The Necessity and the Value of Placebo*

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ABSTRACT: *The use of placebo in clinical trials has been repeatedly challenged as being unacceptable from an ethical point of view. The present paper responds to this criticism by taking up the issue in the light of the pertinent provisions of the Helsinki Declaration. Examples from different therapeutic areas are given that highlight the importance of placebo in situations in which its use is acceptable according to the Declaration. Particular emphasis is given to the question of active control trials, which, under conditions of low assay sensitivity, may become an ethically less acceptable approach than the use of a placebo control.*

Introduction

The increasing public interest in drug discovery in medicine has not only caused enthusiasm about the new and more effective drugs, it has also caused growing awareness of the conditions under which these new drugs are developed and has raised questions whether all investigations involved are ethically acceptable. In particular, one of the cornerstones in the acquisition of reliable information about the efficacy of a treatment, the use of placebo in clinical trials, has met repeated criticism.[1] It is the aim of the present paper to respond to such criticism, to point out the crucial role of placebo, and to make clear that waiving its use altogether may be as unethical as its unjustified use. Regarding the issue of ethics in clinical research the Helsinki Declaration[2] constitutes the most important document. It is the basis on which clinical studies are performed and the obligation to adhere to its provisions is laid down in all relevant Guidelines of research institutions or regulatory bodies. In the following, the provisions pertinent to the use of placebo will be used as a starting point in the discussion on the usefulness and necessity of placebo.

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Provision 6 of the Helsinki Declaration constitutes a clear mission to perform clinical research even in situations that do not seem to require further research. It states:

"Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality."

However, provision 5 adds an important consideration to this mission:

"In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." If this provision were interpreted in an extreme way, one would find it impossible to perform randomization or to use placebo in any trial, because how can it be in the interest of the well-being of an individual to randomize the treatment or to use placebo?

The issue of placebo is taken up in provision 29:

"This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists." This statement seems very reasonable. It is obvious that no harm can come to a patient by the use of a placebo, if there is no treatment for his condition, and the effectiveness of the new treatment is not known. Nevertheless, the statement in its above form caused worldwide criticism from clinical researchers and health agencies (particularly those involved in the registration of new drugs such as the FDA or EMEA). The argument brought forward was that there exist conditions under which the use of placebo is indispensable, even if a proven therapy is available. It was felt that the provision was counterproductive and would severely restrict valuable clinical research.[3,4] In fact, the World Medical Association (WMA) reacted to this public outcry and published a clarification on their website[2] in form of a footnote to provision 29. It provides a list of circumstances under which placebo-controlled trials are ethically justified, even when other proven treatment is available. These circumstances are:

- When for compelling and scientifically sound methodological reasons placebo is needed to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.
- When a method is being investigated for a minor condition in which the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

In the following, examples will be given relating to the contents of provision 29 of the Helsinki Declaration, demonstrating its meaning and the importance of placebo in clinical trials.

Placebo and 'expected' outcomes of clinical trials

A first important consideration in the context of provision 29 is that a "proven" method is not the same as an "established" method, nor is "proven" the same as "reasonably expected". For instance, it is a historic fact that bleeding was for decades a well-established, widely used method to treat various diseases, but it was not proven to be beneficial to the patients. While this may be a simplistic example, the matter becomes

more complicated when we look at instances of trials in which – at first sight – the use of placebo did not seem easily defendable.

The CAST Study, published in 1991,[5] investigated the effect of antiarrhythmic drugs in 1498 patients following myocardial infarction. Knowing that cardiac arrhythmias are an important cause of death in these patients it seemed very logical to try to prevent the occurrence of arrhythmias by prophylactic treatment. However, after 10 months, mortality was 2.1% in the placebo group and 5.7% in the group receiving the antiarrhythmic drugs ($p < 0.0004$)

The CHESS Trial,[6] published in 1994, was a trial testing a monoclonal antibody against endotoxin in 2199 septic shock patients. Knowing the role of endotoxins in this condition it seemed very probable that the patients would benefit from the antibody. However, there was no difference in mortality after 14 days of treatment (32% placebo, 33% antibody).

A third prominent example is a study[7] published in 1998, in which the effect of the antiandrogen flutamide was tested in 1387 patients suffering from metastatic prostate cancer. All patients underwent bilateral orchiectomy and then received the antiandrogen or placebo. The logical outcome would have been an additive effect of the antiandrogen. However, after 5 years, there was no difference in mortality and no difference in disease-free interval between the two groups. By contrast, the number of dropouts because of adverse events was 5% in the flutamide group and only 1% in the placebo group ($p<0.05$).

The results of the three above trials clearly underline the importance of a placebo group. Without it, we might never have learned about the uselessness of the proposed treatments.

Placebo and low assay sensitivity

Another consideration relates to the footnote of provision 29 in which "compelling and scientifically sound" reasons for the use of a placebo are addressed. A very important methodological problem in many clinical situations is low assay sensitivity, i.e. the ability of a trial to distinguish an effective from a less effective treatment. This becomes of crucial importance if a so-called 'non-inferiority' or 'equivalence' trial is performed. In this type of trial the new drug is compared to an active comparator (thus avoiding exposure of patients to placebo). A non-inferiority margin is defined, and if the difference between the two treatments excludes a degree of non-inferiority larger than this margin, equivalence is assumed. However, it must be understood that 'non-inferiority' is not identical with 'efficacy', because if two treatments are not effective in a trial, they can still be equivalent. Low assay sensitivity greatly increases the probability of such an occurrence, i.e. that efficacy is erroneously assumed on the basis of a non-inferiority design. There are a great number of diseases and conditions in which the assay sensitivity of a drug trial is low. Typical examples include Major Depression, Anxiety Disorders, Dementia, Migraine, Symptomatic Congestive Heart Failure, Seasonal Allergies or Gastroesophageal Reflux Disease. Table 1 displays published data on drugs which are proven to be efficacious in their respective indication, but did not show a difference to placebo in certain trials.

Table 1:[8,9] Low assay sensitivity: Negative results in placebo-controlled trials with drugs of proven efficacy

Seasonal allergic rhinitis[8]	Symptom Score Reduction
Desloratadine	-24,5 %
Placebo	-22,8 %
Perennial allergic rhinitis[8]	
Desloratadine	-28,4 %
Placebo	-26,3 %
Migraine[9]	Patients symptom-free after 2 hrs
Sumatriptan	42 %
Zolmitriptan	41 %
Placebo	38 %

A particularly serious problem with low assay sensitivity exists in major depression. Drug trials show placebo effects in responders of 25 to 55 % magnitude as compared to 40 to 65% for the active controls, and about 1/3 of trials shows no difference between placebo and active comparator. Fourteen years ago attention was called to this situation by Leber[10] who reviewed six studies in which nomifensine (the new drug) was compared to imipramine (active comparator) and placebo. There were significant improvements from baseline in all studies with all drugs (including placebo) but only in one study superiority of active drugs over placebo was demonstrated.

The following table gives a recent example of this ongoing dilemma. The data are taken from studies on a new antidepressant drug (not yet licensed, personal communication) compared to two well-established antidepressant drugs of proven efficacy.

Table 2: Low assay sensitivity: three-arm trials on antidepressant drugs

Drug	Reduction in Hamilton-Score (significance vs placebo)
Placebo	6
New drug	6 (n.s.)
Fluoxetine	7 (n.s.)
Placebo	4
New drug	6 (n.s.)
Paroxetine	6 (n.s.)
Placebo	4
New drug	8 ($p < 0.05$)
Paroxetine	6 (n.s.)

In two of the studies there was no difference between the new drug or the comparator vs placebo; in the third, the new drug appeared to be better than placebo, but the active comparator was not. Without the placebo arm all trials would have yielded the result "equivalence of new drug and active comparator" (in one case "new drug numerically better than comparator"), but, in reality, they were inconclusive trials. Thus, the fact that equivalence is not identical with efficacy is a serious disadvantage of this type of trial.

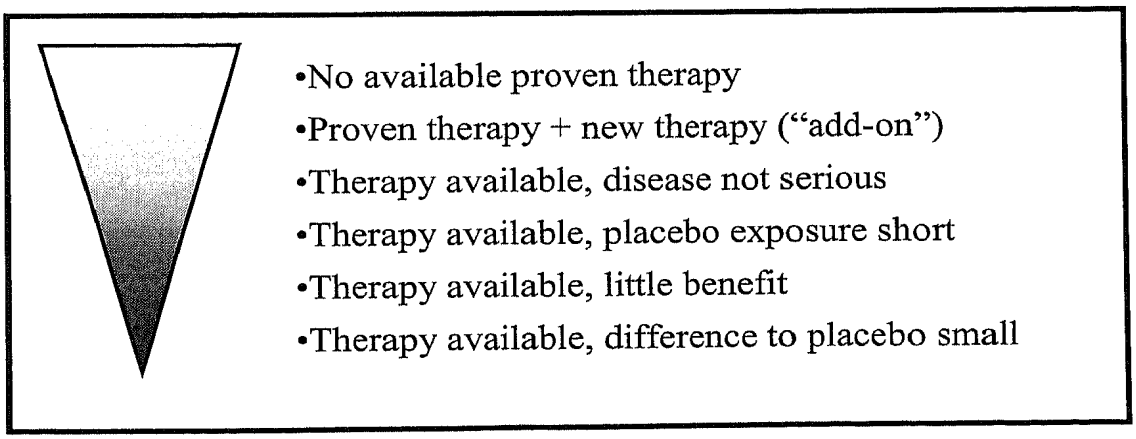
There are, among others, two more significant disadvantages:

- Any methodological flaw, e.g. the inclusion of inappropriate patients, will drive the result of the trial towards equivalence. In fact, the more careless the performance of such a trial is, the more likely the two treatments will be found equivalent.
- As outlined, 'equivalence' or 'non-inferiority' is defined by a margin. If two treatments are accepted as equivalent, it is still possible that they are different within the predefined margin. For instance, if the new drug has in reality 80% efficacy of the comparator drug, it will usually still be defined as non-inferior. If this drug is then introduced to the market and used for some time, it can become an active comparator itself. If this chain of events is perpetuated, i.e. efficacy of new medicines is solely assessed on the basis of active comparator trials, there is a danger of more and more poorly performing drugs gaining access to the market.

Placebo and patient protection

While there is consensus that placebo-controlled studies are necessary and – because of their high scientific value – are also required by regulatory authorities, there is equally consensus that the participating patients must be supported and protected. The bodies deciding whether a particular placebo-controlled study can be performed at a given research site, are ethics committees. It is their responsibility to assess whether the use of placebo is justified in a given situation and whether patient rights are preserved by the protocol in question. Figure 1 gives a list about the defensibility of the use of placebo.

Figure 1: Defensibility of placebo



Using this or a similar list the ethics committee will decide on a case-by-case basis which circumstances apply and will ask the following questions:

- Is the use of placebo is justified according to the Helsinki Declaration as outlined in provision 29 and its footnote (proven vs. established therapy, sound methodological reasons, minor condition)?
- What measures are taken to minimize the risk for the patients?
- Are the patients adequately informed?

In conclusion, the use of placebo is of paramount necessity in clinical research and its use is ethically acceptable, because scientifically invalid research cannot be ethical no matter how favourable the risk-benefit ratio for study participants may be.[11] It is understood, however, that the use of placebo is not the ideal solution. At the same time, clinical research cannot provide ideal solutions, only best possible ones.

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