REFRESHMENT (500–800 words, 6 references)

THE "WH" OF NETWORK META-ANALYSES

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BIOGRAPHY

Riccardo De Giorgi is a Wellcome Trust Doctoral Training Fellow (DPhil in Biomedical and Clinical Sciences) at the University of Oxford, Department of Psychiatry and honorary MRCPsych Clinical Fellow at the Oxford Health NHS Foundation Trust. He works on experimental medicine trials in patients with treatment-resistant depression.

SUMMARY

Currently, network meta-analyses (NMAs) are the only technique allowing to compare and rank numerous treatments across trials. Evidence produced by NMAs relies on pooled data from both direct and indirect comparisons within the studies. As such, NMAs are invaluable tools for informing clinical guidelines.

WHAT

Network meta-analysis (NMA, sometimes called "multiple treatments meta-analysis" or "mixed-treatment comparison") is a method to compare multiple interventions (usually in terms of efficacy/safety) across a network of studies (usually randomised controlled trials).

WHEN

A PubMed search for the terms above yielded 3299 records: the first (and only) NMA was published in 2002, but only between 2009-2011 the number of NMAs reached double figure, followed by an astonishing growth over the last years (Figure 1). The first NMA concerning mental health was published as early as 2006 (King 2006).

WHERE

NMAs established early as publications sought-after by major journals (e.g. JAMA, Arch Int Med). Today, NMAs are found on journals with various impact factors. However, well-conducted NMAs are frequently published on key journals as these studies are likely to support or even spark changes in clinical guidelines (e.g. Cipriani 2018).

HOW (Mavridis 2015)

A NMA shares most of the designing and conducting aspects of a classic pair-wise meta-analysis: defining the research question, specifying eligibility criteria, searching for and selecting studies, assessing risk of bias and quality of evidence, conducting a meta-analysis, and interpreting and reporting of findings (Higgins 2008).

Additionally, a NMA synthesises results from both direct and indirect evidence (Figure 2):

- Direct evidence is produced through the comparison of interventions within the available studies (e.g. comparison of fluoxetine vs control using the pooled results of all trials comparing fluoxetine vs control).
- Indirect evidence compares treatments employed in different studies, for which comparison no studies are available, using a common element (e.g. comparison of fluoxetine vs venlafaxine using pooled results of all trials comparing fluoxetine vs control against all trials comparing venlafaxine vs control).

Direct and indirect evidence are important in their own right, but their combination (i.e. "mixed evidence") can add more strength to a study's conclusion by improving the precision of the estimated result (Cipriani 2013).

All the studies included in a NMA are presented in a "network plot" – hence the name (Figure 3).

NMAs generally make an assumption of "consistency": the estimates of the effects from direct and indirect evidence must be in agreement. In mathematical terms, if three options (A, B and C) are available, trials comparing A vs B, B vs C, and A vs C will estimate the parameters δ^{AB}, δ^{AC} and δ^{BC}, respectively; in this case, there is consistency if $\delta^{AB} + \delta^{BC} = \delta^{AC}$. In lay terms, if skyscraper A's height is 400 metres, skyscraper B is 350 metres, and skyscraper C is 275 metres, the difference between skyscraper A minus B (50 metres) plus the difference between skyscraper B minus C (75 metres) must equal the difference between skyscraper A minus C (125 metres). In clinical terms, an example would be that if sertraline proves better than fluoxetine, and fluoxetine proves better than placebo, then we would expect sertraline to be better than placebo – if that is not the case, we have inconsistency, which can be assessed and dealt with through statistical methods beyond the scope of this refreshment.

Authors can generate "NMA-modified forest plots" ranking all treatments for outcomes such as efficacy/safety by their point estimate against the control condition (e.g. antidepressants can be ranked from the highest to the lowest effect sizes for efficacy versus placebo) (Figure 4).

Finally, it is possible to build "league tables" that allow head-to-head comparisons between the available treatments for efficacy/safety outcomes (e.g. each individual antidepressant is compared to the others and to placebo, reporting the effect size for each comparison and outcome in the table) (Figure 5).

WHY

In medicine, several treatment options employing similar mechanisms of action are often available for the same condition. Evidence-based medicine principles would require for treatments to be compared head-to-head in randomised controlled trials (or in meta-analyses of these) to assert that one treatment is better than another. However, randomised controlled trials rarely include more than two treatment arms, and standard meta-analyses can compare

only two interventions at a time. Therefore, a clinician interested in learning what the best antidepressants are for efficacy or safety would need to review a number of studies with separate head-to-head comparisons. Also, some treatment comparisons may have never been performed in the available trials.

NMAs address both these problems by comparing all different interventions in a single analysis and retrieving indirect evidence from the data available. Furthermore, having access to both direct and indirect evidence increases the significance of that specific result.

WHY (NOT?)

Some researchers are wary of indirect evidence, arguing that data from indirect evidence have not been randomised between different studies. Such lack of randomisation exposes to the risk of selection bias, therefore evidence produced only from indirect comparisons (i.e. indirectness) is downgraded in terms of quality. Indeed, a well-connected network (i.e. rich in direct comparisons) gives results that are more robust than a poorly-connected one; however, indirect evidence is still useful in real-world evidence-based medicine where not all head-to-head comparisons have been performed, and because it supports the findings from the direct evidence.

Another common critique is that NMAs compare "apples with oranges". This is a common problem with all meta-analyses, which is minimised by ensuring that the included studies have similar selection criteria for their participants, thus respecting the principle of transitivity (i.e. any patient within the network could have been randomised to any of the treatments).

Finally, it is important to consider the principle of "garbage-in, garbage-out", whereby if the included studies are conducted poorly, the results of the NMA will be of low quality too. As per any other meta-analysis, the quality of the included studies needs to be assessed and weighed up prior to drawing any conclusions; in NMAs, this is done through a NMA-modified Grading of Recommendations Assessment, Development and Evaluation (GRADE).

CONCLUSION

In view of the several advantages of NMAs, though bearing in mind the potential pitfalls, NMAs have been recommended as the highest level of evidence in treatment guidelines (Leucht 2016), thus representing an exceptional informative tool for clinicians and researchers.

DECLARATION OF INTEREST

None.

ACKNOWLEDGEMENTS

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REFERENCES

Cipriani A, Higgins JP, Geddes JR, et al (2013) Conceptual and technical challenges in network meta-analysis. Annals of Internal Medicine, 159: 130–7

Cipriani A, Furukawa TA, Salanti G, et al (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet, 391(10128):1357-1366

Higgins, JP (2008) Cochrane handbook for systematic reviews of interventions version 5.0.1. The Cochrane Collaboration. http://www.cochrane-handbook.org

King S, Griffin S, Hodges Z, et al (2006) A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamphetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess, 10(23):iii-iv, xiii-146

Leucht S, Chaimani A, Cipriani AS, et al (2016) Network meta-analyses should be the highest level of evidence in treatment guidelines. European Archives of Psychiatry and Clinical Neuroscience, 266: 477–80

Mavridis D, Giannatsi M, Cipriani A, et al (2015) A primer on network meta-analysis with emphasis on mental health. Evidence Based Mental Health, 18: 40–6

FIGURES

Fig 1 Published NMAs over the years according to a PubMed search

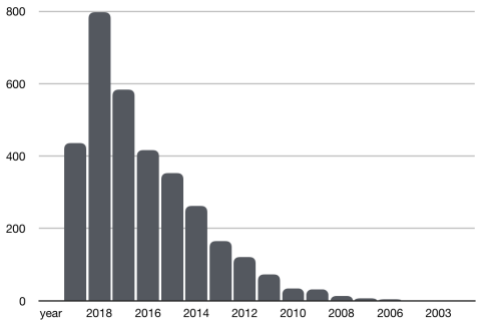

Fig 2 Direct and indirect evidence

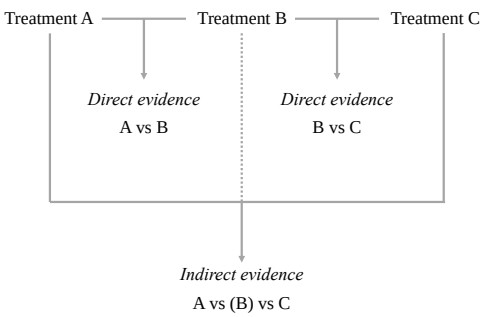

Fig 3 Network plot

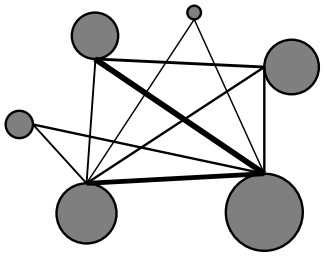

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Fig 4 NMA-modified forest plot

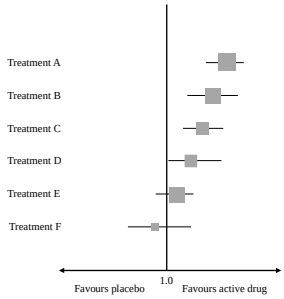

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Fig 5 League table

Safety →

Efficacy ↓

Treatment A	1.11 (0.99-1.20)	1.54 (0.87-1.76)	0.63 (0.46-1.00)	0.98 (0.76-1.02)	0.95 (0.88-1.03)
1.54 (1.01-1.72)	**Treatment B**	1.44 (1.34-1.45)	1.57 (1.01-1.71)	0.55 (0.45-0.65)	0.98 (0.80-1.16)
1.90 (1.85-1.95)	1.62 (1.12-1.73)	**Treatment C**	1.89 (1.22-2.00)	1.43 (1.32-1.48)	0.81 (0.46-1.00)
0.90 (0.70-1.22)	1.44 (1.34-1.47)	0.55 (0.45-0.65)	**Treatment D**	1.54 (1.01-1.72)	0.79 (0.77-0.93)
1.52 (1.00-1.70)	0.95 (0.88-1.15)	0.99 (0.69-1.00)	1.12 (1.01-1.18)	**Treatment D**	1.01 (0.85-1.11)
0.67 (0.55-0.72)	1.54 (1.02-1.58)	1.23 (1.10-1.35)	1.61 (1.10-1.72)	0.96 (0.89-1.11)	**Treatment E**

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