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Editorial

Risks of inadvertently active placebo in randomized trials: an overlooked cause of inconsistency

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The process of randomization in a clinical trial involves creating two populations with comparable prognoses[1]. This implies a balanced distribution of prognostic factors, which can either be pre-known, such as cardiovascular risk factors in the case of cardiovascular outcomes, or unknown. Unknown prognostic factors refer to variables that may or may not influence the occurrence of the measured outcome and are not known prior to the trial.

Difference in outcomes

To confidently attribute the difference in outcomes between two populations to the evaluated intervention rather than an imbalanced distribution of other prognostic variables, the following criteria must be met: 1) allocation concealment, 2) blinding, 3) analysis according to randomization (previously known as intention-to-treat analysis), 4) complete follow-up, 5) no early termination of the study due to demonstrated benefit in the intervention. Failure to meet even one of these criteria could lead to an overestimation of the intervention effect by up to 30%[2-4].

Placebos

Placebos are defined as inert substances with no pharmacological activity. Properly using them as comparators in randomized studies is essential for fulfilling the first two criteria[5].

Allocation concealment refers to procedures designed to prevent both the person assigning the treatment and the patient from knowing the group to which the participant is being assigned. Adequate blinding refers to procedures intended to prevent patients, caregivers, event adjudicators, event recorders, and trial processors from knowing which intervention each arm of the research received. These procedures often involve centralized randomization, sequential numbering of medication, and ensuring identical appearance between the intervention and the placebo.

Essential conditions

Based on the above, we can deduce that a placebo in a randomized study must fulfill two essential conditions: 1) have a neutral effect on the measured outcomes, and 2) be indistinguishable from the intervention.

To fulfill both conditions, one might expect that the placebo should faithfully replicate the composition of the reference product (a formulation that is always well known), except for the active ingredient. This ensures the fulfillment of our first condition.

But what would happen if the absence of the active ingredient resulted in a change in appearance or another characteristic of the placebo that made it easily distinguishable from the intervention? In that case, in order to fulfill adequate blinding while reducing the risk of bias, we should add to the placebo some substance that imitates the perceptible characteristics of the active ingredient.

Disturbing question

This raises an even more disturbing question: What if adding components to the placebo that mimic the active ingredient causes it to no longer have a neutral effect on the outcomes? Could we easily detect it? Let's see an example.

In 2019, the REDUCE-IT study was published[6]. This randomized study, with a placebo comparator, included patients with established cardiovascular disease or diabetes who were receiving statin treatment and had fasting triglyceride levels of 135 to 499 mg/dL. The intervention arm received 2 grams of ethyl eicosapentaenoic acid (EPA). In the control arm, the placebo used contained mineral oil to mimic the color and consistency of EPA. The study evaluated the incidence of a combined outcome of cardiovascular events, demonstrating a difference of almost 5% in absolute terms in favor of the intervention arm after 4.9 years of follow-up (17.2% vs. 22.0%. HR 0.75; 95% CI, 0.68 to 0.83; p <0.001).

These results were surprising to the researchers, both due to their inconsistency with previous studies with other omega-3s and the presence of a greater-than-expected benefit based on the observed triglyceride level changes[7].

To address this question, the results of the STRENGTH study, published in 2020, were awaited[8]. This study tested a combination of two omega-3s (75% EPA and 25% DHA) against a placebo with a composition different from that used in REDUCE-IT (corn oil instead of mineral oil), and no significant differences in the combined cardiovascular events were observed after 3.5 years of follow-up.

One year later, Takahito Doi and colleagues published an analysis based on a cohort study that imitated the designs of REDUCE-IT and STRENGTH[9]. By combining the changes in triglyceride levels, LDL, and C-reactive protein observed in the active oil and respective placebos of the original studies, they estimated hazard ratios for the combined cardiovascular events for all study arms. They concluded that the inconsistency between the two studies could be partly explained by the different effects of the comparators (mineral oil vs. corn oil). These findings were specifically attributed to an effect of the mineral oil used in REDUCE-IT on the intestinal absorption of statins, reflected in a 10.9% increase in LDL in the control arm during the study.

Mechanism of exaggerating the effect of an intervention

This example serves to illustrate a poorly described mechanism of exaggerating the effect of an intervention and the difficulty involved in its systematic detection.

For authors conducting systematic reviews, it would be useful to acknowledge this phenomenon as a potential cause of inconsistency between clinical trial results, and we suggest incorporating it as "inadvertently active placebo risk" in the assessment of bias risk.

Highlight

To highlight this phenomenon, we propose that those assessing the risk of bias in a trial with a placebo comparator consider three questions:

1. Is there potentially any difference between the composition of the placebo and the intervention, other than the active ingredient?
2. Is the observed effect consistent with our previous knowledge?
3. Is the observed effect consistent with that demonstrated in other similar studies?

Final commentary

In a recent systematic review by Cohcrane, Laursen et al. did not find any differences between the use of active placebos vs. standard placebos[10]. However, they defined an active placebo as any intervention designed to imitate the perceptible non-therapeutic effects of an experimental intervention (e.g., anticholinergic effects of tricyclic antidepressants), while a standard placebo was considered to be any intervention designed to mimic only the external properties of the experimental intervention. This analysis does not address our concern, as the issue of an inadvertently active placebo is that it is defined as a standard placebo by the authors of the study in question.

So, future other reviews should elucidate whether the described phenomenon is exceptional and of little significance, or if it is a frequent and underestimated occurrence.

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