*Presidenza del Consiglio dei Ministri*

CNB

COMITATO NAZIONALE
PER LA BIOETICA

# THE IMPROPER USE OF PLACEBO

29th October 2010

## PRESENTATION

The opinion has been drawn up by Prof. Silvio Garattini, coordinator of the working group composed by Profs. Roberto Colombo, Lorenzo d'Avack, Marianna Gensabella, Laura Palazzani and Monica Toraldo Di Francia.

The document is in line with the documents, already drafted by the NBC, on the subject of drug testing, and addresses a specific issue, the abuse of placebo. The document emphasizes that the use of placebo is not necessary if the investigator applies a superiority design to an already approved drug and precautions are taken regarding the high number of patients, the duration of the trial and above all the adoption of parameters for assessment of therapeutic effects. It is obvious that the comparison with a placebo instead of an active drug in itself favours the new drug seeking approval: but ethically the possible experimental advantage must be balanced against the current therapeutic needs with regard to the patients. The NBC emphasises the unethicality of improper use of placebo as it would deprive the patient of a useful drug. On the basis of this it draws attention to the role of ethics committees to ensure that commercial interests do not prevail over the right of patients not to be treated with placebo when an effective treatment is already available for a given therapeutic indication.

The document was discussed in the plenary session on the 29th of October 2010 and approved in unanimity of those present: Profs. Salvatore Amato, Luisella Battaglia, Bruno Dallapiccola, Antonio Da Re, Lorenzo d'Avack, Riccardo Di Segni, Carlo Flamigni, Romano Forleo, Silvio Garattini, Marianna Gensabella, Laura Guidoni, Aldo Isidori, Assunta Morresi, Demetrio Neri, Vittorio Possenti, Giancarlo Umani Ronchi, Grazia Zuffa. The adhesion of Professors Stefano Canestrari, Maria Luisa Di Pietro, Laura Palazzani, Rodolfo Proietti, Monica Toraldo Di Francia, absent from the discussion, was subsequently received.

The President
Prof. Francesco Paolo Casavola

**DOCUMENT**

Placebo (from the Latin “piacerò”) means any harmless substance or any non- pharmacological intervention lacking in therapeutic efficacy. It is precisely for this prerogative that placebo is purposely administered to the person who in due course may consent to take it as an alternative to an active treatment to experiment efficacy and safety. The use of placebo is therefore legitimate only for experimental purposes and only with the informed consent of the patient. According to the Declaration of Helsinki, in addition, the use of placebo is legitimate only if there are no treatments of proven efficacy for the clinical situation subject of experimentation, save for there being important methodological reasons adequately appraised in the interest of the patient and on condition that the patient does not seriously run the risk of irreversible damage. [*] The conscious cooperation of the patient is therefore required in situations in which medicine, affirming its difficulty in deciding, must proceed through experimentation. To administer a potentially effective new drug outside of an experimental context would expose the patient to the risk of unknown toxicity; refusing to administer it *a priori* would deprive the patient of the possibility of benefiting from its possible positive effects. The only ethically and scientifically valid solution is experimentation: arbitrary testing (randomization) will distribute a potentially effective treatment or a placebo to a population of patients and the comparison of the clinical outcome in the two treatment groups will consent to conclude whether the experimental drug is superior to placebo. The administration of placebo, in a formulation identical to that of the experimental drug maintains the blindness of the investigator and/or patient to the treatment; in turn, the blindness, or ignorance of the investigator and / or patient to the treatment assigned by chance, prevents voluntary or involuntary influencing that can affect the outcome of the trial, for or against the experimental treatment.

However, scientific literature contains significant examples of situations where the direction dictated by the Declaration of Helsinki is not followed (1). Supposed scientific reasons or commercial interests related to the approval of a new pharmaceutical product or new therapeutic indication by the regulatory authority expose patients to the risk of not receiving an effective drug.

The use of placebo is encouraged by the current legislation in the pharmaceutical field, this requires that new drugs prove their quality, efficacy and safety but without any need for comparisons with active comparators or any evidence of added value, for example an increase in the efficiency or a decrease in the toxicity (2).

This document takes into consideration three areas of improper use of placebo: 1) the case where a comparator is available, 2) the case of the *add-on* methodology, and 3) the case of trials with three arms (*three-arm trial*).

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[*] Declaration of Helsinki:
Article 32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
• The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
• Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

### 1) Availability of a comparator

It is obvious that the comparison with a placebo instead of an active drug in itself favours the new drug seeking approval. But what matters is that, if the placebo is used improperly, the patient is deprived of a useful drug. Examples of this type are not rare in the scientific literature related to *clinical trial*s. Recently, denosumab, an anti-osteoporosis drug for menopausal women was evaluated compared with placebo (3), when in fact there are several drugs available for osteoporosis such as, for example, tamoxifen for prophylaxis and bisphosphonates for therapy. Similarly, the fingolimod, a drug for the treatment of exacerbations of multiple sclerosis, was initially assessed in comparison with placebo (4), although in reality interferon beta was the treatment of choice in current clinical practice. Even cladribine, an immunosuppressant drug, was used for the treatment of multiple sclerosis versus placebo, although there were already on the market glatimer, copaxone and interferon beta for the same indication (5). Sometimes resistance or intolerance to the drug is the reason provided to avoid "head-to-head" comparison. Sunitimib proved more effective than placebo in the treatment of gastrointestinal stromal tumor (GIST) resistant to imatinib (6). However some patients assigned by randomization to the placebo group may have benefited from continued treatment with imatinib or a gradual adjustment of its dose (7).

Sometimes the use of placebo is artificially justified assigning it only to the subgroup of patients with the same disease, an approach known as "salami slicing" for the progressive selection and diminishing of the target population in the experimental treatment. All this is justified because in current clinical practice even these subgroups of patients would still receive the standard treatment, therefore, it is unacceptable to subtract patients from therapy and expose them to placebo.

### 2) Add-on studies

Treatment of proven clinical efficacy is sometimes used as a common basic treatment for all patients who are then randomized to receive in addition (*add-on*) a new experimental drug or placebo. This approach is certainly acceptable when there are no other drugs to be added to the basic treatment, but in many cases the availability of other drugs is deliberately not considered. For example, in a trial in patients with diabetes, the common basic treatment was a combination of metformin and a glitazone. These patients were randomized to receive exenatide in addition, a new drug that acts on PPAR-□□□□ (peroxisome-proliferator-activated receptors), or placebo. The results clearly favored the triple treatment including exenatide (8), but the comparison is not correct, because the placebo could be replaced by a derivative of the sulphonylurea, for example, or another of the many drugs used to control hyperglycemia in diabetes. In the mentioned *trial* it would have been possible to offer patients a better treatment than the placebo. Another example of this is the treatment of rheumatoid arthritis, a disease for which the drug of choice was methotrexate (9, 10). Again the experimental design according to the add-on strategy provides that methotrexate (or another immunosuppressant) is used for all patients, and these are then randomized to receive placebo or a new drug, for example, an inhibitor of TNF-□ (tumor necrosis factor). However, this approach could be justified for the first inhibitor of TNF-□□□ but it certainly

was not admissible when for example the effectiveness of infliximab was rated (11, 12). In fact, instead of placebo, etanercept should have been used, which had already been approved for this indication (13).

It is clear that in all these cases the patients treated with placebo were damaged because they did not receive the best treatment available. The commercial interest related to achieving favourable results for the new drugs, prevailed in the choice of experimental design of the clinical trials.

### 3) Three-arm studies

In many cases the use of placebo is part of a study with three treatment arms: in addition to placebo, the reference drug and the new drug. In these studies, the use of placebo is adopted to allow further validation of the standard treatment, whose effectiveness is still doubtful. This is the case with Hypericum Depression Trial Study (14) in major depression. In this study, neither sertraline nor hypericum have demonstrated to be different in a statistically significant way from placebo in relation to the two primary measures of outcome adopted: the Hamilton Depression Scale (HAM-D) and Clinical Global Impression Scale (CGI-I). An effect on these scales was recorded in 38.1% of patients treated with hypericum, 48.6% in those treated with sertraline and 43.1% in the placebo arm. These results were difficult to interpret: in the light of the surprisingly high placebo effect the study was probably underpowered, since the underlying assumptions for the test included a 20% difference in complete response between each drug and placebo (15).

However, even though in three arm studies the standard comparator is not different from placebo, one must consider that in current clinical practice, patients still receive the reference drug. Therefore, the presence of placebo does not add any new information, although it forces a group of patients to be deprived of any treatment.

Sometimes such an approach takes on the characteristics of questionable ethics. This is the case of severe acute post-surgical pain in women undergoing abdominal hysterectomy, which is usually controlled by subsequent doses of opioid analgesics. A study intended to assess the efficacy and safety of tapentadol, a centrally acting pain medication, included a period of 72 hours after hysterectomy during which the patients were treated with blind tapentadol (three doses), or 20 mg of morphine, or placebo (16). What is the purpose of leaving 169 out of a total of 854 women without pain control? The declared hypothesis of the study was that at least one dose of tapentadol would prove superior to placebo in controlling pain for 24 hours.

What may prevent the adoption of the placebo is the research of the superiority of the new drug in terms of its better efficacy or safety compared to the current reference drug. In this case there is no need to have an "arm" with placebo, because the study will show whether the new drug is better than the treatment that is considered as a current standard or current clinical practice. However, what requires the presence of placebo is the design of non-inferiority. When the effectiveness of a new drug compared to the existing one is proven accepting that a possible inferiority does not exceed the prescribed limits, it is important to ensure that the results obtained with the new drug do

not include the area of "activities" of the placebo; in other words, the new drug, even if inferior to the reference drug, but within accepted limits, must still prove to be superior to placebo. In the case of the comparison of new antidepressant drugs (SSRIs) with the old "tricyclic" products a demonstration of superiority was not dealt with and the three-arm study was resorted to in order to document nevertheless superiority to placebo. By so doing many patients were unjustly deprived of adequate treatment (17).

Exposing patients to a non-inferiority test, as reiterated by the Italian National Bioethics Committee, is unethical, not only because patients do not receive treatment in the placebo group, but also because the non-inferiority trial can not establish what is the "place in therapy" of the new drug compared to those already in existence (18, 19).

These three conditions are examples of how it is possible to derogate from the Declaration of Helsinki. Unfortunately, in these situations, the legislature and regulatory authorities do not respect the rights of patients. European legislation does not require any added value for new drugs. Therefore, the European Medicines Agency (EMA) can allow market access to new drugs simply on the basis of their intrinsic effectiveness and safety, and as such may be determined in comparison with placebo with no need for active comparators. If legislation required verification of the existence of "added value", studies for superiority in effectiveness and safety should always be carried out.

For its part, in the USA, the FDA (Food and Drug Administration) finds it difficult to interpret the clinical trials with active control (20) as these studies are too small to demonstrate a reasonable clinical difference and are affected by all kinds of shortages which tend to hide the differences; moreover in the absence of a placebo group a result of no difference in the study with active comparator may mean that both drugs are effective, that neither of them is, or simply that the study is not able to distinguish an effective drug from one that is not effective. In fact, all these problems can be solved without the need for placebo, provided that a superiority design is applied to an already approved drug and precautions are taken regarding the high number of patients, the duration of the trial and above all the adoption of objective parameters for evaluation of the effects.

Despite these discouraging assumptions, the FDA's decision not to accept non-inferiority studies on antibiotics (21) and a similar recommendation by the EMA limited to studies on anti-Parkinson drugs (22) and anti-Alzheimer drugs (23) look promising as to the possibility of reducing the inappropriate use of placebo. Meanwhile it is for ethics committees to ensure that commercial interests do not prevail over the right of patients not to be treated with placebo when effective treatment is already available for a given therapeutic indication.

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