoxic alternative treatments. The purpose of this review is to determine, on the basis of a review of the literature, the probability that symptoms and/or quality of life may improve and that tumor response may occur following the administration of placebos to cancer patients. We hypothesized that a substantial improvement in symptom control and quality



of life would follow administration of placebos but that tumor response would occur rarely.

Ethical Concern of Placebo in Children

The use of placebo in children is more restricted than in adults, because children cannot consent. Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions. The use of placebo is often needed for scientific reasons, including paediatric trials. The use of placebo may be warranted in children as in adults when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g., pain, hay fever). As the level of evidence in favour of an effective treatment increases, the ethical justification for the use of placebo decreases.²⁴

Effect of Placebo in Psychiatric Trials

A strong placebo response in psychiatry disorders has been noted for the past 50yrs and various attempts had been made to identify predictors of it by using meta-analysis of RCT and laboratory studies. Placebo controlled trials across psychiatry (depression, schizophrenia, mania, ADHD, autism, psychosis, binge eating disorder and addiction) for factors identified with placebo response. Of the factors discussed only 3 were linked to placebo response: low base line severity of symptoms, more recent trials and unbalanced controlled studies. RCT in non-drug therapy have not added further predictors and laboratory studies with psychological, brain and genetic approaches have not been successful in identifying predictors of placebo responses.²⁵

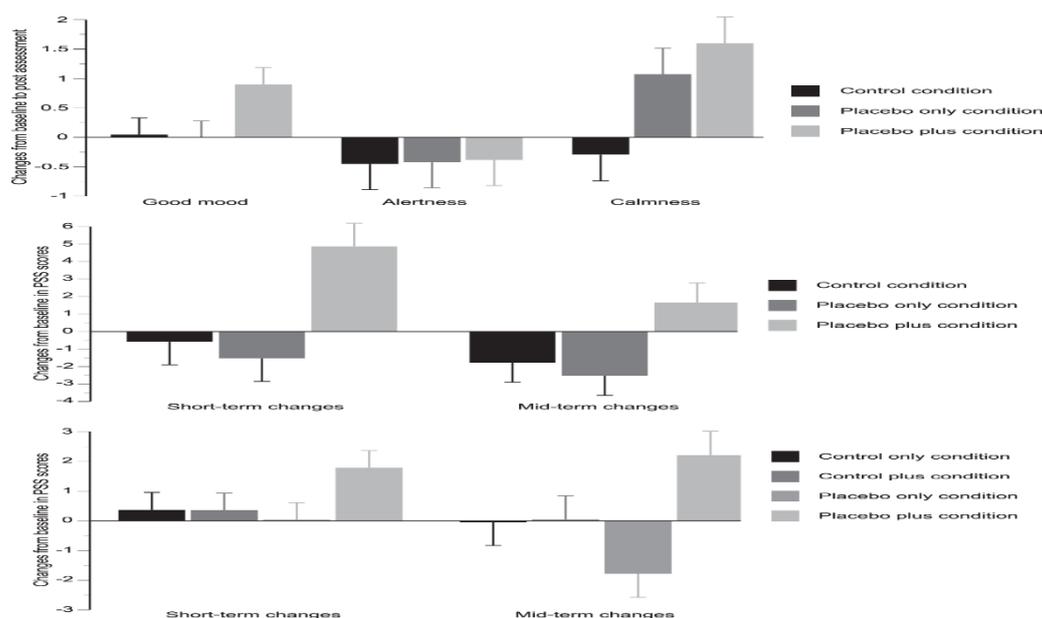


Figure 2: Image representing the drug effect in psychological patients during and after administration of placebo (taken as example)

Literature Review

No.	Literature Review	Reference
1.	Ethical deliberations on using placebos in clinical trials	Pranali M. Wandile, MS, CCRP
2.	Is it always unethical to use placebo in clinical trial?	Hans-werner-hense et al.
3.	The ethics of placebo-controlled trials: methodological justifications	Joseph millium PhD et al.
4.	ETHICS_MANUAL_3RD_NOV2015_EN_1X1\	John R. Williams
5.	Use of placebos in research	Bridget kiely
6.	The use of placebos in clinical trials: the responsible research or unethical practise	Sharona Hoffmann
7.	Scientific and ethical issues in the use of placebos in clinical trials	Pamela I. clark

CONCLUSION

There are valid scientific and ethical considerations for using a control group in a clinical trial. Placebo-controlled trials are justifiable when they are supported by sound methodological consideration and when their use does not expose research participants to excessive risk of harm. Consideration should be given to the 'best-available

therapy' control groups in the evaluation of a new therapy or intervention over an existing therapy. Investigators should bear in mind that one should not sacrifice the scientific merit of a trial to include the best-available therapy control group as long as the placebo control group poses little harm to the participants and, importantly, the trial offers potential benefit to the subjects.

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