Direct comparisons

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

2.2c Consider whether treatments were compared across studies.

Explanation

For many conditions (e.g., depression) there are more than two possible treatments (for example, different medicines, or types of psychotherapy). Only very rarely are all the possible treatments for a condition compared in a single study, so it may be necessary to consider indirect comparisons among treatments. For example, there may be comparisons of drug A with placebo and comparisons of drug B with placebo, but no studies that compare drug A with drug B directly. In this case, indirect comparisons among studies may be needed to inform a decision about whether to use drug A or drug B. However, there can be important differences between the studies examined in addition to the treatments they assessed, for example, differences in characteristics of the participants, or the way the comparisons were done, or in the outcome measures used. These differences can result in misleading estimates of treatment effects.

A systematic review of different doses of aspirin illustrates the problem with indirect comparisons *[Guyatt 2011b]*. The authors found five randomized trials that compared aspirin with placebo to prevent graft occlusion after coronary artery bypass surgery. Two trials tested medium-dose and three low-dose aspirin. Based on the indirect comparison, the relative risk reduction for medium- compared to low-dose aspirin was 0.74 (95% confidence interval 0.52 to 1.06; P = 0.10) suggesting the possibility of a larger effect with medium-dose aspirin. However, there are other characteristics of the trials that might be responsible for any differences found (or undetected differences that might exist). Compared with the low-dose trials, the patients included in the medium-dose trials may be different, interventions other than aspirin may have been differently administered, and outcomes may have been measured differently (e.g., dissimilar criteria for occlusion or different durations of follow-up). Differences in study methods and the risk of bias may also explain the results.

Basis for this concept

Indirect comparisons are non-randomized, even though they are based on two or more randomized trials. For indirect comparisons to be reliable, patient and other characteristics of the treatment comparisons must be similar across the trials included in the indirect comparison. As with other types of non-randomized studies, it is only possible to control for characteristics (confounders) that might modify the effects of treatments that are known, measured, and reported (see Concept 2.1a). Therefore, indirect comparisons can sometimes either overestimate or underestimate treatment effects *[Bucher 1997 , Song 2003 (SR)]*. Informal indirect comparisons – e.g. assuming that drug A is more effective than drug B simply because drug A had a larger effect compared to placebo than drub B – can be misleading and should be avoided *[Song 2009 (SR)]*. A systematic review of meta-analyses of randomized trials found that appropriately analysed indirect comparisons usually, but not always, agreed with those of direct comparisons *[Song 2003 (SR)]*. The reliability of the indirect comparisons depended on the risk of bias in the trials and the similarity of the trials.

However, there are often more than two treatment options for a condition and unreliable or no direct comparisons of all the treatments. When this is the case, indirect comparisons may provide the best available evidence to inform decisions. An increasing number of systematic reviews of

multiple treatments for a condition use what is called “network meta-analysis” to evaluate the comparative effectiveness of multiple treatments. For each pair of treatments, these analyses combine effect estimates from direct and indirect comparisons. As with any systematic review, the reliability of estimates of treatment effects from network meta-analyses depends on the methods used to identify, select, critically appraise, and collect data from relevant studies (see Concept 2.2a). In addition, the reliability of effect estimates, and the ranking of treatments, depends on assessing the similarity of the included trials (apart from the treatments being compared and the consistency of direct and indirect effect estimates) *[Brignardello-Petersen 2018 , Jansen 2014 , Mills 2012 , Puhan 2014]*.

Network meta-analyses rely on the assumption that the different sets of studies included in the analysis are similar, on average, in all important factors that may affect the relative effects *[Chaimani 2021]*, including characteristics of the participants, interventions, and outcome measures. This assumption cannot be tested statistically, but it is sometimes possible to adjust for potential confounders *[Efthimiou 2016 (SR), Hutton 2015 , Jansen 2013]*. Otherwise, it must be assessed conceptually, based on what is known about potential confounders and what information is available from the trials.

Direct and indirect evidence for a treatment comparison should be combined only when the effect estimates are similar *[Hutton 2015]*. Statistical tests can be used to assess whether differences in effect are greater than could be expected to occur by chance. However, the tests have limited ability (“power”) to confirm that differences are larger than could be expected by chance. On the other hand, when multiple tests are undertaken, a few may indicate inconsistency simply by chance. A systematic review found 112 trial groups of trials that included both a direct and indirect comparison of two treatments *[Song 2011 (SR)]*. The direct and indirect comparisons were inconsistent 14% of the time, suggesting that inconsistency may be more common than in the previous systematic review noted above *[Song 2003 (SR)]*. However, assessments of inconsistency may differ depending on the test that is used, the effect measure used in the analysis, and how much variation there is in effect estimates from different studies *[Veroniki 2013 (SR)]*.

Implications

Indirect comparisons are sometimes needed to inform treatment choices. In these circumstances, careful consideration should be given to differences between the studies besides the treatments that were compared.

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Systematic reviews

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