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The Continuing Unethical Use of Placebo Controls

> Is it ethical to use a placebo? The answer to this question will depend, I suggest, upon whether there is already available an orthodox treatment of proved or accepted value. If there is such an orthodox treatment the question will hardly arise, for the doctor will wish to know whether a new treatment is more, or less, effective than the old, not that it is more effective than nothing.
>
> -- A. Bradford Hill[1]

Unaccountably, in these times of raised ethical consciousness, placebo treatments are still commonly used in medical research in circumstances in which their use is unethical. We refer not to the deceptive use of placebo, but to studies in which patients are informed that they may receive a placebo and then give their consent. Even so, such studies are unethical if patients are assigned a placebo instead of a therapy effective in treating their condition. Here we examine why this ethical breach persists and suggest ways to reduce it.

The Ethics of Placebo Controls

The Nuremberg Code, "the cornerstone of modern human experimentation ethics,"[2] was formulated shortly after World War II in response to Nazi atrocities. The World Health Organization adopted a version of the code in 1964 as the Declaration of Helsinki[3]. The declaration elevates concern for the health and rights of individual patients in a study over concern for society, for future patients, or for science. "In any medical study," it asserts "every patient -- including those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic method."[4] This statement effectively proscribes the use of a placebo as control when a "proven" therapeutic method exists. The declaration also directs that a study that violates its precepts should not be accepted for publication.

Nevertheless, studies that breach this provision of the Declaration of Helsinki are still commonly conducted, with the full knowledge of regulatory agencies and institutional review boards. Although some are published in peer-reviewed medical journals, the declaration notwithstanding, many trials that are conducted in order to gain regulatory approval for new drugs or devices never reach libraries. Thus, there is no straightforward way to estimate how many trials are undertaken that involve the unethical use of placebos.

Below are a few examples from among those that have actually been published. Some of these examples might be challenged by specialists in the disciplines involved, who might argue that

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the use of placebo was justifiable in the case under discussion. In the aggregate, however, the examples indicate that patients in trials are often denied "best proven" treatments.

Ivermectin Trial

In 1985 a group of investigators reported the efficacy of ivermectin to treat onchocerciasis, or river blindness[5]. The investigators assigned some of the study participants to placebo when, according to the investigators themselves, the drug diethylcarbamazine had been "the standard therapy ... for over three decades." The study participants were illiterate Liberian seamen, some of whom indicated their "informed consent" by thumbprint.

Rheumatoid Arthritis Trials

In recent years there have been numerous placebo-controlled trials of secondary treatments for rheumatoid arthritis. In many of these trials,[6,7,8,9] some enduring for years, all the patients were assigned to receive a primary therapy, such as a nonsteroidal antiinflammatory agent, and were then randomly assigned to receive either a new secondary treatment or a placebo in addition. New placebo trials of secondary treatments for arthritis continue to be proposed and conducted, even though many such trials have shown various secondary treatments to be more effective than placebo[10]. Participants who receive placebo in these studies are at risk for serious and irreversible degenerative changes that can, to some extent, be prevented.

Antidepressant-Drug Trials

A 1992 report of a randomized trial of treatment for major depression began with the statement "Effective antidepressant compounds have been available for over 30 years"[11]. Nevertheless, the investigators in that study assigned half the seriously depressed patients in the trial to receive placebo and the other half to receive paroxetine. Placebo controls are commonplace in trials of antidepressant drugs, despite the availability of therapies whose success is acknowledged[12,13,14,15,16,17,18].

Ondansetron Trials

Considerable advances have been made in controlling chemotherapy-induced emesis in recent years[19]. Several drugs are available for use singly or in combination; they include metoclopramide, phenothiazines, substituted benzamides, corticosteroids, and benzodiazepines[20,21,22]. Nevertheless, when a new agent, ondansetron, was tested, it was compared with placebo in several trials[23,24,25]. (This use of placebo was criticized in an editorial accompanying the published report of one of the trials[26].)

Trials of Drugs for Congestive Heart Failure

Angiotensin-converting-enzyme inhibitors are accepted as a standard treatment for congestive heart failure[27]. Although a number of these drugs have been approved, new ones, as well as other drugs for congestive heart failure, are commonly evaluated against placebo[28,29,30].

Antihypertensive-Drug Trials

Trials of new drugs for mild-to-moderate hypertension typically use placebo controls, despite the established efficacy of many agents in treating mild-to-moderate hypertension[31,32,33]. For example, in the introduction to a "dose-ranging" study of the calcium antagonist verapamil,[33] verapamil was described as "an effective antihypertensive drug, which is dose dependent, superior to placebo, comparable to or more effective than propranolol, and comparable with nifedipine." Despite these assertions, the investigators assigned some patients in the study to receive placebo.

Placebo Controls and Drug Approval

In the United States, many drug studies are conducted to meet the requirements of the Food and Drug Administration (FDA) so that the drug can be marketed. The Code of Federal Regulations under which the FDA operates is ambiguous about the acceptability of placebo controls. In one place it suggests that they should be avoided: "The test drug is compared with known effective therapy; for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interest of the patient."[34] The regulations go on, however, to suggest including both placebo controls and active-treatment controls in a study: "An active treatment study may include additional treatment groups, however, such as a placebo control. . . ."[34]

In practice, FDA officials consider placebo controls the "gold standard." Agency guidelines specify the study designs required to obtain approval for new drugs. Placebo controls are, in effect, required for disorders of moderate severity and pain, even when an alternative treatment is available. For example, in its "Guidelines for the Clinical Evaluation of Anti-Inflammatory and Antirheumatic Drugs,"[35] the FDA demands the inclusion of a placebo group when new-drug applications are submitted for fixed-dose combinations of nonsteroidal antiinflammatory drugs (NSAIDs) with codeine: "The combination must be shown to be superior to each component and

the NSAID must be superior to placebo in order for the study to be persuasive." For the clinical evaluation of disease-modifying antirheumatic drugs (DMARDs), placebo controls also appear necessary: "In order to develop the body of information necessary for approval of a DMARD, studies using the following different control groups should generally be conducted: Comparison of the drug with a placebo. . . ."

In at least one instance, the FDA refused to approve a new drug, a beta-blocker for use in angina pectoris, even though the application showed that the new drug had an effect similar to that of propranolol, an already approved drug. The application was rejected because the drug had not been tested against placebo,[36] even though a placebo-controlled trial would have violated the Declaration of Helsinki.

Is There a Scientific Rationale for Placebos?

The FDA is not alone in pushing for placebo controls. For example, a recent textbook on clinical drug trials advocates using them because "if a new drug has only been compared to an active control (without a placebo-controlled trial), this is not a convincing proof of efficacy (even if equivalence can be demonstrated)."[37] Without justification, such statements confer on placebo control a stature that ranks it with double blinding and randomization as a hallmark of good science.

The randomized, controlled trial is well recognized as the most desirable type of study in which to evaluate a new treatment. This recognition acknowledges the essential role of comparison and the importance of randomization in enhancing the comparability of two or more treatment groups. Using a placebo for comparison controls for the psychological effects of receiving some treatment and also permits blinding. No scientific principle, however, requires the comparison in a trial to involve a placebo instead of, or in addition to, an active treatment. Why, then, are placebo controls considered important? Three arguments have been advanced, none of which withstands scrutiny.

Establishing a Reference Point

By allowing the investigator to determine whether a new treatment is better than nothing (beyond the psychological benefits of treatment), a placebo control offers a clear benchmark. After all, even if a new treatment is worse than an existing one, it may still be "effective" in that it is better than no treatment. On the other hand, as Hill pointed out in 1963, the essential medical question at issue is how the new treatment compares with the old one, not whether the new treatment is better than nothing[1].

Avoiding Difficult Decisions about Comparison Treatments

Determining whether one treatment is better than another is not always a straightforward matter. Beyond the question of efficacy, one can and should take into account unintended effects, interactions, costs, routes of administration, and other factors. Thus, it may appear simplistic to demand that the best proven treatment be chosen as the standard for comparison, if "best proven" refers only to efficacy. For some patients there may be advantages to a treatment that is inferior to a current standard with regard to efficacy but better with respect to cost or quality of life. For example, the adverse effects of some accepted treatments might offset the therapeutic benefits for some patients sufficiently that a placebo control would be ethically justified. This reasoning involves a complex decision that should be defended in submitted research proposals and published reports. It is not justifiable, however, to assign placebo controls simply to avoid the complex decision of which treatment should be used as a standard. Investigators are ethically obliged to make such decisions.

Bolstering Statistical Significance

One FDA scientist contends that placebo-controlled trials are superior to studies using an active treatment as the control because it is much easier to demonstrate a statistically significant effect in the former case[36]. The FDA relies heavily on statistical significance in judging the efficacy of new drugs[36]. Despite its popularity, however, this tool is not a good one for measuring efficacy[38,39,40,41,42]. The significance of an association depends on two characteristics -- the strength of the association and its statistical variability. A weak effect can be "significant" if there is little statistical variability in its measurement, whereas a strong effect may not be "significant" if there is substantial variability in its measurement. Of the two characteristics, only the strength of the effect should be fundamental to the decision about approval of the drug. Ideally, statistical variability should be reduced nearly to zero when the magnitude of a drug effect is assessed, so that random error does not influence the assessment.

Unfortunately, the main way to reduce statistical variability is to conduct large studies, which are expensive. Statistical significance, on the other hand, can be obtained even in small studies, if the effect estimate is strong enough. When a placebo control is used instead of an effective

treatment, the effect of a new drug appears large and may be statistically significant even in a small study. The scientific benefit, however, is illusory. Because the study is small, the measurement of the effect is subject to considerable statistical error. Thus, the actual size of the effect, even when a new drug is compared with placebo, remains obscure, and the study does not address the question of the effectiveness of the new treatment as compared with currently accepted treatments.

The small placebo-controlled studies fostered by the FDA benefit drug companies, which can more easily obtain approval of an inferior drug by comparing it with placebo than they can by testing it against a serious competitor. Smaller studies are also cheaper. Unfortunately, the costs saved by the drug company are borne by patients, who receive placebos instead of effective treatments, and by the public at large, which is supplied with a drug of undetermined efficacy.

There is no sound scientific basis for these arguments on behalf of placebo controls. Furthermore, regardless of any apparent merit these arguments have, scientific considerations should not take precedence over ethical ones, even if the use of active controls requires more difficult decisions about study design, more costly studies, and more complicated analyses.

Ethical Counterarguments

Two ethical arguments are sometimes advanced to justify the use of placebos when effective therapies exist. First, one can argue that withholding an accepted treatment may not lead to serious harm. For example, treating pain or nausea with a placebo may cause no long-term adverse effects, and the patient can call attention to any treatment failure or even choose to drop out of the study. Nevertheless, although withholding an accepted treatment may occasionally seem innocuous, allowing investigators to do so runs counter to the ethical principle that every patient, including those in a control group, should receive either the best available treatment or a new treatment thought to be as good or better. Instead, it concedes to individual investigators and to institutional review boards the right to determine how much discomfort or temporary disability patients should endure for the purpose of research. Ethical codes in medical experimentation have been developed expressly to shield patients from such vulnerability.

The second justification offered is that of informed consent. This argument says that if patients are fully informed about the risks of entering a trial and still agree to participate, there is no reason to prevent them from doing so. The ethical burden is passed directly to the patients. Informed consent is always desirable, but investigators should not put patients in a position in which their health and well-being could be compromised, even if the patients agree. There are several reasons. Despite the best efforts to inform patients, they will rarely if ever be as well informed about their treatment options as their physicians[43]. Moreover, even informed patients may not be disinterested enough to decide rationally whether it is tolerable to be deprived of an accepted treatment. Finally, patients are given the choice of participating in a trial or not, but they are given no choice about which treatments will be studied. It may be more desirable to a patient to be a part of the trial than to decline to participate, but it might have been preferable to be in a different trial that did not have a placebo arm.

Recommendations

Placebo is likely to continue to be used in place of an effective control until all parties to such studies are held strictly accountable for the ethical conduct of the research. We recognize that in some situations an accepted treatment may not be better than placebo for a given indication and that arguments can be made to justify the use of placebo instead of an existing treatment. The burden of justification, however, should fall not on critics but on those responsible for the research, including investigators, regulatory agencies, research sponsors, institutional review boards, and journal editors. All these parties should adhere to the precept that patients ought not to face unnecessary pain or disease on account of a medical experiment, and they should question the ethical legitimacy of using placebos in any experiment. Investigators should be routinely required by regulatory agencies, institutional review boards, and funding agencies to justify in writing the use of placebos in any study that uses them. This explanation should be part of all proposals, protocols, and published papers. Editors should be vigilant about questioning the use of placebos in experiments involving humans; regardless of assertions authors make about institutional review, editors should always require authors to justify in their manuscripts any use of placebo controls.

The change needed most is the enforcement of ethical guidelines at regulatory agencies, such as the FDA, which review research that may never be published. The FDA should conduct an ethical review of every study submitted to it. Any study proposing to use placebos in place of

effective treatments without making a persuasive ethical justification should be disapproved. Studies involving unethical use of placebos should be ignored in the drug-approval process. Above all, scientific imperatives should never be weighed against established ethical canons.

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