

Ethics of placebos in clinical asthma trials

To the Editor:

We write in response to the attempt by Dr Onder¹ to justify placebo-controlled trials (PCTs) in clinical asthma trials (CATs). Dr Onder¹ argues that asthma is a “middle ground condition, for which effective therapy exists for a potentially severe condition, but for which...[PCTs] might be ethically justified.” He offers 5 scientific reasons a placebo arm might be used in a CAT. PCTs allow researchers to prove statistically significant effects more clearly, more cheaply, and with smaller sample sizes. However, it is important to remember that scientific validity is necessary but not sufficient for a clinical trial to be ethically permissible.

In 1996, the Declaration of Helsinki, an international code of research ethics, was revised to make clear that PCTs cannot be justified when there is a well-established standard of care.² The United States refused to sign, stating that it was too restrictive. In 2000, the declaration was revised to allow PCTs if 2 conditions are met. The first criterion is that there is a “compelling and scientifically sound methodological reason” to use PCTs. The need to compare an inhaled corticosteroid (ICS) to placebo in individuals with more than mild intermittent asthma is erroneous, because the need for anti-inflammatory medicine has been well established internationally for more than a decade.³

The second criterion permits PCTs in the investigation of a “minor condition” provided that “the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.”^{2,3} Dr Onder¹ concedes that asthma is not a minor condition.¹ The avoidance of asthma exacerbations is a primary objective in clinical asthma management because an asthma exacerbation places the patient at risk of serious harm. We examined the number of subjects with asthma who withdrew from CATs because of asthma exacerbation.⁴ We found that subjects in PCTs were more likely to withdraw because of asthma exacerbation than were subjects in active control and add-on studies ($P < .001$).⁴ Not surprisingly, the subjects randomized to the placebo arm were more likely to withdraw in comparison with those randomized to experimental treatment arms ($P < .001$).⁴ In other words, not only were subjects being placed at additional risk of harm, they were actually harmed.

Placebo-controlled trials of ICSs also lack equipoise. Dr Onder¹ makes the claim that using the concept of equipoise to evaluate the ethics of placebo controlled “ignores the ethically relevant distinction between research and clinical practice.” We disagree. Physician-researchers are moral agents and should only enroll subjects in ethically designed research studies. If the researcher or the research community is clear that one arm is superior to the other, the research cannot be offered, even if the subjects would consent.

Unfortunately, the United States continues to remain a nonsignatory of the revised Declaration of Helsinki. The arguments of Dr Onder¹ are similar to those given by our government. It behooves us to resume our role as part of the moral international research community. This means that all subjects who meet the criteria for daily anti-inflammatory medications should receive ICSs or one of their alternatives in all arms of CATs.

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Reply

To the Editor:

I thank Mr Coffey and Dr Ross¹ for their commentary on my article. They clearly enunciate a point of view which Emanuel and Miller² have referred to as “active-control orthodoxy,” that is, the idea that placebo-controlled trials (PCTs) should never be performed for conditions for which there is “standard therapy.”² My article is a brief refutation of this view.

I agree with Coffey and Ross¹ that scientific validity is not a sufficient condition for ethical clinical research, although it is a necessary condition. The first part of my article addressed why many investigators, the Food and Drug Administration, and I believe that there remain “compelling and scientifically sound methodological reason[s]” to use PCTs, despite the existence of “standard therapy.”³

An important point raised by Coffey and Ross¹ is their contention that asthma patients “were actually harmed” by enrollment in PCTs because subjects randomized to a placebo arm were more likely to withdraw for “worsening of asthma.”⁴ This is, of course, expected if the active treatments in the PCTs are efficacious. What do Coffey and Ross¹ mean when they say patients were harmed?