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Mini Review

How To Read a Network Meta-analysis

Angie K. Puerto Nino^{a,*}, Romina Brignardello-Petersen^b^aFaculty of Medicine, University of Helsinki, Helsinki, Finland; ^bDepartment of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

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Abstract

Network meta-analysis (NMA) expands upon traditional meta-analysis by integrating three or more interventions. This allows comparing interventions using evidence from trials that have compared pairs of interventions directly, and indirect evidence through common comparators. We provide an overview of NMA concepts and considerations when interpreting results from a systematic review with a NMA and applying them to clinical practice.

Patient summary: Network meta-analysis is a statistical tool that allows researchers to compare multiple treatments for a medical condition at once, even when treatments have not been compared to each other in research studies. This mini-review explains how to read a network meta-analysis and apply its results in patient care.

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1. Clinical scenario

Consider the case of a 65-year-old male presenting with lower urinary tract symptoms. His International Prostate Symptom Score (IPSS) of 20, maximum flow rate (Qmax) of 4.3 ml/s, prostate-specific antigen of 3.9 ng/ml, and prostate volume of 70 ml on ultrasound suggest a diagnosis of benign prostatic obstruction (BPO). Due to previous side effects with α -blockers and 5 α -reductase inhibitors and the patient's preference, he is a candidate for minimally invasive surgical therapy (MIST) [1]. The question arises as to which MIST has greater benefits over the others. When searching the literature, you find trials comparing some MIST to gold-standard techniques such as transurethral resection of the prostate (TURP), or to sham treatment. However, there are no trials comparing MIST head-to-head. You find a recent systematic review (SR) and network meta-analysis (NMA) that compares the efficacy of MIST [2].

2. Overview of a NMA

In traditional SRs, using meta-analysis, authors compare the effects of two interventions by pooling the results across trials that compared them (ie, direct evidence). When direct evidence is unavailable, SR authors can use trials that compare each of the two interventions of interest with a common comparator (ie, indirect evidence) to estimate their relative effects. NMA, or multiple-treatment comparison meta-analysis, is a statistical technique used in SRs to compare the effectiveness of three or more interventions by combining direct and indirect evidence from studies comparing any pair of interventions included in the network [3]. Table 1 defines key concepts for NMAs [4,5].

SRs with NMAs have gained popularity because of their main appeal: they better reflect many contexts in which clinicians are rarely interested in only two possible courses of action. Theoretically, combining direct and indirect

* Corresponding author at: Faculty of Medicine, University of Helsinki, Helsinki, Finland. University of Helsinki, Biomedicum 2 B, P.O. Box 13, Tukholmankatu 8 B, 00290 Helsinki, Finland.
E-mail address: apuertonino@gmail.com (A.K. Puerto Nino).

Table 1 – Key concepts in network meta-analysis (NMA)**Types of evidence:**

- **Direct evidence:** Information from studies that have compared two interventions head-to-head against one another.
- **Indirect evidence:** Information obtained from comparing two interventions of interest through a common comparator, using two separate sets of studies.
- **Network evidence:** Combination of direct and indirect evidence for estimating the relative effect of pairs of interventions across a network of interventions.

NMA diagram (network plot):

- Graphical representation of the geometry of a network of interventions. The diagram allows depicting whether information comparing each pair of interventions comes from direct evidence, indirect evidence, or both. It is composed of:
 - **Nodes:** Circles representing each intervention included in the NMA.
 - **Links or edges:** Lines connecting two nodes. A link between two nodes indicates that there is direct evidence for the comparison.
- Authors use node size and edge thickness, as well as colors, to represent different characteristics of the network, such as the number of participants randomized to each node across studies, the number of studies comparing two interventions, the number of participants in each comparison, inverse of the variance of direct evidence, risk of bias, etc.

NMA assumptions:

- **Transitivity:** When two interventions (A and B) have not been compared head-to-head, and each of those interventions has been compared against a common intervention (ie, A and B have been directly compared to C), the indirect comparison is unbiased if the study characteristics that impact the treatment effect (effect modifiers) of the direct comparisons are similarly distributed between the two direct comparisons (ie, A vs C, and B vs C) [4].
- **Coherence or consistency:** Level of statistical agreement between direct and indirect evidence [5]. Trustworthy NMA results require that direct and indirect estimates used to calculate the NMA estimates are similar [5].

evidence would lead to having more precise estimates of effect (ie, with narrower confidence intervals). Therefore, NMA has a great potential to reduce research waste and guide policy decisions and clinical practice [6]. In the next section, we present an overview of the main considerations when assessing the trustworthiness of SRs with NMAs and interpreting their results. We focus on aspects particularly relevant to SRs with NMA, but urologists should remember that aspects related to the general methodology of SRs (eg, comprehensive searches, screening, and data abstraction that minimize errors, etc) are also important to consider.

3. Understanding a NMA

3.1. Network geometry

In NMAs, the network diagram is key to understanding what interventions were included in the network and whether the information used to calculate estimates for each pair of interventions came from direct evidence only, indirect evidence only, or both. Figure 1 shows the network diagrams for IPSS and Qmax as the outcomes of interest after treatment for BPO. In this NMA, the authors included several MIST, the standard of care (TURP), and sham interventions. To ensure all relevant information is used and to minimize biases, trustworthy NMAs incorporate all the relevant interventions, including the standard of care, for the specific medical condition. In this example, the authors included all relevant MIST. In addition, because monopolar TURP (mTURP) is the intervention most commonly studied by researchers, we can be confident that the authors included all the relevant evidence.

3.2. NMA assumptions

The trustworthiness of NMA relies on the transitivity and coherence assumptions (Table 1). NMA users should determine if these assumptions were met by looking at the information provided by the authors. NMAs in which the authors

assess the transitivity and coherence either for the network overall or at the pairwise comparison level (see below) are more trustworthy than those in which these assumptions are not mentioned. In our example, the authors assessed the transitivity and coherence for each pairwise comparison and integrated these assessments in their results, which increases the trustworthiness of what they present.

3.3. NMA results

When using NMA results, as in any meta-analysis, urologists should focus on the magnitude of the effect estimates from comparisons of the interventions of interest. Trustworthy NMAs present the relative (odds ratio or risk ratio) and absolute (risk difference) effect estimates for dichotomous outcomes, while mean differences (MDs) and standardized MDs are used for continuous outcomes. As in traditional meta-analysis, the point estimate indicates the direction and size of the effect, while the confidence interval (CI) around the estimate provides a range of uncertainty within which the true effect is likely to lie. For instance, mTURP comparisons against prostatic urethral lift (MD –6.7 ml/s, 95% CI –9.3 to –4.1), transurethral microwave thermotherapy (MD –5.9 ml/s, 95% CI –7.3 to –4.4), prostatic arterial embolization (MD –9.3 ml/s, 95% CI –13.7 to –5.0), and temporary implantable nitinol device (MD –6.7 ml/s, 95% CI –10.0 to –3.5) suggest that these interventions result in a larger reduction in Qmax, with CIs that support conclusions about the direction of the effect.

Some NMAs rank the interventions from best to worst for each outcome. The rankings can be presented as rank probabilities, *p* scores, or the surface under the cumulative ranking curve (SUCRA), among others [7]. NMA rankings have some limitations: (1) the magnitude of the difference in treatment effects among the interventions is not accounted for in the ranking; and (2) the certainty of the evidence (see below) may be low for interventions with a high ranking [7]. Given its limitations, urologists should not rely on NMA's ranking alone when interpreting NMAs.

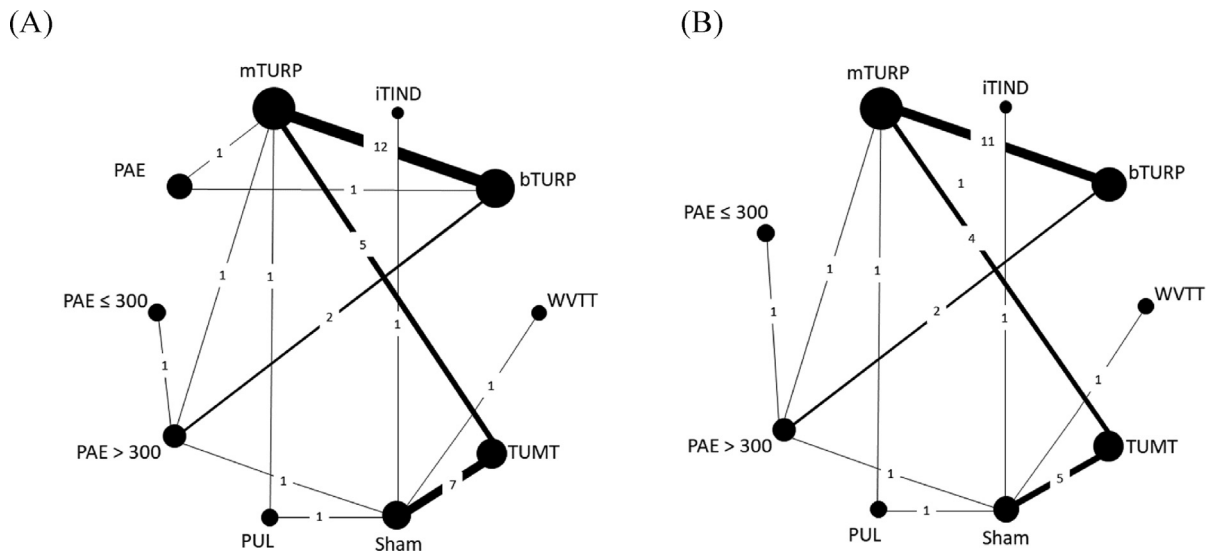


Fig. 1 – Network diagram of treatment comparisons for benign prostatic obstruction (BPO) adapted from Cornu et al [2], for (A) maximum urinary flow rate (Qmax) and (B) International Prostate Symptom Score (IPSS). The authors included a total of 34 studies that examined different interventions for the treatment of BPO. The networks included the following interventions: monopolar transurethral resection of the prostate (mTURP), transurethral microwave thermotherapy (TUMT), water vapor thermal therapy (WVTT), prostatic urethral lift (PUL), prostatic arterial embolization (PAE; ≤300 and >300 μm), temporary implantable nitinol device (iTIND), bipolar TURP (bTURP), and sham intervention. The amount of evidence varied across these comparisons. The size of the nodes represents the number of participants randomized to each node across studies: mTURP is the node to which the largest number of patients was allocated across trials. The thickness of the edges represents the number of studies comparing two interventions: the comparison between mTURP and bTURP is the comparison with the largest number of studies.

3.4. Certainty of evidence

Trustworthy NMAs assess the certainty of the evidence for each comparison in the network [8]. Use of the Grading of Recommendations Assessments, Development, and Evaluation (GRADE) approach or another framework that allows a systematic assessment of the limitations of evidence from NMAs leads to more accurate conclusions [9]. The GRADE approach rates the certainty of evidence from high to very low [8,10]. For example, the authors rated the certainty of the evidence as low for the comparisons mTURP versus temporary implantable nitinol device, mTURP versus prostatic arterial embolization, and mTURP versus water vapor thermal therapy. The certainty of the evidence for other comparisons in the network was rated as moderate.

4. How to apply the results to clinical practice

When applying the results to clinical practice, urologists should consider the network geometry, whether the NMA includes all available interventions, the compliance of the transitivity and coherence assumptions, the magnitude of the effect estimates, and the certainty of the evidence. In addition, NMAs that address all outcomes important to decision-making and include studies that are applicable to the context of interest are more useful to urologists than those in which important information is not addressed or in which there are applicability concerns. On the basis of the magnitude of effect and the certainty of evidence, the example suggests that, prostatic urethral lift and transurethral microwave thermotherapy are the most effective MIST for improving Qmax and IPSS. The NMA seems to be trustworthy. However, decisions on use of these interventions should include the balance of benefits and harms when con-

sidering all the factors critical to decision-making, such as values and preferences, resources, feasibility, among others.

5. Conclusions

NMA is a tool for assessing the effectiveness of multiple interventions. Nevertheless, its use requires assessment of its trustworthiness and appropriate interpretation of its results.

Conflicts of interest: The authors have nothing to disclose.

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