THE AUTHOR REPLIES

Marmor et al. (1) state that my letter (2) “implies that placebos and the maintenance of blinding may not be critical to intervention research” (1, p. 500), which is correct. The terms “placebo” and “placebo effect” have different meanings in different contexts (3). In the following comments, the placebo effect primarily indicates the difference in the treatment effect when the control group is administered a placebo and when it is not.

There are interesting studies reporting that placebo analgesia decreases neural responses in brain regions that are pain sensitive (4) and interaction between the information given to study participants and the effect of a placebo or an analgesic drug (5). However, such studies and those cited by Marmor et al. (1) do not refute my statement that there is no evidence of large and universal placebo effects. A few black swans do not refute the notion that swans are usually white.

Recently, interest in systematic reviews has increased, because they provide a more objective view of a given topic than picking out illustrative examples to support authors’ preconceptions. There are several systematic reviews relevant for estimating the role of placebo control (6–9). In a meta-analysis of 209 trials in the fields of cardiovascular diseases, infectious diseases, and pediatrics, Balk et al. (6) found that the lack of placebo control had no effect in cardiovascular studies but led to biased treatment effects in pediatric studies. All cardiovascular studies measured mortality, whereas all pediatric studies measured soft outcomes related to respiratory diseases. Thus, the divergence between these two fields is explained by the different outcomes; infectious disease studies were in the middle in the types of outcomes and the magnitude of the bias. This divergence is consistent with the findings by Hrobjartsson and Gøtzsche (7), who reported that pain as a continuous outcome was affected by placebo, but binary outcomes as a group were not.

Two recent meta-analyses compared randomized, controlled trials with observational studies on the same clinical topics and found remarkably similar estimates of effect by the two research methods (8, 9). Thus, in the topics studied, reasonably accurate estimates of effect can be derived from studies without randomization and placebo control.

The “powerful placebo” concept can be traced to a meta-analysis published in 1955 (10). Beecher chose 15 illustrative studies covering such conditions as severe postoperative wound pain, cough, headache, seasickness, and so on, and he calculated that 35.2 (standard error: 2.2) percent of participants were relieved by the placebo. However, the studies did not use a control group; instead, the comparison was “before–after.” Thus, the studies did not measure the effect of placebo, as most of the studied conditions were self-limiting (11). Beecher’s paper has been influential and cited over 700 times according to the Web of Science (http://scientific.thomson.com/products/wos/), yet his powerful placebo concept can be dismissed (6–9, 11).

The potential importance of placebo control should be considered case by case. In a short treatment trial with a subjective outcome, for example, a new drug for migraine, it is difficult to trust a reported difference if the control group was not administered a placebo. Such disbelief is emphasized when there is a party getting economic profit from a “positive result.”

Marmor et al. (1) question the relevance of the fact that placebo effects are not universal. There are several examples of treatments with such dramatic effects that controlled trials are unnecessary, showing that firm conclusions of the usefulness of treatments can be drawn with research methods that are far from perfect (12). Because the placebo effect is small or nonexistent on many medical topics (6–9), it seems obvious that many interventions can be shown effective without a placebo control. Thus, the “new drug for migraine” metaphor does not imply that placebo control has universal relevance in intervention research. Furthermore, with subjective outcomes, the use of placebo control can itself cause bias in estimating the effect of intervention, because it modifies the information that a person receives, producing “masking bias” (5, p. 543).

In my letter (2), I mentioned that the CONSORT report (13) cited the trial of Karłowski et al. (14) as an example of the placebo effect. Marmor et al. (1) claimed that my statement was false, thereby making it seem that I had either misread or misrepresented the CONSORT report. The authors described that “we decided . . . to keep only those items for which there was empirical evidence . . . that not reporting them resulted in bias in the estimates of the effects of interventions” (13, p. 637). Thereafter, the Karłowski trial is cited as a justification for the requirement for “masking (blinding)” (13, p. 638).
Given that Marmor is so fastidious about the use of placebo being essential, it is surprising that he is so lax on other important clinical trial principles. Experts of controlled trials stress that “excluding randomized participants from analysis... can lead to biased results of unknown magnitude” and “only baseline factors are appropriate for use in defining subgroups” (15, pp. 284, 304). The subgroup analysis on the placebo effect by Karlowski et al. (14) violates both of these principles. Half of the participants were excluded from the subgroup analysis without explanations, and “guessing the treatment” as a surrogate for “knowing” (used for forming the subgroups, ignoring that many answers were correct purely by guesswork) was asked after the trial was concluded. Furthermore, there are logical inconsistencies in the placebo explanation of Karlowski et al., as detailed elsewhere (16). The principal investigator of the trial by Karlowski et al. did not find errors in my reanalysis (17, 18) nor did Marmor (1) point out any. The Karlowski et al. trial is not a valid example of the placebo effect, although it has often been used as an illustration (13; 15, p. 83).

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REFERENCES

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