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Appraisal

Research Note: Comparing interventions with network meta-analysis

Physiotherapists have become familiar with using research findings to inform practice. A physiotherapist who is interested in using research findings to determine the best physiotherapy intervention for a patient with osteoarthritis of the knee might look for high-quality systematic reviews of randomised, controlled trials (RCTs). A search of PEDro (https://www.pedro.org.au) would identify a Cochrane systematic review[1] on the efficacy of exercise for patients with osteoarthritis of the knee. The review provides high-quality evidence that exercise reduces pain and moderate-quality evidence that exercise improves physical function when compared with not exercising.

However, the results of a systematic review that compares only two interventions may not provide all the information required to make a clinical decision. The clinician, for example, may be interested in discriminating between flexibility and aerobic exercise for osteoarthritis. The osteoarthritis systematic review is not helpful for this purpose because it excluded RCTs that compared exercise interventions with each other. To get an answer, the clinician may compare the benefit of flexibility exercise compared with no exercise to the benefit of aerobic exercise compared with no exercise. Such an indirect comparison, which is not obtained from a single RCT, is valid under certain assumptions.[2–5] If these assumptions are not fulfilled, the indirect comparison may lead to biased conclusions.

Based on the notion of indirect comparison, a new type of evidence synthesis has emerged over the last 20 years to address this challenge. Network meta-analysis compares several available interventions for a clinical problem with each other in a single meta-analysis. The analysed comparisons may include comparisons between interventions that have not been directly compared in RCTs.[2,5–9] A league table of the interventions in the network, displaying all possible pairwise relative effect sizes, can be used to compare and rank the interventions according to efficacy, acceptability or safety. This provides critical information to inform clinical decision-making.

The field of network meta-analysis has developed rapidly.[10–13] Network meta-analysis has far-reaching relevance to clinicians, researchers, guideline-developers, regulators and policy-makers.[14–16] The purpose of this Research Note is to provide a user-friendly overview of the principles and assumptions that underlie network meta-analysis.

What is a network of interventions?

The central element of network meta-analysis is the network, which distinguishes it from conventional pairwise meta-analyses. Networks display the evidence of the effectiveness of interventions for a clinical condition. For example, a network might display evidence of the effectiveness of exercise interventions for hip or knee osteoarthritis,[17] non-pharmacological interventions for cancer-related fatigue,[18] or non-operative treatment for chronic calcific shoulder tendinopathy.[19] A network consists of nodes and edges. Each node in the network represents an intervention. Each edge (a line between two nodes) represents a comparison between two interventions that has been evaluated in at least one RCT. If there is no edge between two nodes, no data from RCTs have compared these interventions. In this way, the network displays all the available comparisons in the evidence base and alludes to all the possible comparisons.

Network construction

Multiple factors contribute to network construction. For researchers conducting a network meta-analysis, a key step is determining the PICOS (Participants, Interventions, Comparisons, Outcomes and Study types). The descriptions of the participants (P) and the comparisons (C) to be studied influence which RCTs will be included and, hence, the presence and size of the edges in the network. The interventions (I) are the nodes in the network. The selection of outcomes (O) is important, as trials without certain outcomes will not be included in the network meta-analysis for that outcome. Network meta-analysis is usually performed using RCTs (S), although methods exist to incorporate non-randomised data.[20] In the networks of interventions for chronic calcific shoulder tendinopathy,[19] the width of each edge reflects the number of trials for that comparison, each node represents an intervention, and the node diameter is proportional to the number of participants allocated to that treatment. It is also shown that the network structure changes according to outcome (Figure 1).

The multiple treatment comparison

The network displays the number of available *direct* comparisons; comparisons for which there are RCT data available. The absent comparisons, termed *indirect* comparisons, have no RCT data available. The relative treatment effects for these comparisons will be indirectly estimated in network meta-analysis. A systematic review is critical to ensure that all the available direct comparisons are included in the network. Clinicians reading a network meta-analysis article should be satisfied that a rigorous systematic review was performed. There are several guides available for this purpose.[21–24]

Making a comparison between interventions in a network

The idea of combining *indirect* with *direct* evidence (when the latter is available) characterises network meta-analysis. To illustrate this, a hypothetical example is used. Three interventions form the simplest possible network of three nodes (Figure 2a). A clinician may want to know the effects of these three interventions compared with each other on a continuous outcome, so that the most effective intervention can be provided to a patient. Studies comparing A with B (AB), when synthesised, would produce a standardised mean difference for the direct comparison AB (SMD_{AB}^{Direct}) and studies comparing C with B (CB) would produce SMD_{CB}^{Direct}. If the comparison between A and C

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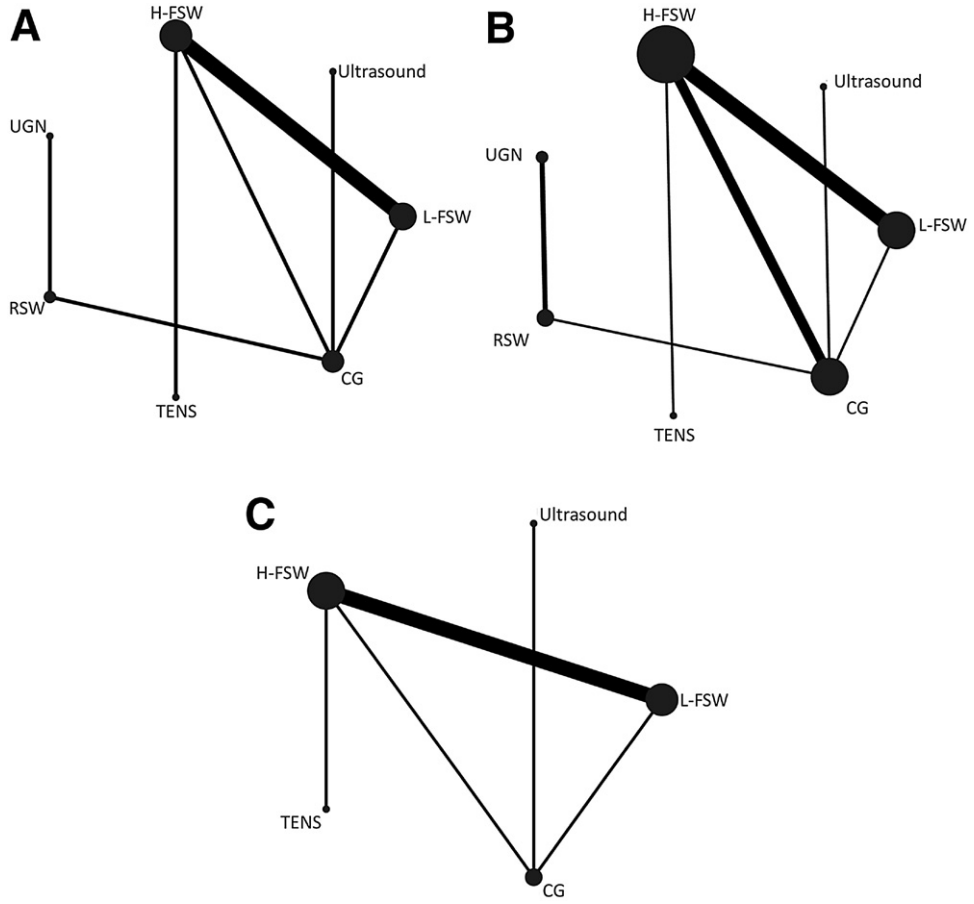

Figure 1. Network plots of interventions for chronic calcific shoulder tendinopathy, displayed according to three outcomes (reproduction from Wu et al [19]).
Reproduced with permission. Figure label size increased from original. Original material available at doi: 10.1016/j.apmr.2017.02.030. Copyright 2017 by the American Congress of Rehabilitation Medicine.
UGN = ultrasound-guided needling, RSW = radial extracorporeal shockwave therapy, H-FSW = high-energy focused extracorporeal shockwave therapy, TENS = transcutaneous electrical nerve stimulation, CG = control group (sham treatment or physiotherapy alone), L-FSW = low-energy focused extracorporeal shockwave therapy.

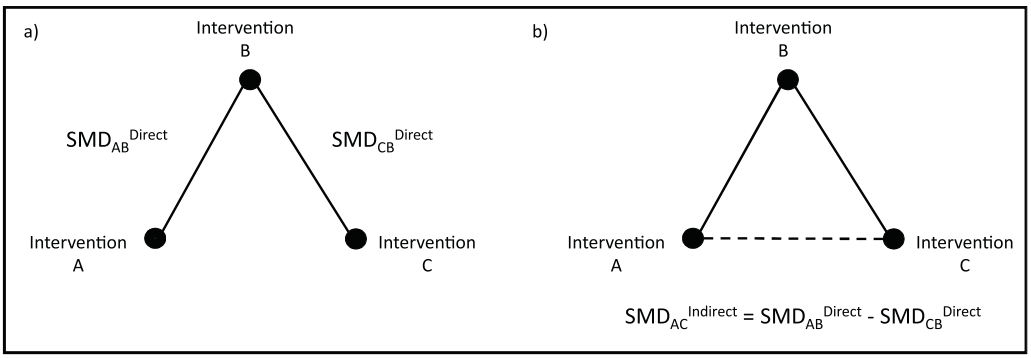

Figure 2. A simple three-node network comparing three interventions.
SMD = standardised mean difference.

(AC) has not been tested in a clinical trial, as Figure 2a indicates, the network meta-analysis model estimates the 'missing' relative treatment effect of AC by using the AB and CB data to estimate an *indirect* effect of AC as $SMD_{AC}^{Indirect} = SMD_{AB}^{Direct} - SMD_{CB}^{Direct}$ (Figure 2b). This is called an indirect treatment comparison.

If there are studies directly comparing intervention A and C, their synthesis will provide a SMD_{AC}^{Direct}. The two estimates, SMD_{AC}^{Direct} and $SMD_{AC}^{Indirect}$ can be synthesised as a weighted average to provide SMD_{AC}^{Mixed}. This is called a mixed treatment comparison. In more complex network structures, all of the other direct comparisons in the network will contribute information to this estimate.[25–27] Thus, network meta-analysis estimates are weighted sums of all direct and indirect comparisons present in the network. The weighting is influenced by precision, as in pair-wise meta-analysis, and network structure.[25,27]

Assumptions underlying indirect comparison and network meta-analysis

All statistical models require assumptions about the data and the underlying parameters. The validity of network meta-analysis depends on the assumption of transitivity. A joint synthesis of the data in the network is valid only if the included studies are similar in all important characteristics except for the interventions being tested.[5,11] This is also equivalent to the assumption that a participant included in any trial could, in principle, be randomised