What is a multiple treatments meta-analysis?

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Standard meta-analyses are an effective tool in evidence-based medicine, but one of their main drawbacks is that they can compare only two alternative treatments at a time. Moreover, if no trials exist which directly compare two interventions, it is not possible to estimate their relative efficacy. Multiple treatments meta-analyses use a meta-analytical technique that allows the incorporation of evidence from both direct and indirect comparisons in a network of trials of different interventions to estimate summary treatment effects as comprehensively and precisely as possible.

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Pair-wise (or standard) meta-analysis is a statistical technique used to synthesize evidence from studies with similar design, addressing the same research question within the frame of a systematic review (Higgins & Green, 2011). Standard meta-analyses are an effective tool in evidence-based medicine, but one of their main drawbacks is that they can compare only two alternative treatments at a time (Cipriani et al. 2011a). For most clinical conditions where many treatment regimens already exist, standard meta-analysis approaches result into a plethora of pair-wise comparisons and do not inform on the comparative efficacy of all treatments simultaneously. Moreover, if no trials exist which directly compare two interventions, it is not possible to estimate their relative efficacy and thus this specific information is missing from the overall picture. All this has led to the development of meta-analytical techniques that allow the incorporation of evidence from both direct and indirect comparisons in a network of trials and different interventions to estimate summary treatment effects as comprehensively and precisely as possible (Caldwell et al. 2005). This meta-analytical technique is called multiple treatments meta-analysis (MTM), also known as mixed-treatment comparison or network meta-analysis. How does MTM work? An example is pictured in the attached Fig. 1.

Consider we want to assess comparative efficacy of all available pharmacological treatments for a specific psychiatric disorder. After carrying out a systematic review of all the available scientific evidence, only randomised controlled trials (RCTs) comparing treatment A versus treatment B (RCT 1) and treatment A versus treatment C (RCT 2) are available. Hence, for these two head-to-head comparisons (namely, A versus B and A versus C), evidence is provided by studies that compare these two pairs of treatments directly (Fig. 1 – Step 1). By contrast, there is no study which directly compares treatment B versus treatment C, and so the direct estimate between
these two treatments is missing. If we used a standard meta-analytical approach, there would be no way to determine the relative efficacy between treatments B and C and this might clearly limit the clinical applicability of results. However, using an MTM approach, indirect evidence can be provided because studies that compared A versus B and A versus C can be analysed jointly, as follows. Treatment A is present in both the RCTs (Fig. 1 – Step 2) and so it is possible to establish how much better (or worse) are treatments B and C relative to the ‘common’ comparator A, by calculating the indirect estimate between treatments B and C via treatment A (Fig. 1 – Step 3). For example, if treatment B is better than treatment A by reducing on average the symptoms by 7 units on a rating scale and treatment C is better than treatment A reducing the symptoms by 5 units, we can conclude that treatment B is better than treatment C by a mean difference of 2 units. In this way, it is possible to have the relative efficacy of all three comparisons, notwithstanding the lack of direct comparison between treatments B and C. The combination of direct and indirect estimates into a single effect size not only can provide information on missing comparisons, but also can increase precision of treatment estimate of already existing direct comparisons and strengthen inferences concerning the relative efficacy of two treatments. Hence, going back to our previous example, if direct evidence were available between treatments B and C, we could merge this information with the indirect estimate (via treatment A) into a mixed effect size to obtain overall estimates with maximum precision. Originally, MTM was the extension of this idea of merging direct and indirect evidences together in a full network of comparisons (Lu & Ades, 2004; Salanti et al. 2008).

Another fruitful role of the MTM technique is to facilitate simultaneous inference regarding all treatments in order to rank them according to any outcome of interest, for instance efficacy and acceptability (Cipriani et al. 2011b; Salanti et al. 2011). Using MTMs within the frame of a more complex statistical procedure, it is possible to calculate the probability of each treatment to be the most effective (first-best) regimen, the second-best, the third-best and so on, and thus to rank treatments according to this hierarchical order. This is a very easy to understand and straightforward way to present MTM results, most of all for clinicians who want to know which is the best treatment to be prescribed to patients on average (Salanti et al. 2009).

Recently, MTMs have become more widely employed and demanded, with the increased

Fig. 1. Graphic explanation of direct–indirect comparisons to be used in MTM (see text).
complexity of analyses that underpin clinical guidelines and health technology appraisals (Barbui & Cipriani, 2011). Expert statistical support, as well as subject expertise, is required for carrying out and interpreting MTM results. Several applications of the methodology have depicted the benefits of a joint analysis, but MTM approaches are far from being an established practice in the medical literature. Concerns have been expressed about the validity of MTM methods as they rely on assumptions that are difficult to test (Salanti et al. 2009). Although randomised evidence is used and MTM techniques preserve the randomisation, indirect evidence is not randomised evidence as treatments have originally been compared within but not across studies. Therefore indirect evidence may suffer the biases of observational studies (i.e. confounding or selection bias). In this respect, direct evidence remains more robust and in situations when both direct and indirect comparisons are available in a review, any use of MTM should be to supplement, rather than replace, the direct comparisons. Several techniques exists which can account for but not eliminate the impact of effect modifiers across studies involving different interventions (Salanti et al. 2009). However, recent empirical evidence suggests that direct and indirect evidences are in agreement in the majority of cases and that methods based on indirect evidence (such as MTM) can address biases that cannot be addressed in a standard meta-analysis, such as sponsorship bias and optimism bias (Song et al. 2008; Salanti et al. 2010).

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References


