Using dose-response information to reduce uncertainty in health technology assessment

Sofia Dias, PhD

Professor of Health Technology Assessment
Centre for Reviews and Dissemination
University of York, York, UK

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@hugopedder

Conflicts of interest

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Evidence synthesis in HTA

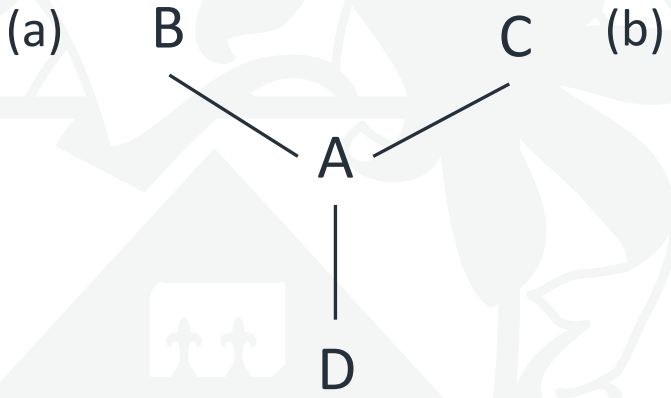
- Most HTAs will involve a meta-analysis of studies comparing the interventions of interest for the decision problem
- Often **multiple treatments** are of interest
- Network meta-analysis (NMA) is an extension of standard meta-analysis to incorporate direct and indirect evidence on multiple treatment comparisons in a coherent way
  - NMA methods now well established and commonly used for treatment reimbursement decisions
  - Respects randomisation
  - Increases precision and robustness of results as multiple sources of evidence are used to estimate the same relative treatment effect.

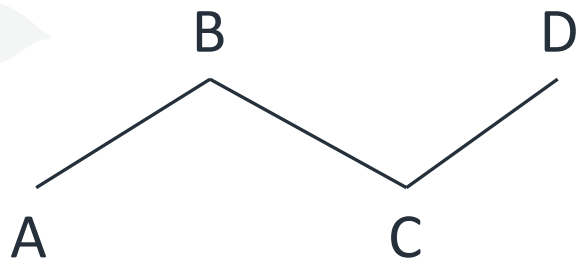
HTA: Health Technology Assessment

What is Network Meta-analysis?

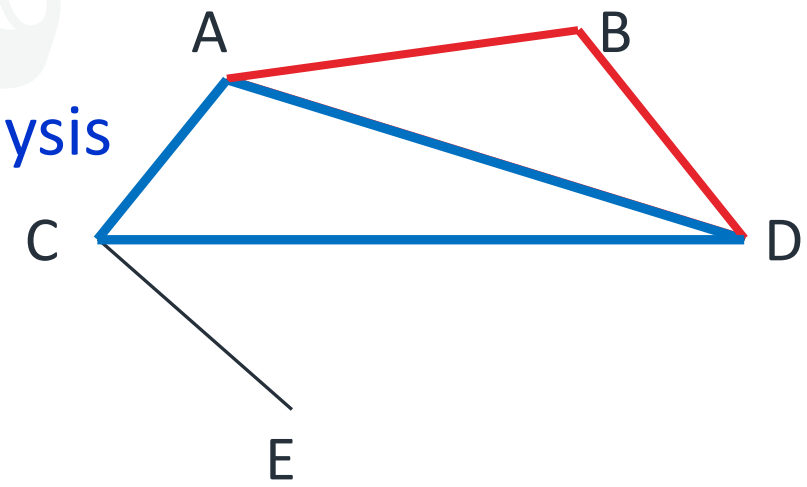
Pair-wise Meta-Analysis

Indirect Comparisons





Network meta-analysis



- The existence of "evidence loops" means that there is both DIRECT evidence and INDIRECT evidence on the same contrast
- More data → estimates more precise, more robust (less sensitive to any one source of data)
- Possible to estimate additional parameters.

Making best use of evidence

BASIC PRINCIPLE TO INCREASE PRECISION

- Evidence synthesis must use all relevant evidence
- Avoid arbitrary selection of studies or outcomes
- Assumptions transparent and acceptable to clinical community
- Often only drugs at the licensed dose can be recommended
  - Intervention (treatment) is defined as a drug **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
  - But this requires data on different doses of a drug of interest to be extracted

Model-based NMA (MBNMA)

- Model-based meta-analysis (MBMA) used in drug development to inform decision-making and future trial designs
  - uses plausible physiological time-course or dose-response models
  - Tends to be arm-based and **not** 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 https://cran.r-project.org/package=MBNMAtime
  - MBNMAdose https://cran.r-project.org/package=MBNMAdose

NMA: network meta-analysis

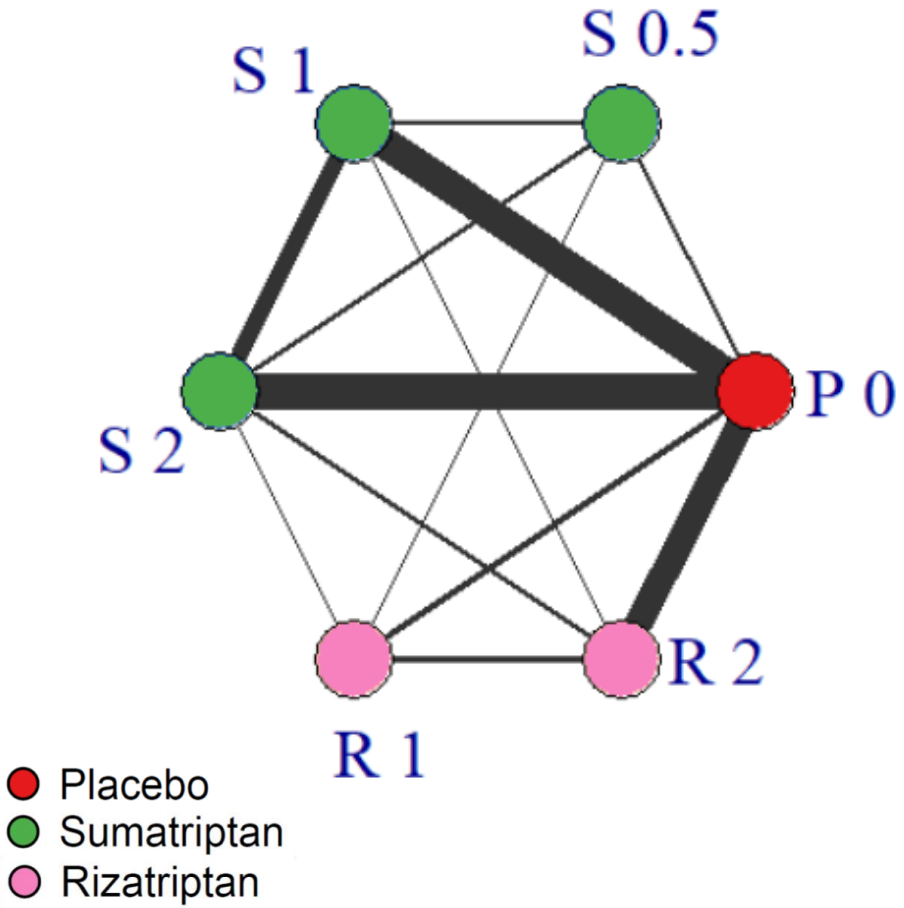
Pedder et al. (2019) https://doi.org/10.1002/jrsm.1351
Mawdsley et al (2016) https://doi.org/10.1002/psp4.12091

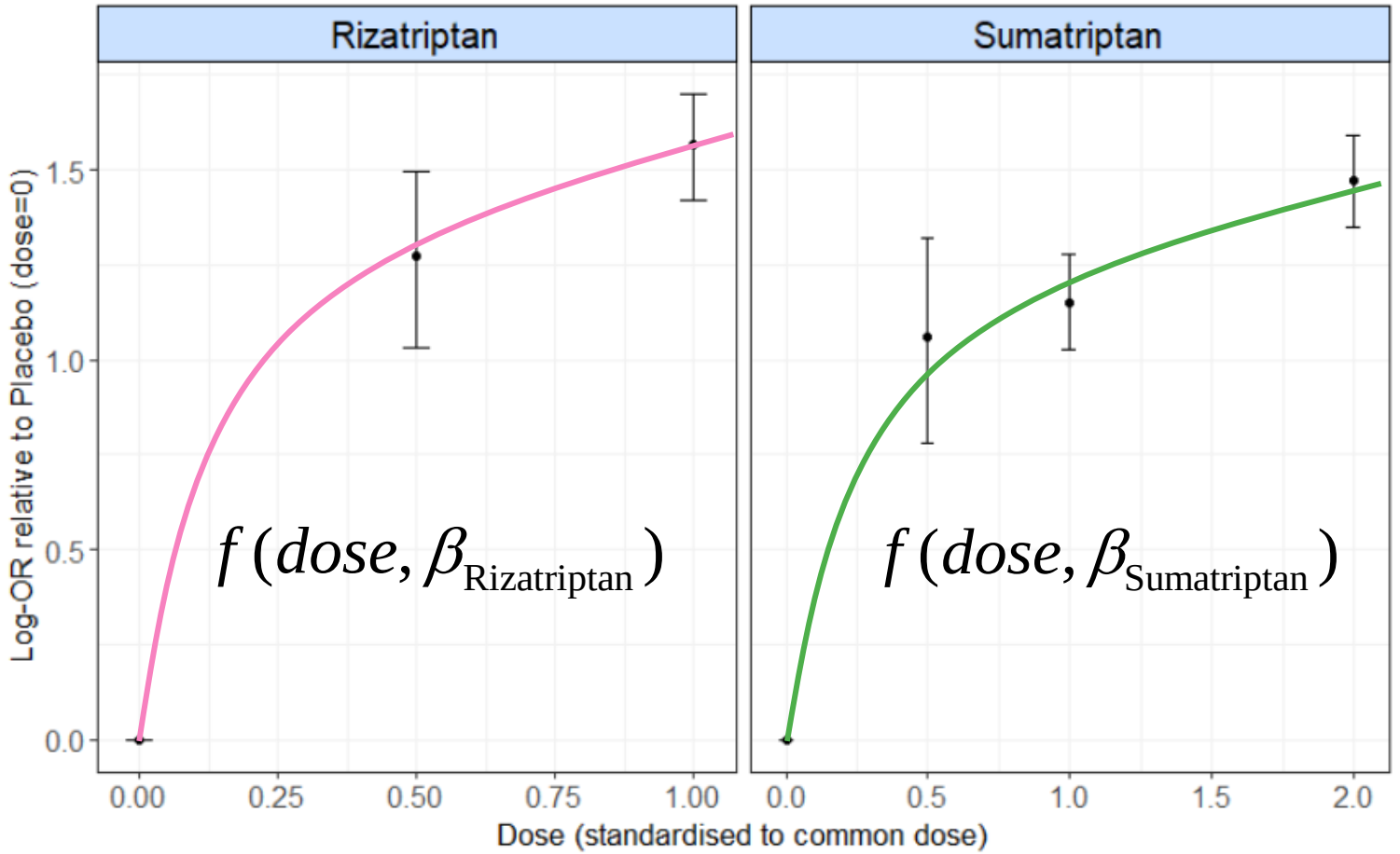
Dose-response NMA

- 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)
  - Consistency assumption can be assessed
- Uses additional evidence from studies (or arms) of doses not of primary interest
  - borrow strength through consistency relationship and dose-response relationship

NMA: network meta-analysis

Fitting dose-response relationship

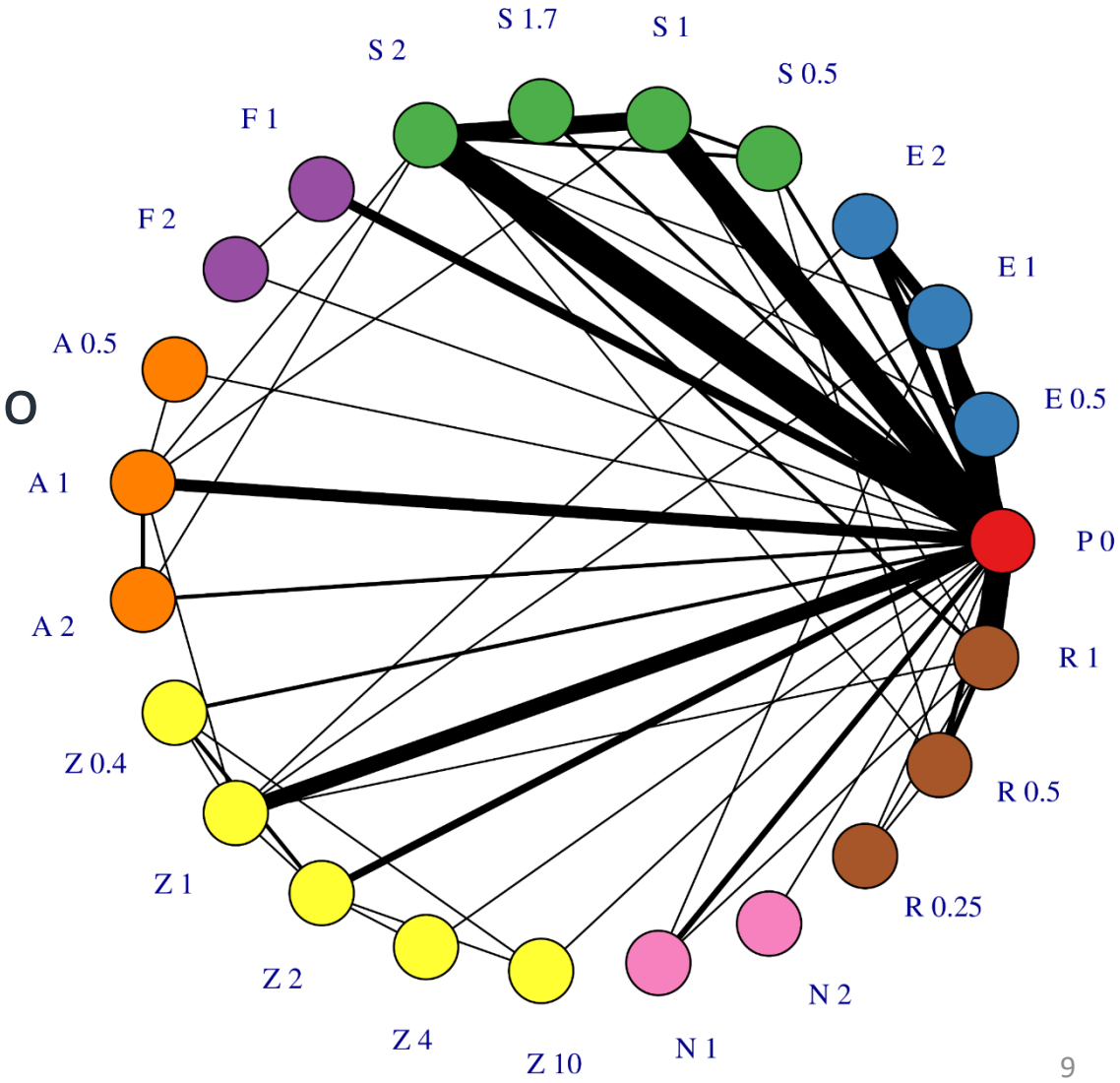




- Requires sufficient doses of an agent to be able to reliably estimate the dose-response function

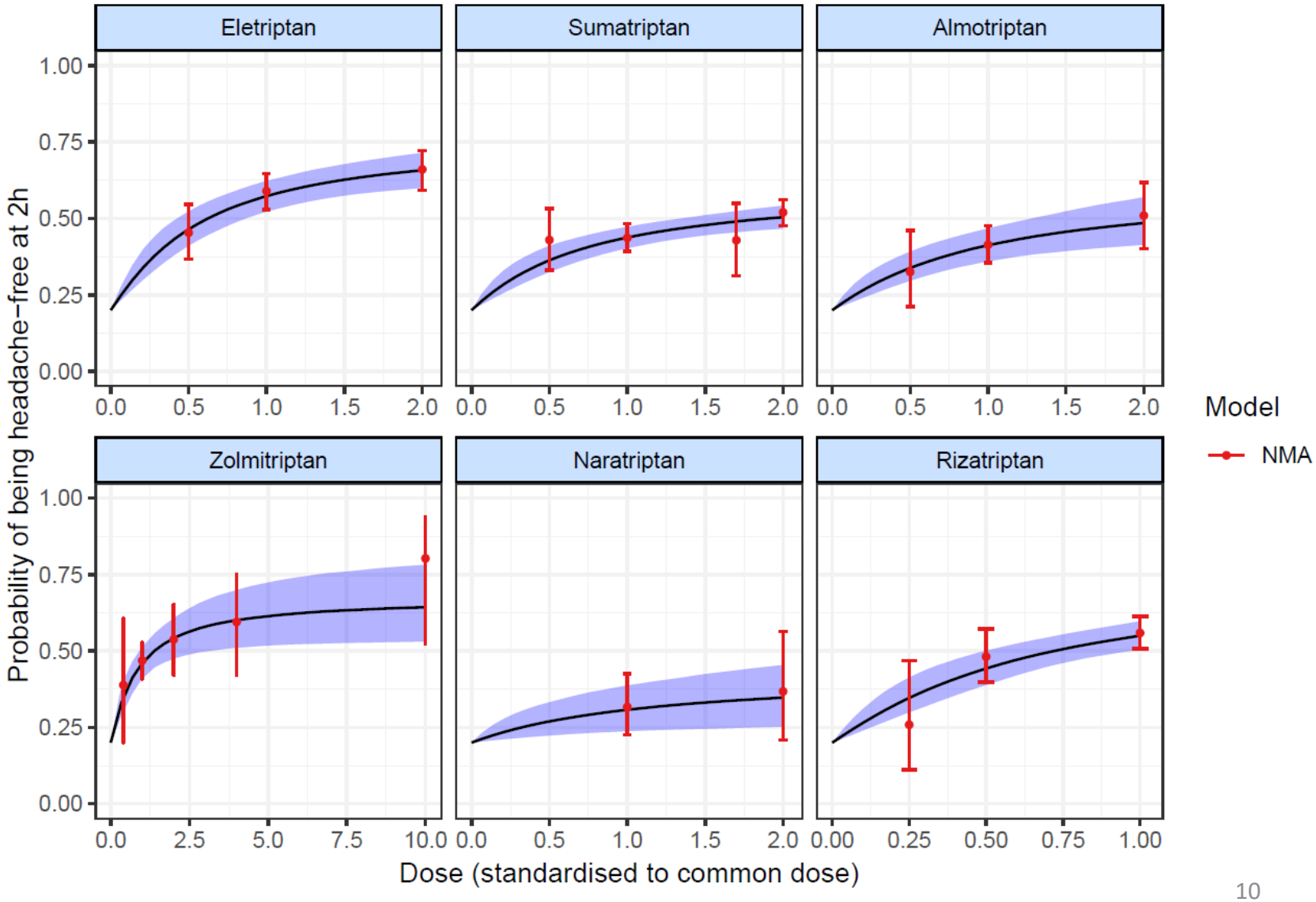
Illustrative dataset: Triptans in migraine

- 70 studies of 8 interventions compared at multiple doses
- Outcome: % patients with pain relief at 2h
- Treatment effect modelled as log-Odds Ratio
- Placebo treated as **zero dose** of all agents



Triptans: connected network

- Fitting structural dose-response function increases precision versus standard “split” NMA…
  - assess fit of dose-response model by comparing to split NMA results
- Assumes that dose-response relationship is correctly specified
  - Here used **Emax function** but could use others

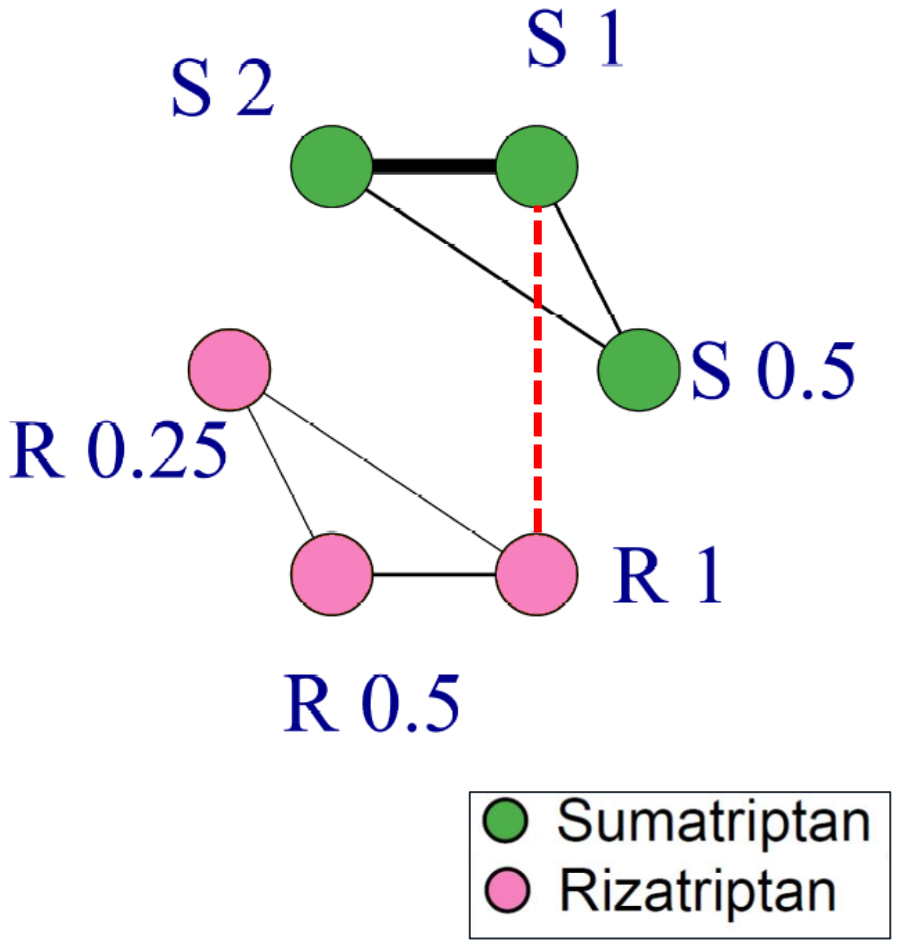


NMA: network meta-analysis

Joining the dots

CONNECTING NETWORKS

- Comparisons between disconnected treatments not possible without making strong assumptions.
- Dose-response MBNMA can be used to connect networks using the assumed dose-response relationship
  - Estimates functional relationships for dose-response models (eg Emax model)
- Allows interpolation to predict outcomes for doses not in the original trials

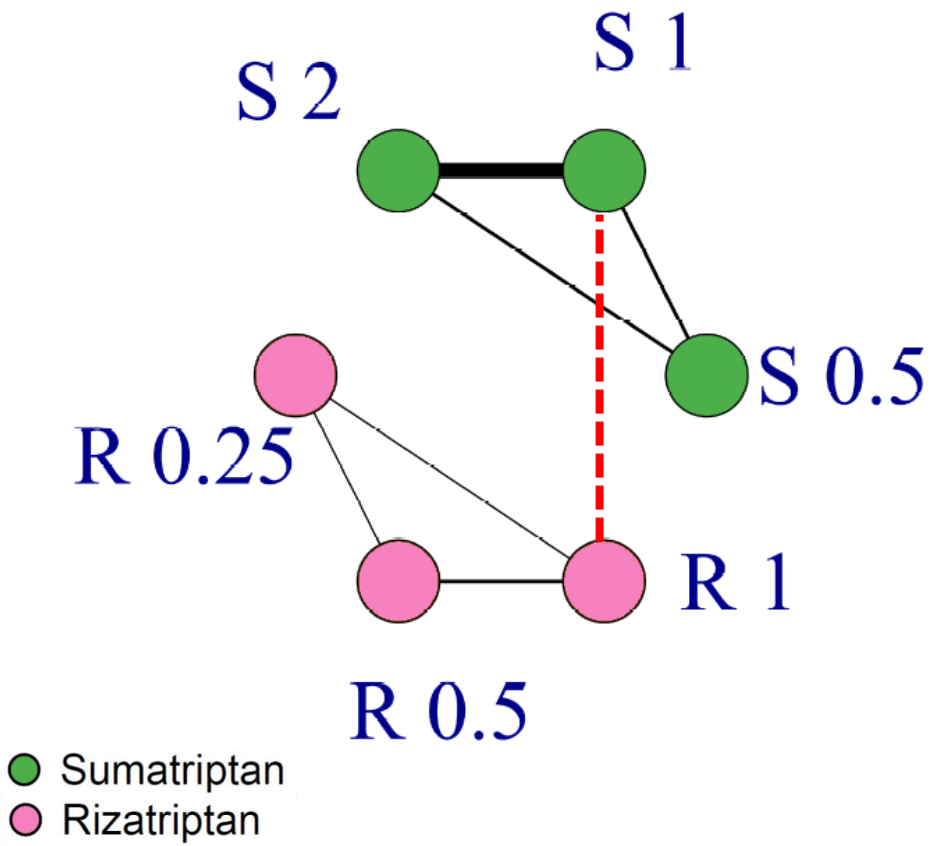


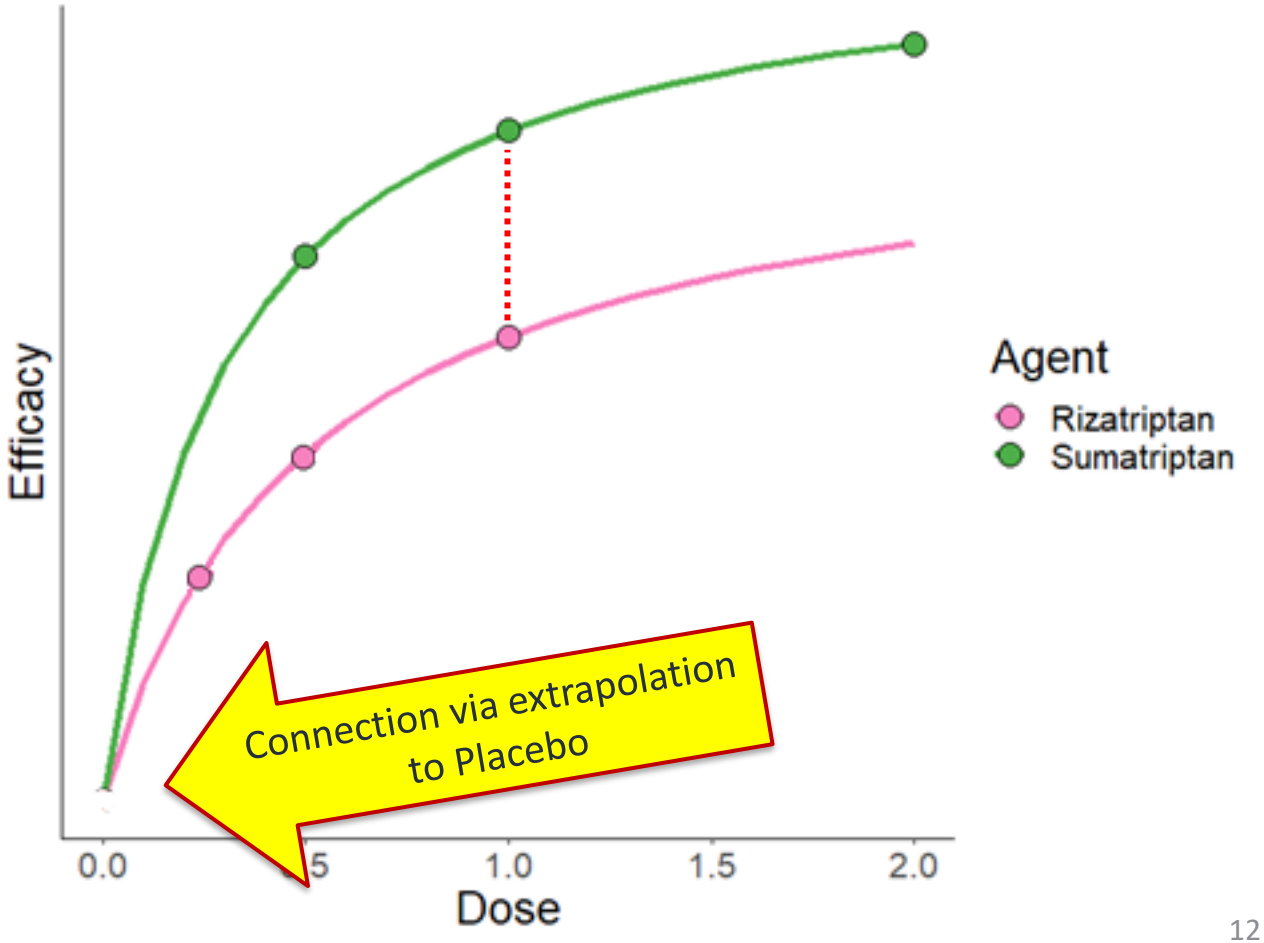
MBNMA: model-based network meta-analysis

Pedder et al. (2021) https://doi.org/10.1177/0272989X20983315

Joining the dots via Placebo

- Interest in comparing licensed doses of Sumatriptan and Rizatriptan: S1 vs R1
- Disconnected network

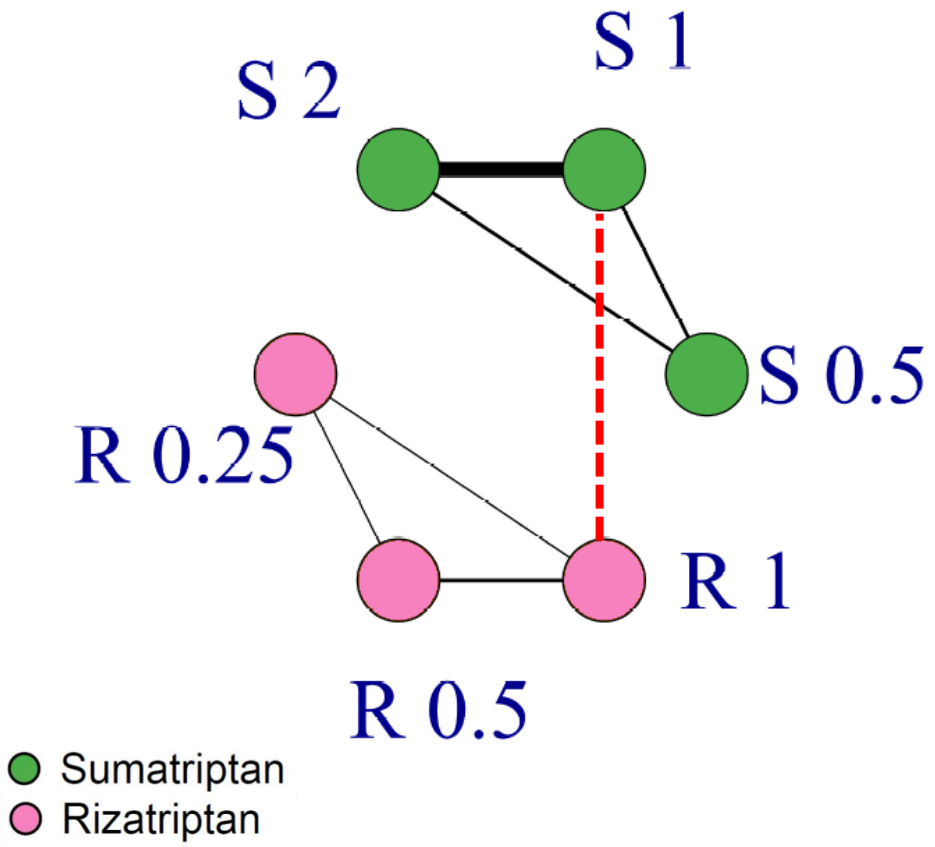


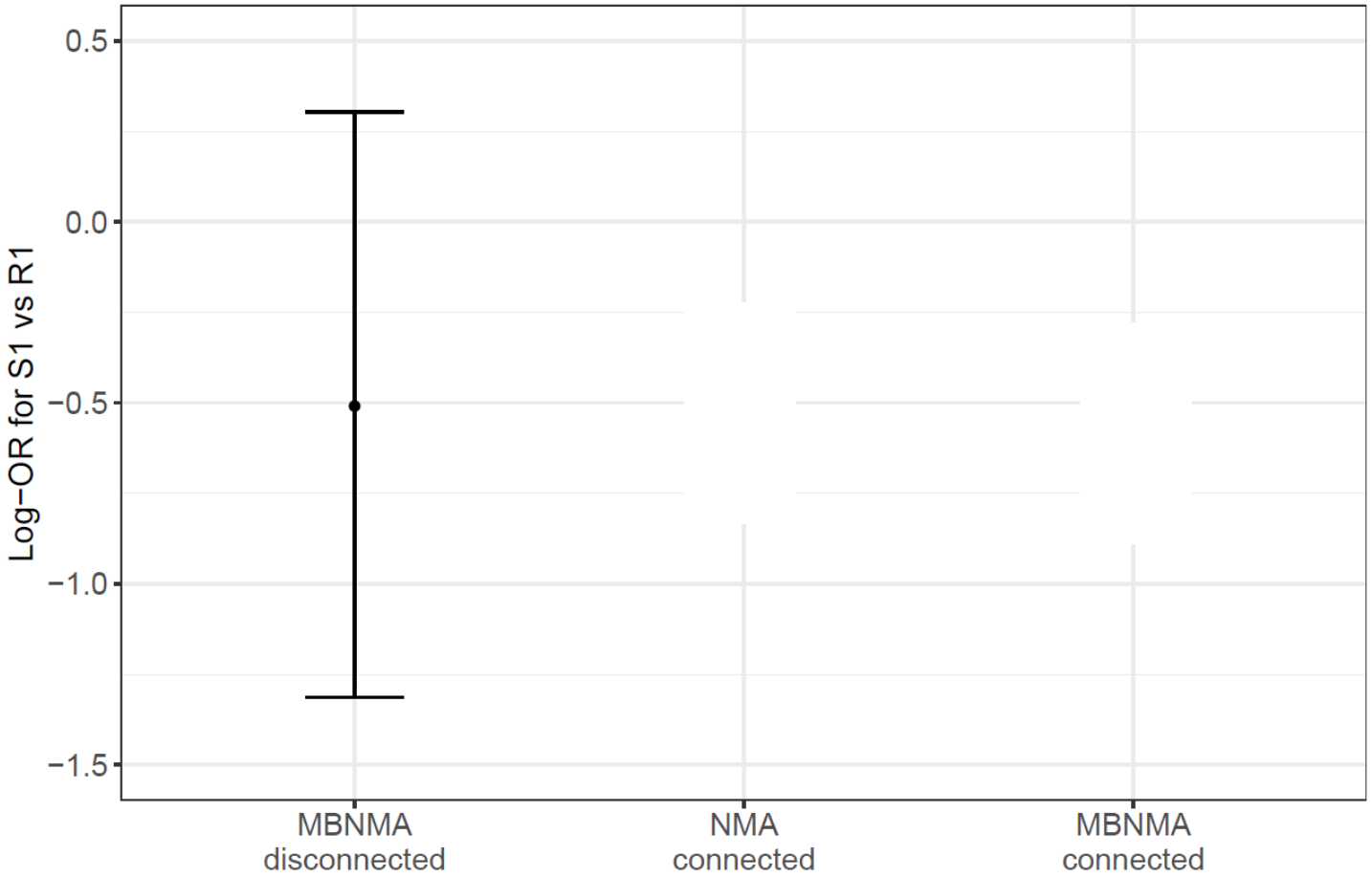


Does it work?

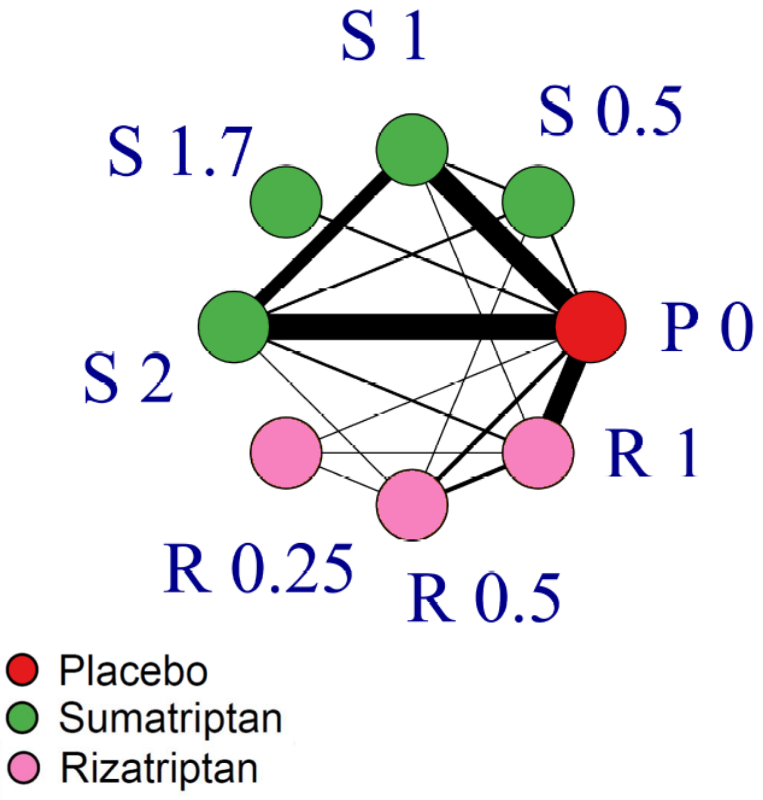
- It can work well when the dose-response function is well estimated in the disconnected network components
  - Needs doses close enough to Placebo, along the curvature and towards the asymptote of the Emax function
- Check assumptions by
  - Comparing MBNMA estimates from disconnected network with NMA estimates from the "full network" connected by adding studies/treatments back into the data set.
  - Also compared full network NMA results to MBNMA results using full dataset

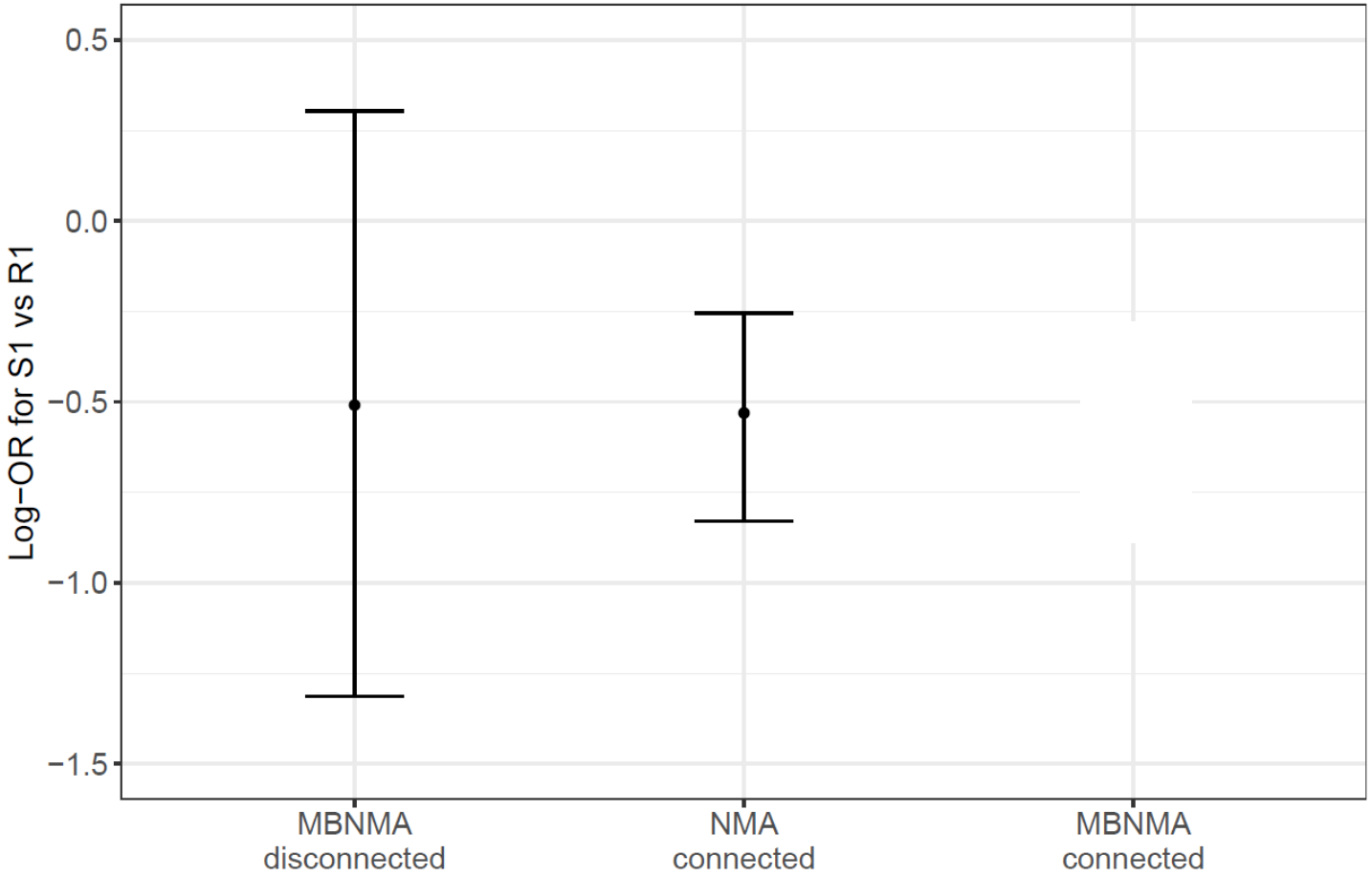
Joining the dots via Placebo: checks





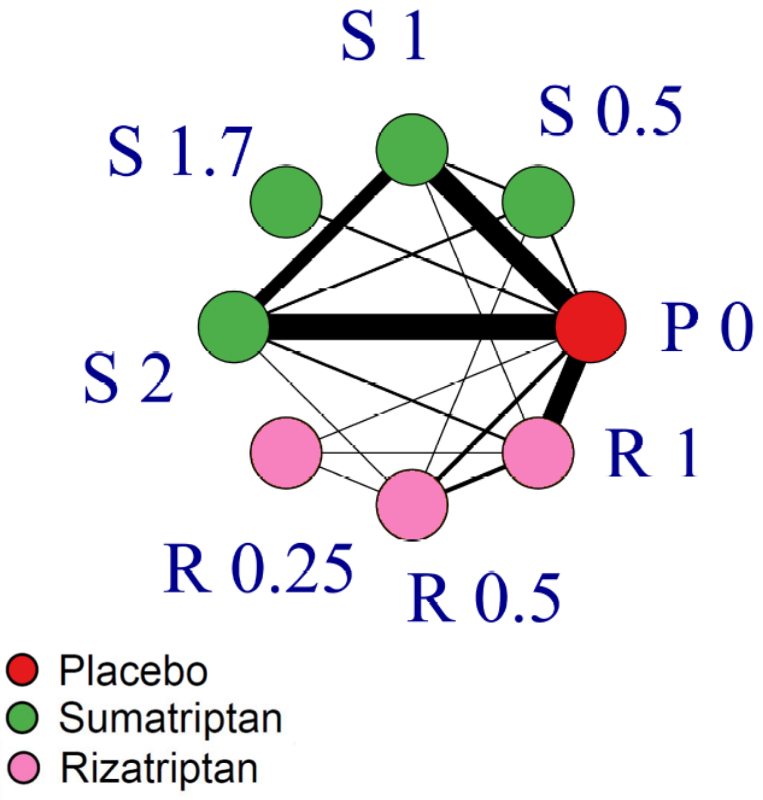
Joining the dots via Placebo: adding in existing evidence

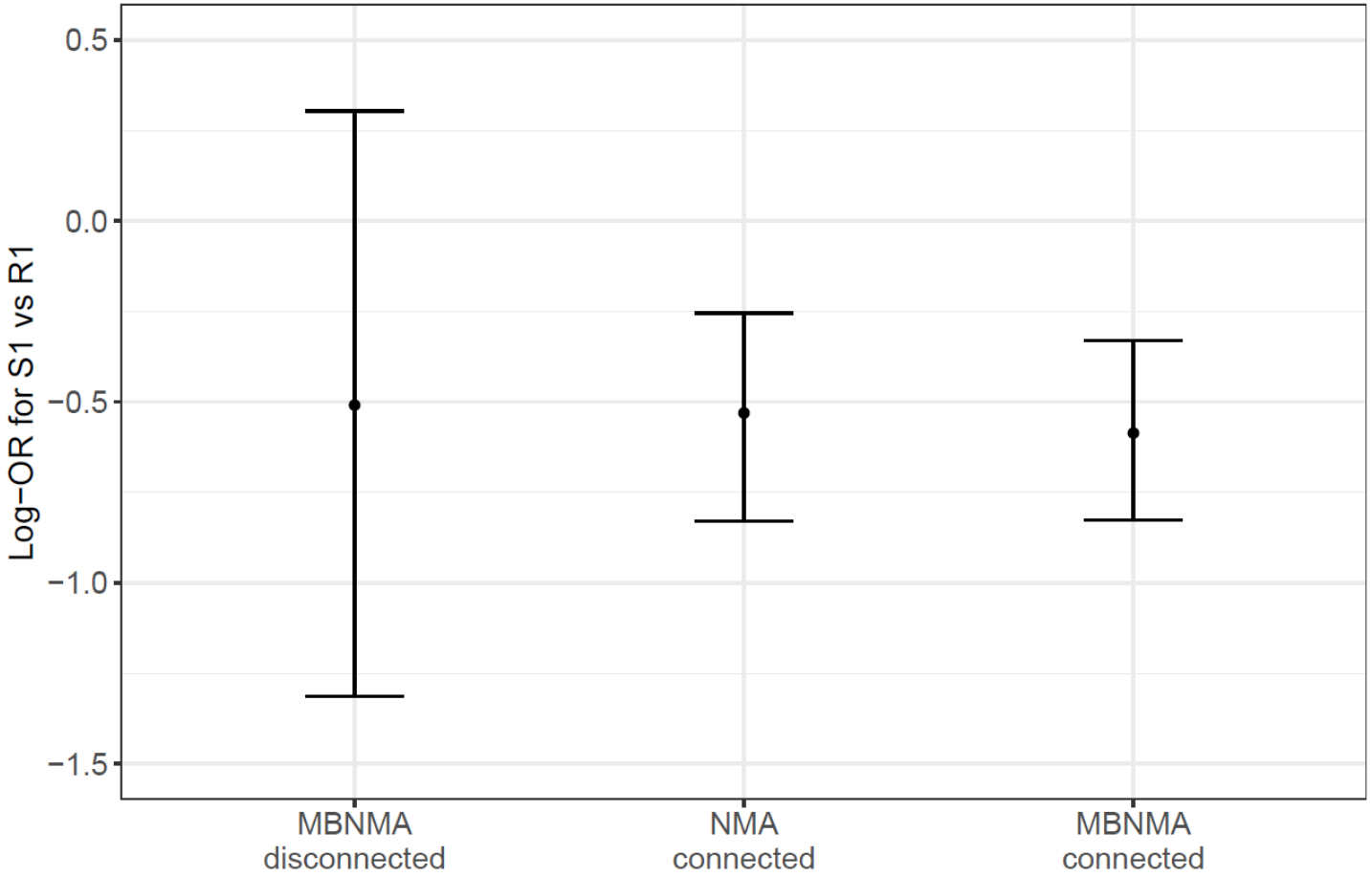




- Added 15 studies to complete the network

Joining the dots via Placebo: adding in existing evidence





- Added 15 studies to complete the network

MBNMAdose

R package

Version 0.4.2 recently released on CRAN

https://cran.r-project.org/package=MBNMAdose

MBNMAdose

https://cran.r-project.org/package=MBNMAdose

- Fits Bayesian dose-response model-based network meta-analysis (MBNMA) that incorporate multiple doses within an agent by modelling different dose-response functions
- Can check consistency in data
- Allows for
  - class effects (sharing of parameters within a class)
  - Including study-level covariates (meta-regression)
- Produces
  - summary tables, treatment ranks and plots of key parameters
  - league tables for comparing results from two models e.g. MBNMA vs NMA
  - Outcome predictions at different doses
- Includes several example networks, including the triptans network

MBNMAdose: Workflow

Functions follow a clear pattern of use:

1. Load data into the correct format using `mbnma.network()` and explore potential relationships (plots can be generated to explore relationships)
2. Perform a dose-response MBNMA using `mbnma.run()`
   - Modelling of effect modifying covariates is possibly
3. Test for consistency at the treatment-level using functions like `nma.nodesplit()` and `nma.run()`
4. Examine model outputs, such as relative effects, forest plots and treatment rankings
5. Use model to predict responses using `predict()`

At each of these stages informative plots can be generated to help understand the data and make decisions regarding model fitting.

MBNMAdose: functions

Various functional forms are implemented

- Log-linear `dloglin()`
- Exponential `dexp()`
- Emax `demax()`
- Polynomial (e.g. linear) `dpoly()`
- Fractional polynomial `dfpoly()`
- Spline functions `dspline()`
- Non-parametric monotonic function (Owen et al. 2015) `dnonparam()`
  - Direction can be specified as "increasing" or "decreasing".
- User-defined function `duser()`
  - Any function that can be explicitly defined by the user
- Agent-specific functions `dmulti()`
  - separate dose-response function fitted to each agent in the network

Interpretation of dose-response parameter estimates will depend on the dose-response function used.

https://cran.r-project.org/web/packages/MBNMAdose/vignettes/runmbnmadose-2.html

Owen et al (2015) https://doi.org/10.1016/j.jval.2014.10.006

Conclusions

- Sharing of information via dose-response relationship can:
  - improve precision
  - link disconnected networks of evidence
- 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
- Model also relevant for non-drug interventions
  - E.g. physical activity: dose is exercise intensity

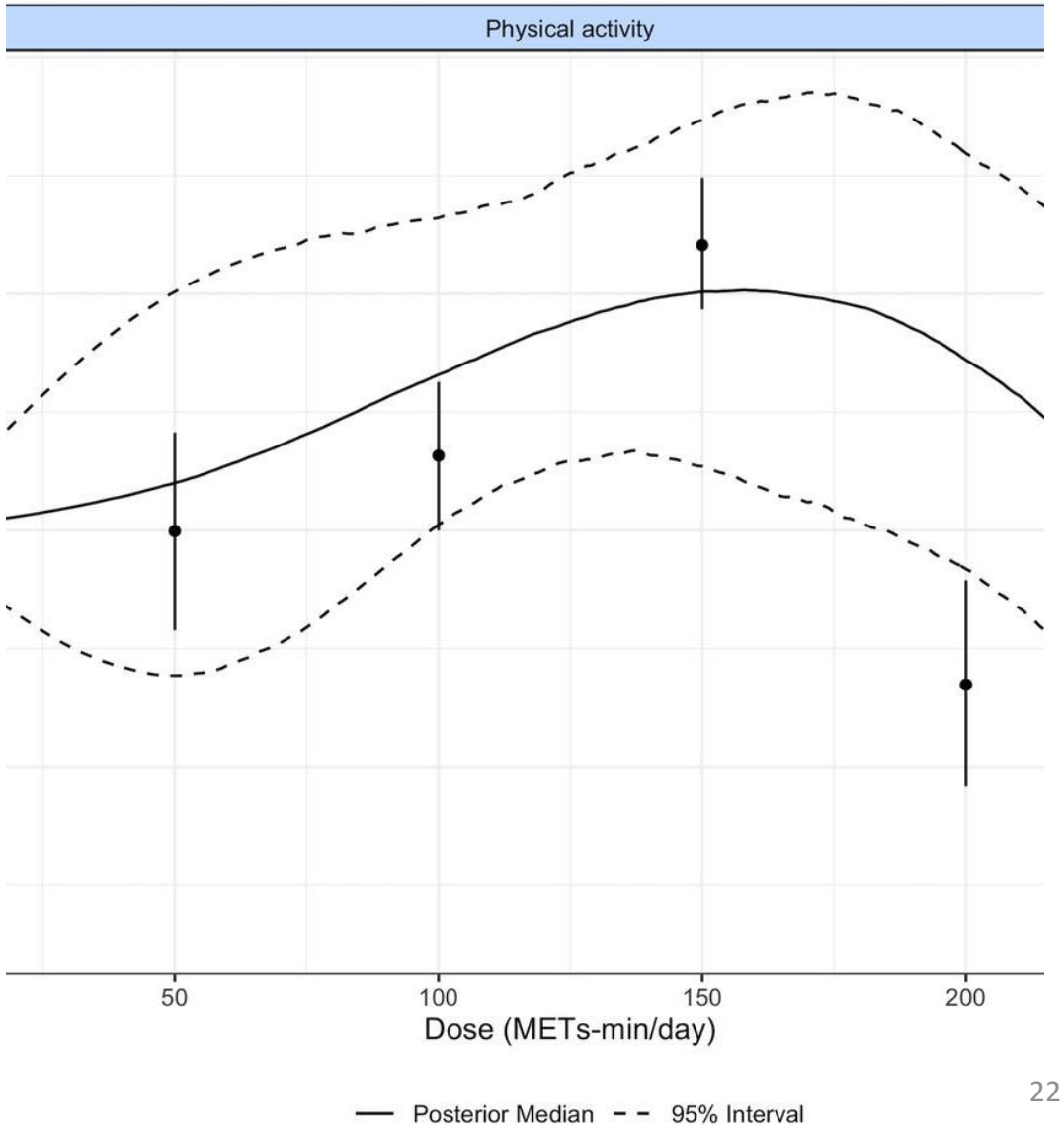
Optimal dose and type of physical activity to improve functional capacity and minimise adverse events in acutely hospitalised older adults (Gallardo-Gómez et al, 2023)

British Journal of Sports Medicine

http://dx.doi.org/10.1136/bjsports-2022-106409

Figure 3 Dose-response relationship between physical activity dosage and functional capacity.

- Point estimates and credible intervals from a ‘split’ network meta-analysis in which each dose of physical activity is treated as an independent intervention).



Discussion

- Relies on correct specification of the dose-response function
  - Expert knowledge is required to assess suitability
- Estimates more precise and allow for better decisions
  - Subject to model assumptions
- Can use information on dose-response function from early phase dose-finding studies
  - To specify functional form
  - To inform prior distributions on some parameters
- Can be used to connect networks
  - Assumptions may be more reasonable than those required for e.g. unanchored population adjustment indirect comparisons (Phillippo et al 2016)
- May not work when evidence is sparse
  - When few doses available, dose-response function parameters estimates will be too uncertain
  - Requires sufficient "spread" of doses across dose-response function
- Additional data searching and extraction burden for all doses of relevant drugs: **When is it worth it?**

Phillippo et al (2016) https://www.sheffield.ac.uk/nice-dsu/tsds/population-adjusted

Thank you

@sdias_stats

sofia.dias@york.ac.uk