Review Article

Placebo in clinical trials

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INTRODUCTION

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 settings. 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.

MECHANISM OF ACTION OF THE PLACEBO

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 paradox 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' placebos.[3-6]

A greater understanding of the placebo effect is the recognition that there is not one placebo effect but many. These mechanisms can be broadly discussed from psychological and neurobiological viewpoints.

Psychological 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]

PLACEBO IN CLINICAL TRIALS

The placebo, a pharmaceutically inert substance (typically

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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]

ETHICS OF PLACEBO-CONTROLLED TRIALS

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.

Critics of placebo-controlled trial or trials that include an untreated control group cite Article 11.3 of the Declaration of Helsinki: "In any medical study, every patient including those of control group, if any should be assured of the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain."[20]

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]

Clinical equipoise in placebo-controlled trials

Another argument proposed against placebo-controlled trials is that they potentially violate the concept of clinical equipoise when proven effective therapy is available. Clinical equipoise refers to the state where clinicians are unsure whether the new treatment or intervention is as good as the standard treatment. Those who reject the use of placebo-controlled trials argue that they violate the therapeutic obligation of physicians to offer optimal medical care. In other words, they compromise the right of the patient to receive the best care possible and violate the ethical principle of therapeutic beneficence. Furthermore, these clinicians have argued that when proven therapy exists, the use of a placebo-controlled trial lacks both scientific and clinical merit.[21-23]

The use of placebo is also questioned in vulnerable groups like children, psychiatric patients, and patients suffering from cancer.

Ethics 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 pediatric 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 favor of an effective treatment increases, the ethical justification for the use of placebo decreases.[24]

Usefulness of placebo

The use of placebo is not equivalent to the absence of treatment, for example, placebo could be used in addition to standard care. In all cases, its use should be associated with measures to minimize exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases. As appropriate, rescue treatment and escape procedures should be set up.

Other situations where the use of placebo should be scrutinized and challenged include run-in periods where a protocol requires active treatment to be withheld.

Situations in which placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the

investigational medicinal product is the first one that may modify the course of the disease process.

It is useful when the commonly used therapy for the condition is of questionable efficacy or carries with it a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.[24]

Guidelines of the office for human research protection on placebo

The Office for Human Research Protection (OHRP) published guidelines in 2008 for the use of placebo and methods to minimize the risk associated with it.[25]

The guidelines state, "Placebos may be used in clinical trials where there is no known or available (i.e., FDA-approved) alternative therapy that can be tolerated by subjects." The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and the subjects must be fully informed of the risks involved in the assignment to the placebo group. Continued assignment of subjects to placebo is unethical, once there is good evidence to support the efficacy of the trial therapy. Some drug trials involve a period during which all participants receive only a placebo prior to the initiation of the study. This period is called a 'placebo washout'. The purposes of a washout period include:

- Terminating the effects of any drug the subject may have been taking before entering the clinical trial, so that the effects of the trial drug-and only the trial drug-may be observed.
- Understanding whether the subjects co-operate with instructions to take drugs.
- Understanding which subjects are 'placebo responders', in that they experience a high degree of placebo effect.
- In some protocols, the investigators plan to exclude those subjects they find either poorly compliant or highly responsive to the placebo.

Methods that can be used to minimize risks associated with the use of placebo. Subjects with an increased risk of harm from non-response may be excluded.

Increased monitoring for deterioration of subjects and the use of rescue medications may be included in the protocol.

'Early escape' mechanisms and explicit withdrawal criteria may be built in so that subjects will not undergo prolonged placebo treatment if they are not doing well.

The size of the population placed on placebo may be kept smaller than the number in the active treatment arms.

Placebo and active treatment may be compared in an 'add-on' method, keeping the subjects on identical maintenance treatments and then adding on the active treatment to one arm and the placebo to the other. This design is especially applicable when the available treatment is known to decrease mortality or morbidity.

Shortened treatment periods reduce the risks associated with delayed treatment. In situations in which long-term placebo treatment would not be acceptable, the use of a placebo group for a short period at the beginning of a trial could establish short-term effects. The trial could then continue without the placebo group.

Unblinded data review by a data safety monitoring board with interim analysis of study results and safety issues is desirable. This is especially important for multicenter site studies.

If a placebo is used in a study, the informed consent form must include all of the following information: The subjects must be informed that they may be given a placebo. A clear lay definition of the term 'placebo' must be given to the subjects. The rationale for using a placebo must be explained to the subjects. If applicable, the subjects must be informed of any viable medical alternatives to being placed on placebo. The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained. Any consequences of delayed active treatment must be explained to the subjects.

A statement in the risk section of the consent that the condition of the subject may worsen while on placebo should be included.

A discussion in the benefits section that subjects who receive placebo will not receive the same benefit as those who receive active treatment if that treatment is effective should also be included.

SUMMARY

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 methodologic 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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