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NETWORK META-ANALYSIS IN PSYCHIATRIC RESEARCH: OPPORTUNITIES AND CAVEATS

Sundar Gnanavel

Child and adolescent mental health services, Northumberland, Tyne and Wear NHS foundation trust, Morpeth, United Kingdom

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SUMMARY

Network meta-analysis is a methodology for comparing different treatments or modalities including both direct comparisons and indirect comparisons based on a common comparator. While this provides a wealth of opportunities in psychiatric research, both designing a network meta-analysis and interpreting the same requires meticulous care. This brief reports lists key features of a network meta-analysis and highlights the importance of careful interpretation with a few examples from recent psychiatric research.

Key words: *network meta-analysis - research method - intrepretation*

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INTRODUCTION

Network meta-analysis has captivated the attention of medical researchers, including psychiatric researchers. It is a new tool that has provided a novel way for data synthesis and arrive at more holistic conclusions. It is a meta-analysis in which multiple treatments are being compared simultaneously using both direct comparisons of interventions within different randomized controlled trials as well as indirect comparisons across trials based on a common comparator (Li et al. 2011). To put in simple words, when a study compares A with B and a different study compares B with C, a network meta-analysis can compare between A,B and C using direct and indirect comparison techniques utilising the fact that A was a common comparator in both studies. It thereby increases the scope of an usual pair-wise meta- analysis and thereby completes the 'evidence matrix'. Many of the assumptions behind a network meta-analysis is similar to those in a traditional meta-analysis. While this is indeed a more powerful tool than a traditional meta-analysis, it requires to be carefully designed and interpreted to avoid any erroneous conclusions being drawn (Leucht et al. 2016). Also, appropriate statistical techniques should be used to ensure valid conclusions are drawn.

GRADE FRAMEWORK FOR NETWORK META-ANALYSIS

Typically, a network meta-analysis provides two types of findings for a specific outcome: the relative treatment effect for all pairwise comparisons and a ranking of the treatments. Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for pairwise meta-analyses suggests the following framework for evaluating a network meta-analysis and highlights the following as the key features: (a) the important role of indirect comparisons (b) the contribution of each piece of direct evidence to the network meta-analysis estimate of effect size; (c) the importance of the transitivity to the validity of network meta-analysis; and (d) the possibility of disagreement between direct evidence and indirect evidence. Here, 'transitivity' assumption can be thought of in simple terms as 'whether it was equally likely that any patient in the network could have been given any of the treatments in the network'. This is, in particular, quite important in designing and interpreting a meta-analysis since if this assumption does not hold true, the results drawn from the network meta-analysis do not hold ground.

The GRADE framework also leads to making judgements about the confidence with which an estimate of treatment effect for any particular outcome can be believed. This includes four levels: high, moderate, low and very low. When the evidence is generated from randomized trials, it is initially assigned to a high quality rating. This is followed by a careful consideration of five components including study limitations, inconsistency, indirectness, imprecision and publication bias. For each component, the quality of the evidence can be maintained the same or downgraded by up to two levels, subject to a maximum downgrade by three levels across the five components mentioned (Salanti et al. 2014). Some authors have suggested modifications of GRADE framework tailored for a network meta-analyses. For example, Dumville et al. (2012) suggested including a separate category 'sensitivity of results' to assess the stability of the network utilised and also consider any unexplained heterogeneity and inconsistency together as one domain titled 'indirectness/ inconsistency' (Brignardello et al. 2017). Salanti et al. (2014) suggest that the ranking of the different treatment modalities compared should be done using probabilistic methods like 'rankograms' or the surface under the cumulative ranking curve (SUCRA), which take into account the estimated effect sizes and their accompanying uncertainty (Dumville et al. 2012). They also refer to routes involving a single intermediate treatment as simple indirect evidence and routes involving two or more intermediate treatments as compound indirect evidence. Indirect comparisons are built on an assumption of transitivity (explained earlier) and are fundamental to network meta-analysis. For the transitivity assumption to hold, the studies making different direct comparisons must be sufficiently similar in all respects other than the treatments being compared. When both direct and indirect evidence is available it can be referred to as 'mixed evidence' (Salanti et al. 2011).

KEY FEATURES IN DESIGNING AND INTERPRETING NETWORK META-ANALYSIS

In psychiatric research, there has been a recent flurry in publication of network meta- analysis. This usually involves comparison of different medication used in psychiatric disorders as well as comparison between psychological therapies/psychosocial interventions or a mixture of the above. Psychiatric research has definitely, benefitted from possibility of a comparison between different pharmacological or non-pharmacological therapies which cannot be otherwise directly compared due to lack of head to head studies.

Authors need to be mindful of the following while designing and interpreting a network meta-analysis:

- A strict definition of eligibility criteria for the studies to be included and the review question. This should take the following into consideration: population studied, interventions used, comparisons possible and outcomes to be included. This is important since different specifications of eligibility criteria may result in differences in the structure or extent of a network. This would lead to inconsistency and discrepancy in findings for network meta-analysis on same topic. One needs to be mindful that different combinations of direct and indirect evidence (some of which are independent and some overlapping) contribute to estimates of treatment effect.
- The validity of findings from a network meta-analysis depends on whether all eligible trials were identified and included in the analysis. Else, this can introduce a selection bias in the treatment effect estimates. A search of multiple data sources for trial data is recommended. This can include include published data, conference abstracts and other sources of grey literature, clinical trial registers, reviews of trials by regulatory agencies and requesting trial investigators for individual patient data. The role of non-randomised trials cannot be overlooked either (Song et al. 2008).
- Assessing quality of evidence, as recommended by GRADE framework (discussed above) is an essential step. Identification of any possible bias and addressing/adjusting the same in final interpretation is vital in ensuring validity of study results. It is interesting to note that network meta-analysis yields a number of effect sizes in comparison to a traditional pair wise meta-analysis that gives one effect size (Salanti et al. 2014).
- Methods utilised in implementing network meta-analysis includes meta-regression, hierarchical models, and Bayesian methods (Cipriani et al. 2013 & Caldwell et al. 2005). A range of methods have been developed to detect, quantify and address heterogeneity, inconsistency, and bias in included studies (Caldwell et al. 2005 & Lu et al. 2006). Most network meta-analyses to date use WinBUGs software which is tough to operate for the non-statistician clinicians (Lu et al. 2006).
- Writing, reporting and interpreting compiled network meta-analysis reports is also a challenging and daunting task. It is important to report all pair-wise effect estimates along with the associated intervals, depending on the statistical model used (Lu et al. 2011). Probability statements can be made about the effectiveness of each treatment modality compared in the network. In addition, clinical and methodological characteristics as well as potential biases within included trials must be included to enable the authors gain a more balanced perspective.

SOME EXAMPLES FROM PSYCHIATRIC RESEARCH

- A recent study compared cognitive behaviour therapy (CBT), psychoeducation alone, psychoeducation in combination with CBT, psychoeducation and personalized Real-time Intervention for stabilizing mood, family focused psychotherapy and carer-focused interventions as adjunctive treatment in bipolar disorder (Chatterton et al. 2017). They focused on outcomes including relapse to mania or depression, medication adherence and symptom scales for mania, depression and Global Assessment of Functioning (GAF). They concluded that carer-focused interventions significantly reduced the risk of depressive or manic relapse and psychoeducation alone and in combination with cognitive behavioural therapy (CBT) significantly reduced medication non-adherence. They also demonstrated that psychoeducation plus CBT significantly reduced manic symptoms and increased GAF while no intervention was associated with a significant reduction in depression symptom scale scores. It is of importance, to note that, many of these psychological or psychosocial interventions have never been studied head to head and in absence of network meta-analytic techniques, these conclusions could not have been arrived at. While the network meta-analysis itself is well devised and executed, there are some generic problems in research involving psychotherapy/psychosocial interventions including (but not limited to) small scale, lack of blinding and demand characteristics when assessing outcomes and publication bias. This might affect the validity of overall results.

- A recent network meta-analysis compared different methods of repetitive transcranial magnetic stimulation (r TMS) in depressive disorder. Techniques like prime r TMS (p TMS), deep r TMS (d TMS) and bilateral TMS were compared by pooling in these those trials where they were individually compared to sham TMS. It concluded that p TMS was a superior technique. However, in response, it was argued that by equating direct clear superiority (of one modality over another) in trials and indirect non-inferiority trials (one modality and another), the conclusion drawn need not be accurate (Roth et al. 2017).

These studies demonstrate the wide spread utility of network meta-analysis in psychiatric research in an attempt to answer still unanswered questions while also emphasising some of the still inherent limitations of a network meta-analysis (particularly, if not very carefully devised).

CONCLUSION

While, network meta-analysis can be considered 'the highest level of evidence' particularly for the purpose of treatment guidelines, it is worth remembering that devising as well as interpreting a network meta-analysis requires meticulous planning and a systematic approach (Leucht et al. 2016). If this can be ensured, this provides an abundance of opportunity in comparing treatment modalities for psychiatric disorders in a scientifically reliable manner.

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Correspondence:
Sundar Gnanavel, MD, Speciality doctor
Child and adolescent mental health services, Northumberland, Tyne and Wear NHS foundation trust
Morpeth, United Kingdom
E-mail:sundar221103@yahoo.com