

Evidence synthesis for decision making: making best use of relevant evidence

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Evidence synthesis in HTAS Most HTAs will involve a meta-analysis of studies comparing the interventions of interest for the decision problem Typically randomised controlled trials considered Relative effects pooled across studies Often multiple treatments are of interest Network meta-analysis (NMA) is an extension of standard meta-analysis to incorporate direct and indirect evidence on multiple treatment comparisons in a coherent way Increases precision and robustness of results as multiple sources of evidence are used to estimate the same relative treatment effect. Often most directly relevant evidence is sparse, leading to imprecise estimation of key parameters













PRIORS DISTRIBUTIONS

Typically vague for relative treatment effect parameters

- Informative prior distributions for these parameters are rarely used and would require strong justification. $M = N(0, 100^2)$ h > 1 = (d = 0)

Log-odds ratios can take any value

 $d_k \sim N(0, 100^2) \quad k > 1 \quad (d_1 = 0)$

 $\mu_i \sim N(0, 100^2)$ i = 1, ..., ns

Between studies heterogeneity often given a wide (scale-dependent) Uniform prior

- eg Uniform(0,5) or Uniform(0,2)
- Specification of vague priors on variance components is complex area

Bayesian approach allows incorporation of external evidence on heterogeneity, based on empirical evidence

- Higgins and Whitehead (1996) https://pubmed.ncbi.nlm.nih.gov/8981683/
- Turner et al. (2012, 2015) <u>https://doi.org/10.1093/ije/dys041</u>, <u>http://dx.doi.org/10.1002/sim.6381</u>
 Rhodes et al. (2014) <u>https://doi.org/10.1016/j.jclinepi.2014.08.012</u>
- Frequentist estimation is also possible







Making best use of evidence

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BORROWING INFORMATION ACROSS DOSES

- Intervention (treatment) is defined as a drug/agent given at a particular dose
- Whilst interventions at unlicensed doses may not strictly be of interest for decision-making, studies that compare different doses can provide additional, **relevant**, evidence for synthesis.
- Use a synthesis model that "borrows" information across doses
 - requires data on different doses of a drug of interest to be available
 - Combine with NMA to compare different agents, given at different doses

Model-based NMA (MBNMA)



 Model-based meta-analysis (MBMA) used in drug development to inform decisionmaking and future trial designs

- uses plausible physiological time-course or dose-response models
- Tends to be arm-based and **<u>not</u>** respect randomisation
- Model-based NMA combines MBMA with NMA
 - works at the level of the relative effects so respects randomization
 - allows estimation and prediction of treatment effects at multiple time points or doses
 - Allows assessment of evidence consistency across comparisons
- R packages available on CRAN:
 - MBNMAtime <u>https://cran.r-project.org/package=MBNMAtime</u>
 - MBNMAdose <u>https://cran.r-project.org/package=MBNMAdose</u>

Pedder et al. (2019) <u>https://doi.org/10.1002/jrsm.1351</u> Mawdsley et al (2016) <u>https://doi.org/10.1002/psp4.12091</u>

Dose-response NMA



- Information sharing via "model-based" approach that functionally incorporates a dose-response relationship
 - Bayesian framework
- Dose-response function fitted to study-specific relative effects
 - Preserves within-study randomisation
 - Model fit compared to "split" NMA (where possible)
 - Assess consistency assumption
- Uses additional evidence from studies (or arms) of doses not of primary interest
 - borrow strength through consistency relationship *and* dose-response relationship

Mawdsley et al (2016) https://doi.org/10.1002/psp4.12091 16

















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Comments

- Sharing of information via dose-response relationship can:
 - improve precision
- Uses relevant evidence on the interventions of interest
 - If there is a dose-response relationship, then evidence on an agent at one dose provides evidence that is relevant for other doses
- Availability of evidence at different doses is key
 - Phase II and non-licensed dose studies should be included in systematic review
 - Will increase burden of data extraction, but can strengthen inferences
- It may be possible to share dose-response parameters from different populations based on understanding of pharmacometrics
 - E.g. adults to children
- Can be useful to link disconnected networks of evidence





Does it work?

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 It can work well when the dose-response function is well estimated in the disconnected network components

- Needs doses close enough to Placebo, along the curvature and towards the asymptote of the Emax function
- Typically unable to check assumptions since no data
 - See Pedder et al. (2021) for an example where a large network was artificially disconnected https://doi.org/10.1177/0272989x20983315
- Ongoing work to explore different scenarios.

Class models



- Sometimes there are many treatment options, but treatments fall into classes
- Treatments in the same class are assumed to have similar (but not identical!) effects
 - Eg if one SSRI works for depression, the others are likely to work too, to a similar extent
- A class model borrows strength across treatments in the same class
 - Effects of treatments in a class are distributed around a common class mean with a within-class variance
 - Treatment effects are shrunk to class mean (like a random effects meta-analysis)
- Estimates are more precise
- The original treatment definitions are retained
- Can help connect networks when disconnected treatment(s) are within a class







Discussion



ADVANTAGES

• Models with functional relationships or borrowing of information across studies (e.g. by class) rely on correct specification of the dose-response function or borrowing conditions

- Expert knowledge is required to assess suitability
- Estimates more precise and allow for better decisions

 Subject to model assumptions
- Need to have a priori clinical plausibility as usually very few data/class elements to check assumptions
 - Especially useful when data sparse or when certain combinations are missing
- But needs to be convincing
 - Expert opinion and biological plausibility will be crucial
- Can be used to connect networks
 - Assumptions may be more plausible than other methods to connect networks Thom et al. (2022) <u>https://doi.org/10.1177/0272989X221097081</u>

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Discussion

DISADVANTAGES

- Requires sufficient data
 - Doses per treatment
 - Treatments per class
- May not work when evidence is too sparse
 - When few doses available, dose-response function parameters estimates will be too uncertain
 - Requires sufficient "spread" of doses across dose-response function
- Can use additional information on dose-response function from early phase dose-finding studies
 - To specify functional form?
 - To inform prior distributions on some parameters?
- Class assumptions can be combined with dose-response modelling
 - Class assumptions on treatment effects or dose-response parameters
- Additional data searching and extraction burden for all doses of relevant drugs: When is it worth it?

