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In their paper discussing the importance of double-blinding in controlled trials, Furberg and Soliman stated that “one of the established and fundamental principles for avoiding the problem of bias is to keep the study participants and the investigators blinded, or masked, to the identity of the assigned interventions” [1]. As a support to this argument they described the subgroup findings of Karlowski et al.’s trial, which examined the effect of vitamin C supplementation on the common cold [2,3].

Furberg and Soliman put a great weight on the importance of double-blinding, yet they are lax on other fundamental principles of controlled trials. A popular textbook of clinical trials emphasizes that “excluding randomized participants from analysis and subgrouping on the basis of outcome or response variables can lead to biased results of unknown magnitude” [4, p. 284]. The subgroup analysis by Karlowski et al. [2,3] violates both of these principles.

First, Karlowski et al. [2] excluded about half of the randomized participants from the subgroup analysis without any explications. Second, the division of participants to the “blinded” and “unblinded” subgroups was based on “guessing the treatment” which is an outcome variable assessed after the trial. Moreover, a “correct answer” was used as a surrogate for “knowing” the treatment although it is obvious that many of the guesses were correct purely by chance, yet this was not considered by the authors [5,6]. In addition, there are several logical inconsistencies in Karlowski et al.’s placebo-effect explanation, refuting its validity as I have shown elsewhere [5,6]. The principal investigator of the Karlowski et al. trial did not find errors in my reanalysis [7,8]. The Karlowski et al. trial is not a valid example of the placebo effect.

Recently, systematic reviews have become popular, because they provide a more objective view of a given topic than the selection of illustrative examples to support authors’ preconceived notions. There are systematic reviews relevant to assessing the importance of placebo control and double-blinding. In a meta-analysis of 209 randomized trials in the fields of cardiovascular diseases, infectious diseases, and pediatrics, Balk et al. concluded that “double blinding and allocation concealment, 2 quality measures that are frequently used in meta-analyses, were not associated with treatment effect” [9, p. 2980]. Furthermore, Balk et al. found that the lack of placebo control had no effect in cardiovascular trials, but led to biased treatment effects in pediatric trials. All cardiovascular trials measured mortality, whereas all pediatric trials measured soft outcomes related to respiratory diseases. Thus, the divergence between these two fields is explained by the different outcomes. In another meta-analysis, Hrobjartsson and Gøtzsche examined whether there is difference between placebo groups and no-treatment groups, mostly in trials with three arms so that the third arm received an active intervention [10]. They found no effect of placebo administration on binary outcomes, whereas placebo caused a statistically significant but rather small effect on
pain measured as a continuous outcome. Hence there is no evidence of a large and universal bias caused by the lack of a placebo control or double-blinding.

The importance of blinding should be considered case by case. In a short trial with a subjective outcome, such as a new drug for pain, the lack of double-blinding raises suspicions towards the trial, in particular if there is a company getting profit from a “positive finding.”

However, there are several examples of interventions with such spectacular benefits that controlled trials are unnecessary, showing that in some cases firm conclusions of the benefit of a treatment can be drawn with research methods that are far from perfect [11]. Therefore, illustrative examples such as the “new drug for pain” cannot be generalized as evidence for the universal importance of blinding.

Paradoxically, with subjective outcomes, blinding can itself cause bias in the estimation of the effect of intervention, because it modifies the information that a person receives, producing “masking bias” [12, p. 543]. In this respect, the assessment of treatment effect in the real life can sometimes be more complicated than testing whether there is a pharmacological effect in a double-blind trial.

The restricted importance of blinding has important implications. For example, in systematic reviews of binary and objective outcomes, it would often seem reasonable to include trials which did not use a placebo and to test their influence in a sensitivity analysis, rather than exclude such trials routinely. The purpose of controlled trials is not just to determine whether a treatment works or not, but the findings usually direct further research. Excluding trials to maximize safety against speculative biases can lead to inefficient utilization of published information.

Because of the commercial interests, methodological rigor should be required from pharmaceutical companies when they test new drugs. However, exaggerating the potential biases caused by methodological shortcomings can lead to an overemphasized role of pharmaceutical products in health care, because it is usually easy to carry out double-blind trials with new drugs and companies have resources for such trials. In contrast, it is often difficult or impossible to carry out double-blind trials on interventions that are non-pharmaceutical. It does not seem reasonable to disregard the latter type of studies on the basis of exaggerated problems due to the lack of double-blinding. Therefore, assessment of the importance of blinding should be objective and based on systematic reviews, instead of overstating the problem on the basis of a few illustrative examples.

**Disclosure of Conflict of Interest**

The author states that he has no conflicts of interest.
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