Response to Rothman and Michels on Placebo-Controlled Clinical Trials

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There has been continued debate over the use of placebo controls in the evaluation of medication. The problem is that for many illnesses, patients may recover spontaneously. Further, the caregiving setting may have beneficial effects in addition to providing a putative medication. It is only for illnesses that quickly and invariably lead to death, such as rabies, that past experience with the outcome of untreated cases (historical controls) can be viewed as definitive. However, most illnesses, even such poor prognosis illnesses as AIDS, have an extremely variable rate of decline, so that applying past experience to any given sample is dubious.

When there is no standard treatment for a disorder, the use of a placebo control group is essential. But if a proven therapy has been developed, does this affect the design of therapeutic experiments?

Rothman and Michels, in the prestigious New England Journal of Medicine, assert that it is unethical to use placebo, given a proven treatment. They discount three arguments as if they were the only scientific rationales for placebo controls. They argue that given a proven treatment, one should no longer be interested in comparison of the new putative medication to placebo, but only to the standard. They also state that it is not justifiable to assign placebo controls to avoid the complex decision of which treatment should be used as a standard. Finally, they argue that even if all placebo-controlled trials are cheaper and quicker than studies using active treatment as the standard, the costs saved by the drug company are borne by patients who receive placebos instead of effective treatment. However, they ignore the most important argument for placebo-controlled trials: the combination of diagnostic unreliability with the loose linkage between diagnosis and therapeutic effect.

To be concrete, the authors apparently argue that imipramine, among the oldest and best established antidepressants, should serve as an adequate reference standard in any antidepressant trial. This neglects the fact that in approximately one third of placebo-controlled imipramine trials, imipramine could not be distinguished from placebo. This was true even in large trials where type II errors were unlikely, so fluctuation in sample composition is the likely culprit. In some of those trials, both imipramine and placebo showed good outcomes.

Let us say that a new drug was compared to imipramine in a sample similar to these latter trials. If it did as well as imipramine, it might seem that both drugs had been effective. However, this would be a misleading artifact of sample composition. The general public would have an ineffective treatment foisted upon it.
This is not a fantasy. Rush et al. compared cognitive therapy to imipramine in major depression. In this sample, cognitive therapy proved distinctly superior to imipramine. By Rothman and Michels' standards, cognitive therapy would have been established not only as an active treatment, but as a superior treatment that lacks pharmacological toxicity. However, in the NIMH-supported Collaborative Study of Depression, cognitive therapy was contrasted with both placebo and imipramine. Cognitive therapy could not be distinguished from placebo and, in the more severe patients, was distinctly inferior to imipramine. Among the less severely depressed major depressives, there was no difference between imipramine and cognitive therapy, which, by Rothman and Michels' standards, would affirm that cognitive therapy was equivalent to imipramine for the moderately depressed. However, because there was a placebo control, it was shown that for such patients, although cognitive therapy was equivalent to standard medication, both could not be distinguished from placebo, which yields a substantively different conclusion.

Rothman and Michels consistently raise the issue of “effective” drugs or “standard therapy” without realizing that a drug may indeed be both standard and effective but still have an enormous range of effect, even within a well-defined target population. Similar problems exist in other clinical areas they cite, such as drugs for nausea, congestive heart failure, and hypertension.

Their ethical absolutism and failure to see complexity is evident when they state that there may be “advantages to a treatment that is inferior to a current standard with regard to efficacy, but better with respect to cost of quality of life.” They conclude that “It is not justifiable, however, to assign placebo controls simply to avoid the complex decision of which treatment should be used as a standard.”

This misunderstands and confuses the problem. Say a new agent does appear less effective than a standard agent in some ways but better in others. Is this sufficient grounds to release it as an effective treatment? This is fallacious, since placebo is often superior to an active agent in some ways because it lacks some of the toxic features that occur with most active agents. There is no way to determine if the apparent partial superiority was illusory without a placebo control.

The authors argue that the mere fact that placebo-controlled trials allow an easier establishment of efficacy than the much larger and longer trials needed when comparing a new drug against a standard agent is not justified. They state that smaller placebo-controlled studies are cheaper and faster, but the costs are borne by the placebo-exposed patients. However, there are also costs to patients in delaying an effective drug from getting to market by insisting on lengthy trials.

Rothman and Michels argue that such drugs may be inferior to current drugs. In fact, it is rare for an effective drug to be consistently inferior to a standard drug. Rather, there are sufficient differences in side effect profiles and heterogeneity of response that the physician is pleased to have a second- or third-line drug available for those patients where the first-line drug proves ineffective or intolerable.

The authors also misunderstand the legal charge to the Food and Drug Administration. The FDA requires that a drug is safe and effective, but is not charged with demanding that a drug be shown superior to standard treatment. This makes good sense in determining marketability.

Unfortunately, there is very little in the current system that helps the physician practice correctly with regard to the sequential choice of drugs. The clinical use of comparing drugs should be supported, but not at the cost of delaying drug development. Rather, this is an area for post-marketing experimentation. The major problem here is that such studies are of little academic interest and are rarely supported by industry. This type of services research remains poorly funded. That is a topic worth discussing.

One final objection is to the authors' condescending attitudes toward informed consent. There is a conflict between two positive goals: beneficence and respect for autonomy. The authors paternalistically state that “withholding an accepted treatment may occasionally seem innocuous,” but allowing investigators to do so runs counter to their ethical principles. But where is their regard for the ethical principle of autonomy, which states that people may rationally volunteer for discomfiting or even dangerous situations? The authors' statement that patients are given the choice of whether to participate in a trial but they are given no choice about which treatments will be studied is an irrelevant attempt to obscure the issues by a council of paralytic perfection.

The authors conclude that “We recognize that in some situations, an accepted treatment may not be better than placebo for a given indication.” The problem is not simply one of a given indication, but of the variation within any given diagnostic sample of treatment-resistant and treatment-responsive patients, which allows for the sort of errors described above.

Rothman and Michels completely ignore how unethical it is to erroneously affirm that a treatment is effective when, in fact, it is not. The amount of suffering and death that such treatments produce far outweigh the limited difficulties that may occur in a properly monitored placebo-controlled trial. Isn’t that an ethical concern?
Their chilling suggestion to develop procedures of mandatory regulatory and journal challenges to all placebo-controlled studies is, unfortunately, appealing to those unaware of the complex realities of properly designed clinical research.8

The authors state that scientific imperatives should never be weighed against "established ethical canons." However, the authors' selective, simplistic citation of canons as well as their failure to recognize the ethical importance of quickly and definitively establishing innovative therapeutic use makes their argument sanctimonious rather than useful.

REFERENCES

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