BMJ Evidence-Based Medicine 2023 (in press). Publisher DOI: 10.1136/bmjebm-2022-112136

Implementing hierarchical network meta-analysis incorporating exchangeable dose effects compared to standard hierarchical network meta-analysis

Jennifer A. Watt, MD, PhD[1,2,3*] jennifer.watt@utoronto.ca
Mark Hofmeister, RN, MSc[4] mrhofmei@ucalgary.ca
Cinzia Del Giovane, PhD[5,6] cinzia.delgiovane@biham.unibe.ch
Rebecca M. Turner, PhD[7] becky.turner@ucl.ac.uk
Andrea C. Tricco, PhD[1,3] andrea.tricco@unityhealth.to
Dimitris Mavridis, PhD[8] dmavridi@uoi.gr
Sharon E. Straus, MD, MSc[1,2,3] sharon.straus@utoronto.ca
Areti Angeliki Veroniki, PhD[1,3] areti-angeliki.veroniki@unityhealth.to

[1]Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[2]Division of Geriatric Medicine, Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[3]Institute of Health Policy, Management and Evaluation; University of Toronto, Toronto, Ontario, Canada
[4]O'Brien Institute of Public Health, University of Calgary, Calgary, Alberta, Canada
[5]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland
[6]Department of Medical and Surgical Sciences for Children and Adults, University-Hospital of Modena and Reggio Emilia, Modena, Italy
[7]MRC Clinical Trials Unit, University College London, London, United Kingdom
[8]Department of Primary Education, School of Education, University of Ioannina, Ioannina, Greece

*Corresponding Author
Dr. Jennifer A. Watt
Li Ka Shing Knowledge Institute, St. Michael's Hospital-Unity Health Toronto
209 Victoria Street, East Building, Room 723
Toronto, Ontario, Canada, M5B 1W8
Phone: 416-360-4000, ext. 77554, Fax: 416-864-5805
Orcid: 0000-0002-5296-6013

Word count: 1491 (text); 1 table, 2 figures, 2 boxes, 1 supplementary file

Introduction

Network meta-analysis (NMA) compares the efficacy or safety of more than two treatments or treatment doses that are directly or indirectly compared through a common comparator.[1 2] Treatment doses are not routinely incorporated into NMAs, which potentially limits the applicability and validity of results.[3 4] In this paper, we will introduce readers to NMA incorporating dose effects, specifically, how they can implement a hierarchical random effects NMA incorporating exchangeable dose effects. In particular, we share a motivating clinical example describing the comparative risk of vomiting associated with different cholinesterase inhibitor doses (that is, donepezil, galantamine, and rivastigmine) and use this example to illustrate (1) key similarities differences between the standard NMA and NMA incorporating exchangeable dose effects; (2) why incorporating dose effects in NMA is important; (3) steps to follow when completing a systematic review with NMA incorporating dose effects; (4) results derived from a hierarchical random effects NMA incorporating exchangeable dose effects and how they will facilitate clinical decision-making; and (5) how to consider potential dose effects when evaluating NMA relevance and credibility. Please refer to our companion publication for a more in depth theoretical discussion of hierarchical NMA models incorporating dose effects and alternative NMA models incorporating dose effects.[5]

Motivating clinical example

Clinicians prescribe cholinesterase inhibitors (that is, donepezil, galantamine, and rivastigmine) to slow cognitive decline in people with dementia.[4] Cholinesterase inhibitors are associated with potential side effects, including headaches, nausea, and vomiting.[4 5] Understanding if certain cholinesterase inhibitor doses are associated with a higher risk of side effects than others could inform, or even change, clinical decision-making. To describe potential dose effects, we used a subset of data from a published systematic review with NMA describing treatment level risk of vomiting associated with cholinesterase inhibitor use (see Supplementary Table 1 for dataset).[4] We implemented the categorization schema proposed by Lee et al: low-dose (≤5 mg/day) and high-dose donepezil (>5 mg/day); low-dose (<16 mg/day) and high-dose galantamine (≥16 mg/day); and low-dose (<6 mg/day) and high-dose rivastigmine (≥6 mg/day).[6]

What are the similarities and differences between a standard hierarchical random effects network meta-analysis and a hierarchical random effects network meta-analysis incorporating exchangeable dose effects?

Both the standard hierarchical random effects NMA and hierarchical random effects NMA incorporating exchangeable dose effects are conducted in a Bayesian framework.[7] In the hierarchical random effects NMA incorporating exchangeable dose effects, consistency and transitivity are assumed on the dose level as opposed to the standard hierarchical random effects NMA where consistency and transitivity are assumed on the treatment level, which means these assumptions must be evaluated on the dose level in a hierarchical random effects NMA incorporating exchangeable dose effects. While it is possible to implement the standard hierarchical random effects NMA to model dose effects, this model assumes that doses are unrelated to each other and the parent treatment, which ignores the treatment-dose relationship; whereas, the hierarchical random effects NMA incorporating exchangeable dose effects explicitly models this treatment-dose relationship by incorporating an additional model parameter for the differences between doses within treatments (that is, the between-dose variance within-treatment level).

Why did we model dose effects in our systematic review with network meta-analysis?

If clinicians always prescribe the same dose of a drug to patients, then a NMA incorporating dose effects is unnecessary and does not reflect real life clinical experiences; the standard NMA incorporating only treatment effects would be appropriate.[1] However, if clinicians prescribe different treatment doses, then a NMA incorporating dose effects may be more clinically relevant; results derived from a NMA not incorporating these dose effects could limit applicability. Empirical studies demonstrate the importance of modeling treatment dose effects when clinically relevant.[3-5] The question proposed in our motivating clinical example was better answered by understanding cholinesterase inhibitor dose effects (Figure 1 panel B) as opposed to just treatment effects (Figure 1 panel A).[1 5]

What steps did we follow for conducting a systematic review with network meta-analysis incorporating dose effects?

Steps for conducting a systematic review with NMA incorporating dose effects are similar to those for a systematic review with standard hierarchical NMA, but tailored for unique aspects of

incorporating dose effects (Box 1).[8] In particular, we abstracted outcome data per treatment dose (see example in Supplementary Table 1).[5] We implemented published OpenBUGS code for conducting a hierarchical random effects NMA incorporating exchangeable dose effects in a Bayesian framework, assuming an informative prior for the between-study variance ($\tau^2 \sim LogN(-3.02, 1.85^2)$) and a half-normal prior for the between-dose variance ($\sigma \sim N(0,1), \sigma > 0$).[5 9]

Box 1. Completing a systematic review with hierarchical random effects network meta-analysis incorporating exchangeable dose effects

1. Create a systematic review PICO* question that includes all relevant treatment doses.
2. Develop a literature search strategy for the PICO* question that identifies studies reporting outcomes by treatment dose.
3. Develop and publish a systematic review protocol that, in addition to reporting requirements of the *Preferred reporting items for systematic review and meta-analysis protocols* (PRISMA-P) statement, describes elements specific to conducting a systematic review with NMA incorporating dose effects.[10] Be explicit about what NMA model will be implemented to model dose effects. Justify NMA model choice by discussing information such as whether a dose response association can be assumed. If more than one NMA model is being considered, specify the model selection process.
4. Complete all article screening, data abstraction, and risk of bias appraisal independently and in duplicate.[11] Abstract outcome data at the treatment and dose level (see Table 1 for an example of abstracted dichotomous dose level outcome data).
5. Inspect network plots at the treatment and dose levels to understand network geometry and connectivity.
6. Inspect transitivity tables or plots of potential effect modifiers at the dose level.
7. Assess the consistency assumption at the dose level.[12-14]
8. Derive and present (a) dose and/or treatment effects for all dose and/or treatment comparisons and (b) estimates of between-study and between-dose heterogeneity, as appropriate. If model fit statistics were derived, present these statistics, and describe how they were used to support decision-making in the model selection process. Consider presenting ranking statistics by dose and/or treatment ranking.[15] Ensure dose and treatment effects are presented in a way that is meaningful to decision makers.[16 17] Rank-heat plots can help decision-makers to visualize treatment and dose rankings across outcomes.[18]
9. Perform subgroup, sensitivity, and meta-regression analyses to understand potential effect modifiers that could contribute to dose level intransitivity, inconsistency, and heterogeneity.
10. Assess for small-study effects and publication bias at the dose level, treatment level, or both, depending on whether meta-analytic effect estimates are presented at the dose level, treatment level, or both.[19 20]
11. Assess evidence certainty at the dose level.[21 22]
12. Report systematic reviews with NMAs incorporating dose effects as per the PRISMA 2020 statement and the PRISMA extension statement for the reporting of NMAs.[23 24]

Incorporate additional information specifically related to conducting a systematic review with NMA incorporating dose effects such as the model selection process.

*PICO = population, intervention, comparator, outcome
Abbreviations: network meta-analysis (NMA)

What were our results and how will incorporating dose effects inform decision-making?

Our NMA included 37 randomized trials (18,002 patients). All dose comparisons formed a connected network (Figure 1). There was no evidence of inconsistency globally in the network using the design-by-treatment interaction model (p=0.52), but there was evidence of inconsistency locally in two closed network loops using the loop-specific approach (inconsistency factor for the closed network loop containing placebo, low-dose donepezil, and high-dose galantamine was 2.79, 95% confidence interval 0.19 to 5.39; inconsistency factor for the closed network loop containing low-dose donepezil, high-dose donepezil, and high-dose galantamine was 2.79, 95% confidence interval 0.06 to 5.52). On visual inspection of potential effect modifiers, they were balanced across treatment dose comparisons in the NMA (Supplementary Table 2). There was moderate to large within-network heterogeneity, compared to Turner et al.'s empirical distribution (Table 1).[9] Only one comparison was informed by at least 10 studies (high-dose donepezil versus placebo). There was evidence of small-study effects on visual inspection of the funnel plot and by Egger's test for the comparison of high-dose donepezil versus placebo (p=0.01; Supplementary Figure 1).

High-dose donepezil was associated with greater odds of vomiting than low-dose donepezil (odds ratio [OR] 2.22, 95% credible interval [CrI] 1.17 to 4.20) and high-dose rivastigmine was associated with greater odds of vomiting than low-dose donepezil (OR 6.12, 95% CrI 2.75 to 12.98), high-dose donepezil (OR 2.75, 95% CrI 1.56 to 4.73), high-dose galantamine (OR 2.21, 95% CrI 1.24 to 3.86), and low-dose rivastigmine (OR 3.37, 95% CrI 1.61 to 6.35) (Table 1). Based on treatment dose ranking, placebo is the safest treatment dose (surface under the cumulative ranking curve [SUCRA] value of 100%) and high-dose rivastigmine is associated with the greatest risk of vomiting (SUCRA 0%). To investigate network inconsistency, we performed a sensitivity analysis where one randomized trial of greater than 30 weeks duration comparing the risk of vomiting associated with high-dose galantamine compared to low-dose donepezil was removed from the NMA. In this sensitivity analysis, there was no evidence of inconsistency in the NMA and results did not substantively change.

Table 1. Odds of vomiting associated with cholinesterase inhibitor use, per treatment dose

Comparison	Odds Ratio (95% CrI)
low-dose donepezil vs. placebo	1.18 (0.62 to 2.32)
high-dose donepezil vs. placebo	2.62 (1.72 to 4.04)
high-dose donepezil vs. low-dose donepezil	2.22 (1.17 to 4.2)
low-dose galantamine vs. placebo	4.08 (1.66 to 10.83)
low-dose galantamine vs. low-dose donepezil	3.47 (1.18 to 10.82)
low-dose galantamine vs. high-dose donepezil	1.56 (0.61 to 4.21)
high-dose galantamine vs. placebo	3.26 (2.18 to 4.91)
high-dose galantamine vs. low-dose donepezil	2.78 (1.3 to 5.72)
high-dose galantamine vs. high-dose donepezil	1.25 (0.73 to 2.11)
high-dose galantamine vs. low-dose galantamine	0.8 (0.31 to 1.92)
low-dose rivastigmine vs. placebo	2.14 (1.1 to 4.51)
low-dose rivastigmine vs. low-dose donepezil	1.83 (0.74 to 4.52)
low-dose rivastigmine vs. high-dose donepezil	0.82 (0.38 to 1.9)
low-dose rivastigmine vs. low-dose galantamine	0.53 (0.16 to 1.64)
low-dose rivastigmine vs. high-dose galantamine	0.66 (0.31 to 1.51)
high-dose rivastigmine vs. placebo	7.2 (4.61 to 11.08)
high-dose rivastigmine vs. low-dose donepezil	6.12 (2.75 to 12.98)
high-dose rivastigmine vs. high-dose donepezil	2.75 (1.56 to 4.73)
high-dose rivastigmine vs. low-dose galantamine	1.76 (0.62 to 4.66)
high-dose rivastigmine vs. high-dose galantamine	2.21 (1.24 to 3.86)
high-dose rivastigmine vs. low-dose rivastigmine	3.37 (1.61 to 6.35)
Common within-network between-study variance within-dose level: 0.24 (95% CrI 0.07 to 0.62)	
Common within-network between-dose variance within-treatment level: 0.55 (95% CrI 0.10 to 3.05)	

Abbreviation: credible interval (CrI)

In a published systematic review with NMA that implemented a standard hierarchical NMA, donepezil, galantamine, and rivastigmine were associated with increased odds of vomiting, but authors did not derive dose effects.[3 4] By implementing the NMA model with exchangeable dose effects, we derived effect estimates by cholinesterase inhibitor dose and we found that risk of vomiting varies by treatment dose (e.g., high-dose rivastigmine is associated with the highest risk and low-dose donepezil is associated with the lowest risk across cholinesterase inhibitor doses), which will help clinicians to tailor decision-making.

How do you consider potential dose effects when assessing the relevance and credibility of network meta-analysis?

The International Society for Pharmacoeconomics and Outcomes Research tool for interpreting NMAs in health care decision-making assesses NMA relevance and credibility.[25] In assessing the relevance of NMA results, this tool asks readers to consider whether all relevant drug doses and schedules of administration have been considered, but it does not specifically ask readers to assess the credibility of how different treatment doses were modeled in the NMA.[25] In the JAMA Users' Guide to the Medical Literature on How to Use an Article Reporting a Multiple Treatment Comparison Meta-analysis, readers are asked to consider if NMA results are valid and applicable to patient care.[26] Specifically, this tool asks readers to consider whether appropriate doses were included in the NMA, how treatment doses were modeled in the NMA, and how different doses could impact the consistency assumption.[26] Importantly, if authors do not implement a NMA model incorporating dose effects, they need to explain why. In this case, authors could describe evidence of inconsistency or intransitivity when evaluating dose level comparisons, disconnected networks, or a lack of biological plausibility (e.g., patients are prescribed only one treatment dose) (Box 2).

Box 2. Evaluating assumptions of hierarchical random effects network meta-analysis incorporating exchangeable dose effects

1. Network connectivity: Do dose comparisons form a connected network?
2. Transitivity: Are effect modifiers balanced across dose comparisons in the network (i.e., in theory, could trial participants have been randomized to any other trial in the network)?
3. Consistency: Are direct and indirect effect estimates derived from closed network loops in agreement with one another?
4. Heterogeneity: Is there evidence of clinical, methodological, or statistical heterogeneity between randomized trials that make the same treatment-dose comparisons? What effect modifiers (e.g., age, sex, frailty status) between randomized trials making the same dose comparison could influence the effect estimate?

Concluding remarks

Describing dose effects will facilitate tailored clinical decision-making beyond what is possible from treatment level outcomes.[3 5] Implementing a hierarchical random effects NMA incorporating exchangeable dose effects is preferred to the standard hierarchical NMA for deriving dose effects because it explicitly models the treatment-dose relationship with an additional model parameter (between-dose variance within-treatment level) that is not contained

in the standard hierarchical NMA. Where possible, researchers should work with content experts and knowledge users (e.g., patients, policymakers) to incorporate an assessment of dose effects in NMA. Peer reviewers and people critically appraising NMA should routinely assess for the inclusion of dose effects, which will strengthen confidence in review findings.

Figure

Figure 1. Treatment level network plot (panel A) and dose level network plot (panel B) for a network meta-analysis describing the risk of vomiting associated with cholinesterase inhibitor use incorporating 37 randomized trials (18,002 patients), six direct treatment level comparisons, and 15 direct dose level comparisons. Nodes connected by lines represent direct treatment and dose comparisons. Line thickness is proportional to the number of times this comparison is represented in the network meta-analysis. Node size is proportional to the number of patients included in each treatment or dose group.

Figure 2. Forest plot of odds of vomiting associated with each cholinesterase inhibitor dose compared to placebo, illustrating that high-dose donepezil is associated with greater odds of vomiting than low-dose donepezil and high-dose rivastigmine is associated with greater odds of vomiting than low-dose rivastigmine.

Data sharing

A dataset for our clinical example is published in this manuscript (Supplementary Table 1).

Patient and public involvement

There was no patient or public involvement in this study.

Dissemination

We will disseminate our manuscript to relevant knowledge user groups (e.g., graduate trainees and clinicians).

Ethics approval

Not applicable.

Transparency statement

JAW affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Role of the funding source

There was no funding for this study. ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis. SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation. RMT is supported by the UK Medical Research Council (grant No MC_UU_00004/06).

Contributors

All study authors contributed to the conception and design of this study. JAW drafted the first version of the manuscript. All authors contributed to the manuscript's revision. JAW is the guarantor of this article.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work. AAV is on the editorial board of BMJ Evidence Based Medicine but was not involved with the peer review process or decision to publish.

References

1. Dias S, Sutton AJ, Ades AE, et al. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Med Decis Making* 2013;33(5):607-17. doi: 10.1177/0272989X12458724 [published Online First: 2012/10/30]
2. Watt J, Del Giovane C. Network Meta-Analysis. In: Evangelou E, Veroniki AA, eds. Meta-Research: Methods and Protocols. New York, NY: Springer US 2022:187-201.
3. Watt JA, Goodarzi Z, Veroniki AA, et al. Safety of pharmacologic interventions for neuropsychiatric symptoms in dementia: a systematic review and network meta-analysis. *BMC Geriatr* 2020;20(1):212. doi: 10.1186/s12877-020-01607-7 [published Online First: 2020/06/18]

4. Tricco AC, Ashoor HM, Soobiah C, et al. Comparative Effectiveness and Safety of Cognitive Enhancers for Treating Alzheimer's Disease: Systematic Review and Network Metaanalysis. *J Am Geriatr Soc* 2018;66(1):170-78. doi: 10.1111/jgs.15069
5. Watt JA, Del Giovane C, Jackson D, et al. Incorporating dose effects in network meta-analysis. *BMJ* 2022;376:e067003 doi: 10.1136/bmj-2021-067003
6. Lee PE, Hsiung G-YR, Seitz D, et al. Cholinesterase Inhibitors. *BC Medical Journal* 2011;53(8):404-08.
7. Sadeghirad B, Foroutan F, Zoratti MJ, et al. Theory and practice of Bayesian and frequentist frameworks for network meta-analysis. *BMJ Evidence-Based Medicine* 2022:bmjebm-2022-111928. doi: 10.1136/bmjebm-2022-111928
8. Watt J, Tricco AC, Straus S, et al. Research Techniques Made Simple: Network Meta-Analysis. *J Invest Dermatol* 2019;139(1):4-12.e1. doi: 10.1016/j.jid.2018.10.028 [published Online First: 2018/12/24]
9. Turner RM, Davey J, Clarke MJ, et al. Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. *International Journal of Epidemiology* 2012;41(3):818-27. doi: 10.1093/ije/dys041
10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015;4(1):1. doi: 10.1186/2046-4053-4-1
11. Higgins JP, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions: Cochrane 2022.
12. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of interventions. *International journal of epidemiology* 2013;42(1):332-45.
13. Jackson D, Barrett JK, Rice S, et al. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Stat Med* 2014;33(21):3639-54. doi: 10.1002/sim.6188 [published Online First: 2014/04/30]
14. Pedder H, Dias S, Boucher M, et al. Methods to assess evidence consistency in dose-response model based network meta-analysis. *Stat Med* 2022;41(4):625-44. doi: 10.1002/sim.9270 [published Online First: 2021/12/07]
15. Salanti G, Nikolakopoulou A, Efthimiou O, et al. Introducing the Treatment Hierarchy Question in Network Meta-Analysis. *American Journal of Epidemiology* 2021 doi: 10.1093/aje/kwab278
16. Watt JA, Veroniki AA, Tricco AC, et al. Using a distribution-based approach and systematic review methods to derive minimum clinically important differences. *BMC Med Res Methodol* 2021;21(1):41. doi: 10.1186/s12874-021-01228-7 [published Online First: 2021/02/28]
17. Mavridis D, Porcher R, Nikolakopoulou A, et al. Extensions of the probabilistic ranking metrics of competing treatments in network meta-analysis to reflect clinically important relative differences on many outcomes. *Biometrical Journal* 2020;62(2):375-85. doi: https://doi.org/10.1002/bimj.201900026
18. Veroniki AA, Straus SE, Fyraridis A, et al. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. *Journal of clinical epidemiology* 2016;76:193-99. doi: https://doi.org/10.1016/j.jclinepi.2016.02.016
19. Chaimani A, Higgins JP, Mavridis D, et al. Graphical tools for network meta-analysis in STATA. *PLoS One* 2013;8(10):e76654. doi: 10.1371/journal.pone.0076654 [published Online First: 2013/10/08]

20. Mavridis D, Welton NJ, Sutton A, et al. A selection model for accounting for publication bias in a full network meta-analysis. *Stat Med* 2014;33(30):5399-412. doi: 10.1002/sim.6321 [published Online First: 2014/10/16]
21. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLOS Medicine* 2020;17(4):e1003082. doi: 10.1371/journal.pmed.1003082
22. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ : British Medical Journal* 2014;349:g5630. doi: 10.1136/bmj.g5630
23. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162(11):777-84. doi: 10.7326/M14-2385
24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
25. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research* 2014;17(2):157-73. doi: 10.1016/j.jval.2014.01.004 [published Online First: 2014/03/19]
26. Mills EJ, Ioannidis JPA, Thorlund K, et al. How to Use an Article Reporting a Multiple Treatment Comparison Meta-analysis. *JAMA* 2012;308(12):1246-53. doi: 10.1001/2012.jama.11228