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WITHHOLDING PROVEN TREATMENT IN CLINICAL RESEARCH

THE use of placebo-controlled trials began just before World War II, and the Declaration of Helsinki, which arose from the Nuremberg Code, was formulated after the war. Placebo-controlled studies soon became the gold standard of evidence, and the Declaration of Helsinki became the gold standard of research ethics. However, the practices of the first collided with the principles of the second, and researchers and ethicists have been trying to resolve this problem ever since. The debate over placebo-controlled trials is implicitly and inextricably linked to concern about withholding treatment — specifically, withholding proven or standard treatment — in the course of investigating new therapies.

We believe that the concern about withholding treatment in research has been inappropriately focused on the use of placebos. To move toward a resolution of the debate over placebo-controlled trials, we need to develop a broader understanding of the ethics of withholding treatment.

In this issue of the *Journal*, there are three reports on placebo-controlled trials of the effectiveness of angiotensin-receptor antagonists in slowing the progression of renal disease in persons with type 2 diabetes and evidence of mild-to-moderate renal dysfunction.¹⁻³ In the light of the reported benefit of angiotensin-converting-enzyme (ACE) inhibitors in slowing the progression of other renal diseases, would trials comparing angiotensin-receptor antagonists with

ACE inhibitors have been more appropriate? Even in the late 1980s and early 1990s, when these studies were planned, data indicated that ACE inhibitors might slow the development of renal dysfunction in persons with type 2 diabetes.⁴⁻⁶ These were small studies, but the results were consistent.

In the 1990s, a placebo-controlled trial was generally considered unethical if the placebo replaced standard care.⁷ At that time, ACE inhibitors were not commonly used in clinical practice to prevent nephropathy in persons with type 2 diabetes, in part because of concern about the risk of adverse effects on the kidney. In addition, the progression of renal disease was linked with the presence of hypertension, but it was not clear whether the development of nephropathy was related solely to blood-pressure control. In the three trials reported in this issue, all the patients were treated for hypertension. When there was compelling evidence not only of the direct protective effect of ACE inhibitors on the kidney but also of nephropathy as an independent risk factor for the development of heart disease,⁸ in one trial, it was stopped early.² At the time these studies were planned, standard care did not yet reflect the growing body of evidence that ACE inhibitors directly prevent the progression of renal disease in patients with type 2 diabetes. Thus, the conduct of these trials appears to have been consistent with the ethical standards at the time.

However, the criteria for acceptable use of placebos in clinical trials are changing. In 2000, the Declaration of Helsinki was revised. Principle 29 of the document now states, "A new method should be tested against . . . the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists."⁹ Also in 2000, the International Conference on Harmonisation issued guidelines for regulatory authorities and industry on the choice of a control group.¹⁰ According to these guidelines, a comparison with placebo may be necessary for the initial assessment of an investigational drug, and this practice is ethical provided that there is no risk of irreversible harm to the subjects, appropriate measures are taken to ensure their safety, and proper informed consent is obtained. Although no one would argue about the need for safety measures and informed consent, there is an acrimonious debate about the disconnection between the Declaration of Helsinki's criterion of no proven treatment and the regulatory criterion of no irreversible harm as standards for the appropriate use of placebo groups in clinical trials.

In this issue of the *Journal*, Emanuel and Miller highlight an encouraging trend in the placebo debate — the need to justify the use of placebos both scientifically and ethically.¹¹ This concept is not new, but it is topical, valid, and appealing.

Others have taken a similar stance. The European Agency for the Evaluation of Medicinal Products supports the judicious use of placebo even in the context of proven treatment, when such use is essential and does not pose a risk of irreversible harm.¹² In the draft revisions of the International Ethical Guidelines for Biomedical Research Involving Human Subjects, guideline 7 states that the principle stated in the Declaration of Helsinki should be used unless there are sound scientific and ethical reasons to use a control other than the best current treatment.¹³ Two reasons are noted: withholding the best current treatment will result in only temporary discomfort and no serious adverse consequences, and a comparative study of two treatments would yield no reliable scientific results. In Canada, a joint initiative is under way with the regulatory branch of Health Canada (which is similar to the Food and Drug Administration in the United States) and the Canadian Institutes of Health Research to develop a unified policy on the use of placebo. This new trend will probably result in a decrease in the number of placebo-controlled trials, although the criteria for determining what is methodologically essential and ethically appropriate are still the subject of intense debate.

Two points about Emanuel and Miller's ethical criteria deserve comment. First, placebo-controlled trials that were acceptable in the past may not be in the future, and ethical concerns may greatly reduce the number of placebo-controlled trials that can be conducted. Second, although they advocate restrictive use, Emanuel and Miller do not address the concern about withholding proven treatment. Their ethical criteria simply raise the bar for the criterion of no irreversible harm by including serious but reversible harm and serious discomfort. The concern about withholding treatment is the basis of the Declaration of Helsinki's policy on placebos. Those who support the intent of the declaration will be unlikely to accept Emanuel and Miller's proposed criteria as the middle ground in the debate.

Should the withholding of proven treatment be considered when the appropriateness of placebo-controlled trials is assessed? The interests of the patient may be undermined whenever proven treatment is withheld. Should the withholding of proven treatment be contemplated at any point in clinical research? For example, during the washout phase of a clinical trial, a specific treatment is withheld from all participants, a step that raises the same ethical and safety issues as the assignment of patients to a placebo group. The courts will soon consider whether the withholding of treatment during the washout phase of a trial constitutes a breach of care. The case arises from a clinical trial in which two patients with schizophrenia became floridly psychotic during the washout phase of a trial, and one of the patients committed suicide.¹⁴

The ethics of withholding proven treatment goes beyond the placebo debate to the heart of the Nuremberg Code, which identified the conflict of interest that clinical investigators may experience in trying to serve both the best interests of their patients and the best interests of their research.¹⁵ We have to consider whether the concern about withholding treatment can be addressed solely by identifying an acceptable level of risk and ensuring the safety of subjects with careful monitoring.

The ethics of withholding proven treatment in research needs to be considered in the broader context of the clinical trial. One could argue, for example, that proven care may be withheld from patients in the experimental group of a trial in which the control is active treatment. The Declaration of Helsinki promotes the use of trials with active controls on the basis that patients in the experimental group receive at least some form of treatment, so treatment per se is not withheld. However, those who support the use of placebo controls point out that the patients in a placebo group may receive adjunctive treatment. In fact, in some placebo-controlled trials, patients in the placebo group have fared better than those who were eligible for the trial, declined to participate, and received standard care.¹⁶ In the light of these findings and the uncertainty about what constitutes treatment, it is understandable that standards based on the level of risk and careful monitoring of subjects seem reasonable. Yet whether a research subject receives an experimental treatment or a placebo, in both cases, proven treatment is withheld. Furthermore, in focusing on the definition of an acceptable level of risk, it is easy to lose sight of the potential for a conflict of interest between the researcher and the subject each time treatment is withheld.

More circumscribed use of placebo groups, justified on both scientific and ethical grounds, will probably become common. The debate about the ethical use of placebos will not be resolved, however, until the larger issue of withholding proven treatment is addressed. This issue encompasses currently acceptable practice (testing an experimental therapy against an active control), unacceptable practice (testing an experimental therapy against a placebo when there is a risk of irreversible harm to subjects in the placebo group), and practice about which there is uncertainty (withholding treatment during the washout phase of a trial). People who participate in trials trust that their best interests will be protected. Addressing the ethics of withholding proven treatment in clinical trials may help ensure that nothing is done to breach that trust.

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