Sounding Board

THE ETHICS OF PLACEBO-CONTROLLED TRIALS — A MIDDLE GROUND

THE first placebo-controlled trial was probably conducted in 1931, when sanocrysin was compared with distilled water for the treatment of tuberculosis.[1] Ever since then, placebo-controlled trials have been controversial, especially when patients randomly assigned to receive placebo have forgone effective treatments.[2-5] Recently, the debate has become polarized. One view, dubbed "placebo orthodoxy" by its opponents, is that methodologic considerations make placebo-controlled trials necessary.[6-11] The other view, which might be called "active-control orthodoxy," is that placebo orthodoxy sacrifices ethics and the rights and welfare of patients to presumed scientific rigor.[10-14] The latest revision of the Declaration of Helsinki, although controversial,[15,16] embraces the active-control orthodoxy.[17] Both views discount the ethical and methodologic complexities of clinical research. In this essay, we argue that placebo-controlled trials are permissible when proven therapies exist, but only if certain ethical and methodologic criteria are met.

PLACEBO ORTHODOXY

Advocates of placebo-controlled studies argue that it is ethical to conduct such trials even in the case of medical conditions for which there are interventions known to be effective, because of the methodologic limitations of trials in which active treatment is used as the control.[6-9] Sometimes therapies that are known to be effective are no better than placebo in particular trials because of variable responses to drugs in particular populations, unpredictable and small effects, and high rates of spontaneous improvement in patients. Consequently, without a placebo group to ensure validity, the finding that there is no difference between the investigational and standard treatments can be misleading or uninterpretable.[8,9] New treatments that are no better than existing treatments may still be clinically valuable if they have fewer side effects or are more effective for particular subgroups of patients.[18] However, no drug should be approved for use in patients unless it is clearly superior to placebo or no treatment. Despite the methodologic rigor of placebo-controlled trials, commentators acknowledge that they are unethical in some circumstances, especially when withholding an effective treatment might be life-threatening or might cause serious morbidity.[8,9]

There are serious problems with placebo orthodoxy. First, in our opinion, the criteria for ethical use of placebo controls are never precisely stated. In a recent review, for instance, Temple and Ellenberg[8,9] claimed that the use of placebo controls is ethical if the research participants who receive placebo will experience "no permanent adverse consequence," if there is a risk of "only temporary discomforts," or if they "will not be harmed." We think that these formulations are not equivalent. Since patients may be harmed by temporary but reversible conditions, the criterion of no harm would exclude many placebo-controlled trials that meet the criterion of no permanent adverse consequence.

Second, the criteria permit intolerable suffering on the part of study participants. This point is illustrated by trials of the antinausea medication ondansetron.[8] In 1981, research demonstrated clinically and statistically significant differences between metoclopramide and placebo for the treatment of vomiting induced by chemotherapy.[19] In the early 1990s, placebo-controlled trials of ondansetron for chemotherapy-induced vomiting, some of which involved patients who had not previously received chemotherapy, were reported.[20-22] These trials were unethical.[23,24] Although vomiting induced by chemotherapy, especially with highly emetic drugs such as cisplatin, is not life-threatening and does not cause irreversible disability, it causes serious, avoidable harm that is more than mere discomfort. Indeed, the need for better antiemetic medication had been justified in the first place by the argument that "uncontrolled nausea and vomiting [from chemotherapy] frequently results in poor nutritional intake, metabolic derangements, deterioration of physical and mental condition, as well as the possible rejection of potentially beneficial treatment."[22] Even in 1990, patients receiving the chemotherapeutic drugs evaluated in the ondansetron trials were routinely given antiemetic prophylaxis. Other trials conducted at the time used active controls.[25,26]

Finally, the proponents of placebo controls seem to focus on physical harm. In arguing for placebo-controlled trials of antidepressants, Temple and Ellenberg suggest that the only relevant harm is depression-induced suicide.[8,9] Psychological and social harms caused by depression — such as mental anguish, loss of employment, and disruption of relationships — are either not considered or dismissed. Yet psychological and social harms are invoked to justify the value of the research. This is contradictory. In evaluating the risk–benefit ratio, psychological and social harms must be addressed.

ACTIVE-CONTROL ORTHODOXY

Because of these problems, commentators have attacked placebo orthodoxy as unethical.[10-14] Proponents of active controls contend that whenever an effective intervention for a condition exists, it must be used in the control group. Furthermore, they argue that placebo controls are inappropriate because the

clinically relevant question is not whether a new drug is better than nothing but whether it is better than standard treatments. To justify this approach, they cite the Declaration of Helsinki,[13,14,17] the most recent version of which states, "The benefits, risks, burdens and effectiveness of a new method should be tested against those of 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."[27] Advocates of active controls criticize placebo orthodoxy for placing the demands of science ahead of the rights and well-being of study participants.

Active-control orthodoxy also has several problems. First, the dichotomy between rigorous science and ethical protections is false. Scientific validity constitutes a fundamental ethical protection.[24] Scientifically invalid research cannot be ethical no matter how favorable the risk–benefit ratio for study participants.[24,28] If placebo controls are necessary or desirable for scientific reasons, that constitutes an ethical reason to use them, although it may not be a sufficient reason.

Second, in some cases, the harm and discomfort associated with the use of placebo controls are nonexistent or are so small that there can be no reasonable ethical requirement for new treatments to be tested only against standard treatments. Who could persuasively argue that for trials involving conditions such as baldness or some types of headaches, it is unethical to withhold effective treatments from some study participants and give them placebo instead?[29] There is no meaningful harm that stringent ethicists should worry about in letting a person who has given informed consent continue to suffer temporarily from a headache or untreated baldness as part of a clinical trial. Some critics of placebo controls contend that such trials are unethical because physicians owe medical care to patients who are seeking treatment for these ailments.[11] This argument conflates clinical research with clinical care. Clinicians frequently do not treat such ailments and patients often forgo treatment, indicating that there can be no ethical necessity to provide it.[9] The absolute prohibition against the use of placebo controls in every case in which an effective treatment exists is too broad; the magnitude of harm likely to be caused by using placebo must be part of the ethical consideration.

Third, opponents of placebo-controlled trials pay insufficient attention to the power of the placebo response. Substantial proportions of patients receiving placebo have measurable and clinically meaningful improvements — for example, 30 to 50 percent of patients with depression[30] and 30 to 80 percent of those with chronic stable angina.[31] A recent meta-analysis of randomized clinical trials with both placebo and no-treatment groups found little evidence of the therapeutic benefits of placebo over no treatment.[32] However, the patients given no treatment received clinical attention that may have contributed to observed improvements. This clinical attention may account for the placebo effect. Placebo-controlled trials in which patients receive potentially therapeutic clinical attention test whether an investigational treatment is better than this attention, not whether it is better than nothing.[33]

Most important, trials with active controls may expose more patients to harm than placebo-controlled trials. Equivalence trials, which evaluate the hypothesis that one drug is equivalent to another, typically require larger samples to achieve sufficient power, because the delta, or difference between the rates of response to the two drugs, is likely to be smaller than that between the rates of response to an investigational treatment and placebo.[18,34] Consider an equivalence trial in which an investigational drug is compared with a standard drug that is known to have a 60 percent response rate. With a delta of 10 percent (if they were equivalent, the difference between the standard and investigational drugs would be less than 10 percent) and a one-sided statistical test to show equivalence, each group must contain 297 participants. Conversely, if a placebo is hypothesized to have a 30 percent response rate and the investigational drug a 60 percent response rate, then only 48 participants are needed in each group.

With the sample required for the equivalence trial — larger by a factor of six than the sample required for the placebo-controlled trial — many more subjects will be exposed to an investigational drug that may be ineffective or even more toxic than the standard drug. Moreover, if it turns out that the rate of response to the investigational drug is 53 percent — still within the 10 percent range for equivalence — more participants will actually be harmed by not receiving the standard treatment than if a placebo-controlled trial were conducted instead. That is, in an equivalence trial of an investigational drug with a response rate of 53 percent, there will be 21 more subjects without a response in the group of 297 receiving the investigational drug than in the group of 297 receiving the standard drug with a known response rate of 60 percent. Conversely, consider a placebo-controlled trial with a 30 percent rate of response to placebo and a 53 percent rate of response to the investigational drug. Then, there will be 18 more subjects without a response in the group of 96 patients participating in the trial than if all 96 patients had received the standard drug. Indeed, the lower the rate of response to the investigational drug, the larger the number of participants in an equivalence trial who will be exposed to the harms associated with nonresponse. It is therefore simplistic to argue that placebo-controlled trials involving conditions for which the existing interventions are only partly effective necessarily sacrifice the well-being of patients.

A MIDDLE GROUND

For clinical research to be ethical, it must fulfill several universal requirements. Among other requirements, it must be scientifically valid and must minimize the risks to which the research participants are exposed.[24] When these requirements conflict, advocates of placebo controls opt for maintaining scientific validity, whereas advocates of active controls opt for minimizing risks. We believe these absolute positions are neither tenable nor defensible.

There is a middle ground. First, both sides agree that certain placebo-controlled trials are clearly unethical. If effective, life-saving, or at least life-prolonging treatment is available, and if patients assigned to receive placebo would be substantially more likely to suffer serious harm than those assigned to receive the investigational drug, a placebo-controlled trial should be prohibited. The efficacy of streptokinase in reducing morbidity and mortality after myocardial infarction made it unethical to conduct placebo-controlled trials of tissue plasminogen activator.[35]

Second, advocates of active controls should agree that for ailments that are not serious, if there is only a minimal chance that patients randomly assigned to receive placebo will suffer harm or even severe discomfort, the use of placebo controls is ethical.[36] A placebo-controlled trial of a new treatment for allergic rhinitis would be ethical because the moderate discomfort associated with allergic rhinitis typically does not impair health or cause severe discomfort.[29] Indeed, the risks associated with such trials are no greater than those deemed acceptable in natural-history and epidemiologic studies in which blood samples are obtained solely for research purposes and in pharmacokinetic studies in which medications are administered to healthy volunteers and blood samples obtained from them even though there is no prospect of a benefit to the study participants.

The disagreements center on whether it is ethical to use placebo controls when there is a treatment known to be effective and there is some potential for harm to participants receiving placebo. In this context, it is important to recognize that placebo-controlled trials and those in which active treatment is used as the control frequently have distinct objectives, and each type of trial may have a role in a sequential approach to evaluating new interventions. Whenever the risks of research with placebos are similar to the risks in these other types of studies, the use of placebo should be ethically justifiable. Placebo-controlled trials are often deemed important to determine the efficacy of a new treatment and to facilitate the design of larger trials in which the new treatment is compared with standard interventions. In addition, a trial comparing standard and new interventions may include a placebo group for internal validity when high placebo-response rates are anticipated.[32] However, proponents of active controls deem even these initial efficacy and three-group trials unethical when effective standard therapies exist. Placebo-controlled trials of treatments for angina and depression have been the focus of this disagreement, as have short-term trials designed to establish the efficacy of new treatments for asthma and hypertension before large, randomized trials are conducted to compare the new intervention with standard therapies.

When effective treatments exist, there must be compelling methodologic reasons to conduct a placebo-controlled trial. Proving that a new treatment has sufficient efficacy before large-scale equivalence trials are conducted is such a reason, whereas conducting a scientifically valid study with a smaller sample is not. A placebo-controlled trial has a sound scientific rationale if the following criteria are met: there is a high placebo-response rate; the condition is typically characterized by a waxing-and-waning course, frequent spontaneous remissions, or both; and existing therapies are only partly effective or have very serious side effects; or the low frequency of the condition means that an equivalence trial would have to be so large that it would reasonably prevent adequate enrollment and completion of the study.

If these methodologic criteria are met, then the risk of using a placebo control should be evaluated according to several criteria. Research participants in the placebo group should not be substantially more likely than those in the active-treatment group to die; to have irreversible morbidity or disability or to suffer other harm; to suffer reversible but serious harm; or to experience severe discomfort. There is no way of removing qualifying words such as "serious" or "severe" from these criteria, since ethical evaluation necessarily calls for contextualized judgments. Just as courts are empowered to make contextualized judgments about the standard of a separation between church and state, federal regulations empower institutional review boards to determine the levels of risk and severity of harm associated with research.

Although placebo-controlled trials that meet these methodologic and ethical criteria may be justifiable even though the participants forgo therapies known to be effective, they remain worrisome because of the potential to cause suffering. Consequently, standard precautions must be scrupulously implemented for these trials. When such a trial is proposed, the institutional review board must ensure that the following safeguards are instituted to minimize harm: participants at increased risk of harm from nonresponse are excluded; the placebo period is limited to the minimum required for scientific validity; subjects will be carefully monitored, with inpatient observation when appropriate; rescue medications will be administered if serious symptoms develop; and there are explicit and specific criteria for the withdrawal of subjects who have adverse events. In addition, as part of the informed-consent process, the investigators must clear-

ly disclose the rationale for using placebo, explain that subjects who are randomly assigned to the placebo group will not receive standard effective treatments, and state the risks associated with forgoing such treatments. The protocol should include provisions to ensure optimal treatment for participants who withdraw early or who remain symptomatic at the conclusion of the trial.

A CASE EXAMPLE

Chronic stable angina can cause substantial functional impairment and suffering. It is associated with a placebo-response rate of 30 to 80 percent.[31] Patients with chronic stable angina typically have fluctuating courses with spontaneous remissions, and for some patients, current therapies are partly effective at best. The long history of positive findings from open trials of cardiovascular treatments that have subsequently been disproved by blinded, placebo-controlled trials — including ligation of the internal mammary artery for angina,[37,38] chelation for claudication,[39] encainide and flecainide for arrhythmias,[40] and most recently, laser systems that create holes in cardiac tissue[41] — provides good scientific reasons for conducting placebo-controlled trials of treatments for chronic angina.

Even if it is methodologically sound, a placebo-controlled trial of a new treatment for chronic angina should satisfy the ethical criteria for an acceptable level of risk — that is, participation in the trial would not cause death, irreversible disability, reversible but serious harm, or severe discomfort. There is no evidence that medical management of chronic angina prolongs survival. Furthermore, a comprehensive review of double-blind, placebo-controlled, randomized trials of treatment for chronic angina showed that the risk of adverse events did not differ significantly between the drug and placebo groups.[42] The authors concluded that "withholding active treatment does not increase the risk of serious cardiac events." Nonetheless, patients at high risk for myocardial infarction and other cardiac events should be excluded from such trials, nitroglycerin should be provided for breakthrough anginal pain, and the period of treatment with placebo should be brief, usually less than 10 weeks. Patients should be contacted frequently to ensure careful monitoring of their condition, and those whose symptoms exceed an explicit threshold should be withdrawn from the trial. The informed-consent process must make it clear to patients that their angina may worsen and that they are free to withdraw from the trial at any time.

CONCLUSIONS

Placebo-controlled trials are caught in a battle between two orthodoxies. One is that placebo should be used as a control unless there is an increased risk of death or irreversible morbidity associated with its use. The other view is that if an effective therapy exists, the use of a placebo should be prohibited. These two positions are both absolute and indefensible. We propose a middle ground in which placebo-controlled trials are permitted but only when the methodologic reasons for their use are compelling, a strict ethical evaluation has made it clear that patients who receive placebo will not be subject to serious harm, and provisions have been made to minimize the risks associated with the receipt of placebo. This framework provides a basis for deliberation in difficult cases, with the recognition that reasonable people might make divergent judgments in a particular case.

EZEKIEL J. EMANUEL, M.D., PH.D.
FRANKLIN G. MILLER, PH.D.
National Institutes of Health
Bethesda, MD 20892-1156

REFERENCES

1. Lilienfeld AM. The Fielding H. Garrison Lecture: *Ceteris paribus:* the evolution of the clinical trial. Bull Hist Med 1982;56:1-18.
2. Lasagna L, Mosteller F, von Felsinger JM, Beecher HK. A study of the placebo response. Am J Med 1954;16:770-9.
3. Lasagna L. Placebos and controlled trials under attack. Eur J Clin Pharmacol 1979;15:373-4.
4. Feinstein AR. Should placebo-controlled trials be abolished? Eur J Clin Pharmacol 1980;17:1-4.
5. Way WL. Placebo controls. N Engl J Med 1984;311:413-4.
6. Temple R. Government viewpoint of clinical trials. Drug Inform J 1982;16:10-7.
7. *Idem.* Problems in interpreting active control equivalence trials. In: Accountability in research. Vol. 4. New York: Gordon and Breach, 1996:267-75.
8. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. I. Ethical and scientific issues. Ann Intern Med 2000;133:455-63.
9. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. II. Practical issues and specific cases. Ann Intern Med 2000;133:464-70.
10. Freedman B, Weijer C, Glass KC. Placebo orthodoxy in clinical research. I. Empirical and methodological myths. J Law Med Ethics 1996; 24:243-51.
11. Freedman B, Glass KC, Weijer C. Placebo orthodoxy in clinical research. II. Ethical, legal, and regulatory myths. J Law Med Ethics 1996; 24:252-9.
12. Freedman B. Placebo-controlled trials and the logic of clinical purpose. IRB 1990;12(6):1-6.
13. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. N Engl J Med 1994;331:394-8.
14. Rothman KJ. Declaration of Helsinki should be strengthened. BMJ 2000;321:442-5.
15. Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. N Engl J Med 2001;345:139-42.
16. Koski G, Nightingale SL. Research involving human subjects in developing countries. N Engl J Med 2001;345:136-8.
17. Enserink M. Helsinki's new clinical rules: fewer placebos, more disclosure. Science 2000;290:418-9.
18. Active control equivalence studies. In: Senn S. Statistical issues in drug development. Chichester, England: John Wiley, 1997:207-17.
19. Gralla RJ, Itri LM, Pisko SE, et al. Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. N Engl J Med 1981;305:905-9.
20. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. N Engl J Med 1990;322:810-6.

21. Gandara DR, Harvey WH, Monaghan GG, et al. The delayed-emesis syndrome from cisplatin: phase III evaluation of ondansetron versus placebo. Semin Oncol 1992;19:67-71.

22. Beck TM, Ciociola AA, Jones SE, et al. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. Ann Intern Med 1993;118:407-13.

23. Hait WN. Onadansetron and cisplatin-induced nausea and vomiting. N Engl J Med 1990;323:1485-6.

24. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA 2000;283:2701-11.

25. Marty M, Pouillart P, Scholl S, et al. Comparison of the 5-hydroxy-tryptamine$_3$ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. N Engl J Med 1990;322:816-21.

26. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. J Clin Oncol 1991;9:721-8.

27. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Edinburgh, Scotland: World Medical Association, October 2000. (Accessed August 31, 2001, at http://www.wma.net/e/policy/17-c_e.html.)

28. Rutstein DD. The ethical design of human experiments. In: Freund PA, ed. Experimentation with human subjects. New York: George Braziller, 1970:383-401.

29. Senn S. The misunderstood placebo. Appl Clin Trials (in press).

30. Khan A, Warner HA, Brown WA. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the Food and Drug Administration database. Arch Gen Psychiatry 2000; 57:311-7.

31. Bienenfeld L, Frishman W, Glasser SP. The placebo effect in cardiovascular disease. Am Heart J 1996;132:1207-21.

32. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001; 344:1594-602.

33. Miller FG. Placebo-controlled trials in psychiatric research: an ethical perspective. Biol Psychiatry 2000;47:707-16.

34. Leon AC. Placebo protects subjects from nonresponse: a paradox of power. Arch Gen Psychiatry 2000;57:329-30.

35. Brody BA. When are placebo-controlled trials no longer appropriate? Control Clin Trials 1997;18:602-12.

36. Vastag B. Helsinki discord? A controversial declaration. JAMA 2000; 284:2983-5.

37. Dimond EG, Kittle CF, Crockett JE. Evaluation of internal mammary artery ligation and sham procedure in angina pectoris. Circulation 1958; 18:712-3.

38. Cobb LA, Thomas GI, Dillard DH, Merendino KA, Bruce RA. An evaluation of internal-mammary-artery ligation by a double-blind technic. N Engl J Med 1959;260:1115-8.

39. van Rij AM, Solomon C, Packer SGK, Hopkins WG. Chelation therapy for intermittent claudication: a double-blind, randomised, controlled trial. Circulation 1994;90:1194-9.

40. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406-12.

41. Winslow R. Placebo study questions effectiveness of laser heart treatment. Wall Street Journal. October 19, 2000:B14.

42. Glasser SP, Clark PI, Lipicky RJ, Hubbard JM, Yusuf S. Exposing patients with chronic, stable, exertional angina to placebo periods in drug trials. JAMA 1991;265:1550-4.