Participants unaware of health action

From: Key Concepts for assessing claims about treatment effects and making well-informed treatment choices (Version 2022)

2.1c Consider whether the people being compared knew which treatments they received.

Explanation

People in a treatment group may behave differently or experience improvements or deterioration because they know the treatment to which they have been assigned. If this phenomenon is associated with an improvement in their symptoms it is known as a placebo effect; if it is associated with a harmful effect it is known as a nocebo effect. If individuals know that they are receiving a treatment that they believe is either better or worse than an alternative (that is, they are not "blinded"), some or all the apparent effects of treatments may be due either to placebo or nocebo effects. For example, a systematic review found 10 randomized trials of acupuncture that included both a "no acupuncture" group and a "sham acupuncture" (placebo) group *[Hróbjartsson 2014a (SR)]*. The non-blinded comparison (of acupuncture compared to no acupuncture) resulted in an overestimate of the effect of acupuncture compared to the blinded comparison (of acupuncture compared to sham acupuncture).

Patients who are aware of the treatment to which they are allocated may also seek additional care or behave differently based on which treatment they receive and their prior beliefs about the effectiveness of the treatment. If they believe a treatment is effective and they are allocated to "no treatment", they may decide to use the treatment anyway (resulting in "contamination"), to use some other treatment, or to withdraw from the study (resulting in "attrition bias"). For example, in a randomized trial, a new type of counselling to help people lose weight was compared to "usual care". People allocated to the counselling were satisfied with their allocation, whereas those allocated to usual care were disappointed *[McCambridge 2014 (RS)]*. Their disappointment may have led some participants to "take control" and change their diet or to seek support elsewhere. This could have resulted in underestimating the effect of the counselling compared to usual care.

Basis for this concept

A systematic review of placebo treatments found 202 studies that randomized participants to a placebo or "no treatment" *[Hróbjartsson 2010 (SR)]*. On average, across 44 studies that reported yes/no (dichotomous) outcomes there was a small effect, but the effect varied. There was also a small effect on average across studies with patient-reported outcomes, with variation in the effect. In trials that reported pain as an outcome, the effect was very variable. Larger effects were associated with physical placebos, such as sham acupuncture. This is consistent with a systematic review of physiotherapy for pain, which found that trials that compared physiotherapy to a sham treatment had smaller effects than trials that compared physiotherapy to "no treatment" *[Ginnerup-Nielsen 2016 (SR)]*. Trials with sham surgery have demonstrated that the act of performing surgery can have a large placebo effect *[Sihvonen 2013 (RS)]*.

In the Hróbjartsson review *[Hróbjartsson 2010 (SR)]*, trials with the explicit purpose of studying placebo effects and trials that did not inform patients about the possible placebo treatment also had larger effects. Randomized trials that have evaluated the effects of a placebo with and without the care provider being positive support the finding that what is communicated about a placebo (or a

treatment) has an impact on the placebo effect. One trial found a placebo effect with sham acupuncture with minimal communication (compared to being on a waiting list) and an even larger effect with sham acupuncture with positive communication *[Kaptchuk 2008 (RS)]*. The other trial did not find an effect of a placebo tablet (compared to no placebo) in patients with a variety of different symptoms without a diagnosis, but did find an effect of the general practitioner being positive (with or without the placebo) compared to not being positive *[Thomas 1987 (RS)]*. These studies suggest that the placebo effect depends on patient expectations and that those expectations are influenced by what is communicated to the patient.

Several systematic reviews have investigated the influence of blinding and other characteristics of randomized trials on effect estimates, as described in the basis for Concept 2.1b. Some have found that, on average, studies with inadequate blinding have larger effect estimates than studies with adequate blinding, primarily for subjective outcomes *[Page 2016a (SR), Savović 2012b (SR)]*, whereas others have had inconclusive results *[Dechartres 2016 (SR), Moustgaard 2020 (SR), Wang 2021 (SR)]*. The extent to which overestimation of effect sizes in randomized trials with inadequate blinding is due to measurement bias or co-intervention rather than a placebo effect is uncertain. Moreover, these reviews are based on comparisons between studies and have a high risk of confounding by other characteristics of the trials included in each meta-analysis. Consequently, the extent to which comparisons of treatments with inadequate or no blinding of patients are misleading because of placebo effects is uncertain. It likely varies and is difficult to predict. The risk of being misled is probably greater for patient-reported outcomes, such as pain, and likely depends on the patients' beliefs about the treatments being compared and what they are told.

It is not always possible to blind the people who receive the treatments in randomized trials, and it is rarely possible in non-randomized studies such as cohort studies or case-control studies. When information about whether study participants' exposure to a treatment is collected retrospectively, apparent treatment effects may be either overestimates or underestimates of an effect or association, because of "recall bias". For example, a claim that the measles, mumps, and rubella vaccine caused autism in children received a great deal of attention following publication of a fraudulent study. After this, parents of autistic children tended to recall the start of autism as being soon after the child was vaccinated more often than parents of similar children who were diagnosed prior to publication of that study *[Andrews 2002 (RS)]*.

It is possible to blind participants in randomized trials for many different types of treatments, not just in drug trials. For example, participants can be blinded in comparisons of surgical and technical treatments, treatments that involve attention, devices, and physical therapy *[Armijo-Olivo 2017 (SR), Monaghan 2021 , Wartolowska 2014 (SR)]*. When blinding is not possible, it is important to consider the possibility of placebo and nocebo effects, especially for patient-reported outcomes.

Implications

Be cautious about relying on the results of treatment comparisons if the participants knew which treatment they had received. This may have affected their expectations or behaviour. The results of such comparisons can be misleading.

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