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

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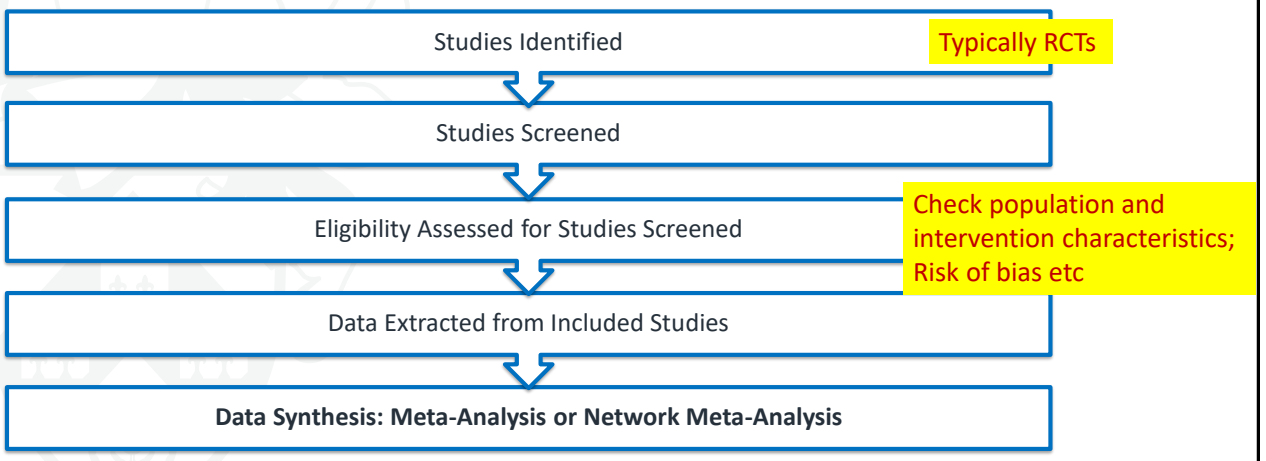
Context

- Health technology assessment (HTA)
  "…a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle. The purpose is to inform decision-making in order to promote an equitable, efficient, and high-quality health system."
  Health Technology Assessment International http://www.htai.org/index.php?id=428
- In the UK
  - Manufacturer submissions to NICE for reimbursement decisions on new technologies
  - NICE writes guidelines for managing different conditions
  - Academic or other agency led projects…
- Usually involve a systematic review to collect and synthesise the relevant evidence
  - Typically a meta-analysis will be done
- Results of the evidence synthesis used in a decision model
  - Consider costs and benefits of alternative interventions
- New methods or extensions to current methods appear all the time
  - NICE Decision support Unit: critical review of existing and emerging methods for evidence synthesis on clinical effectiveness for decision-making in HTA, April 2020
    https://www.sheffield.ac.uk/nice-dsu/methods-development/chte2020-sources-and-synthesis-evidence

NICE: National Institute for Health and Care Excellence

Evidence selection



RCT: randomised controlled trial

3

Evidence synthesis in HTA

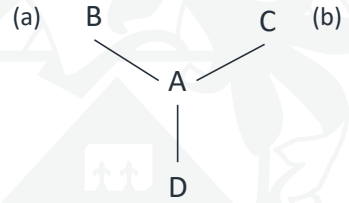
- Most HTAs will involve a meta-analysis of studies comparing the interventions of interest for the decision problem
  - Typically randomised controlled trials considered
  - Relative effects pooled across studies
- Often **multiple treatments** are of interest
- Network meta-analysis (NMA) is an extension 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

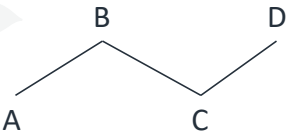
4

What is Network Meta-analysis?

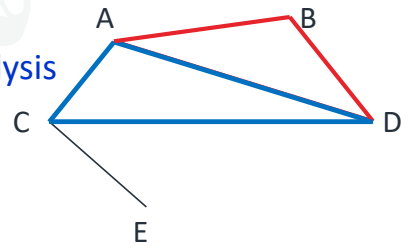
Pair-wise Meta-Analysis

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.

5

Basic & Functional parameters

1. Four treatments 1, 2, 3, and 4
2. Take treatment 1 as the reference treatment
3. Then the treatment effects (log odds ratios) of 2, 3, and 4 relative to 1 are the basic parameters
4. Give them priors: $d_{12}, d_{13}, d_{14} \sim N(0,100^2)$

Remaining contrasts are functional parameters

$$d_{23} = d_{13} - d_{12}; \quad d_{24} = d_{14} - d_{12}; \quad d_{34} = d_{14} - d_{13}$$

- Consistency equations define these relationships: $d_{ck} = d_{1k} - d_{1c}$
- Consistency follows from the decision to synthesise the data and confidence in study selection criteria
  - Can/should be statistically checked when possible

Lu & Ades (2004) https://doi.org/10.1002/sim.1875

6

Inconsistencies

In a pre-specified population…

- The **true** treatment effects **must be** consistent
- But there may be inconsistencies in the **EVIDENCE**

- Check for conflict across different evidence sources
- Different methods proposed for
  - Global checks
  - Local checks
  - Active area of research

Dias et al. https://doi.org/10.1177/0272989X12455847

Notation for the Model: binary data

- Define

$r_{i,k}$ – the number of events in arm k of trial i
$n_{i,k}$ – the number of patients in arm k of trial i
$p_{i,k}$ – the probability of an event in arm k of trial i
$t_{i,k}$ – the treatment given in arm k of trial i

$k = 1,2,3, \ldots, na_i$
$i = 1, 2, \ldots, ns$

na_i=number of arms in study i
ns=number of studies
nt=number of treatments in the network

Random Effects NMA Model

For treatment in arm k in study i

Likelihood: $r_{i,k} \sim Binomial(p_{i,k}, n_{i,k})$

Probability of an event in arm *k* of study *i*

Model:

$$\text{logit}(p_{i,k}) = \begin{cases} \mu_i & k = 1 \\ \mu_i + \delta_{i,k} & k = 2,\ldots,na_i \end{cases}$$

log-odds of event in arm 1 of study *i* (note treatment in that arm)

log-odds ratio for treatment in arm *k* of study *i* compared to treatment in arm 1 of study *i*

$$\delta_{i,k} \sim N\left(d_{t_{i,k}} - d_{t_{i,1}}, \sigma^2\right)$$

Consistency equation, ensures correct comparison made

Between study variance (heterogeneity): Assumed **common** across treatment comparisons

μ_i is considered a nuisance parameter, not of interest
d_k is the log-odds ratio for treatment *k* compared with treatment 1
Set d_1 =0 (log-odds ratio for treatment 1 compared with itself)

9

Bayesian framework

PRIORS DISTRIBUTIONS

- Typically vague for relative treatment effect parameters
  - Informative prior distributions for these parameters are rarely used and would require strong justification.
  - Log-odds ratios can take any value

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

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

- 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) https://doi.org/10.1093/ije/dys041 , http://dx.doi.org/10.1002/sim.6381
  - Rhodes et al. (2014) https://doi.org/10.1016/j.jclinepi.2014.08.012
- Frequentist estimation is also possible

10

Generic NMA RE model

THE UNDERLYING MODEL IS

$$\theta_{ik} = \mu_i + \delta_{ik}$$

- θ_{ik}: continuous measure of the treatment effect
- μ_i: effect of baseline treatment in trial i
- δ_{ik}: trial-specific treatment effect of treatment in arm k relative to the treatment in arm 1

Priors

$$\sigma \sim U(0,5)$$

$$d_{1k} \sim N(0,100^2) \quad k > 1$$

$$\mu_i \sim N(0,100^2) \quad i = 1,\ldots,N$$

Set $\delta_{i1} = 0$

$$\delta_{ik} \sim N\left(d_{t_{i1},t_{ik}}, \sigma^2\right), k > 1$$

$$d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$$

RE: random effects

Making best use of evidence

RELEVANT EVIDENCE

- Often restrict dataset to only include treatments of interest
- Leads to sparse networks
  - Few comparisons (no indirect evidence)
  - Few studies per comparison
- Wastes evidence that has been generated and could provide more meaningful inferences
  - Particularly important when quantification of relative treatment effects and associated uncertainty is used for decision-making

Making best use of evidence

BASIC PRINCIPLES TO INCREASE PRECISION

- Evidence synthesis must use all relevant evidence
- Avoid arbitrary selection of studies or outcomes
- Assumptions must be transparent and acceptable to all stakeholders
  - Often requires clinical opinion to validate
- Use "all relevant evidence" which may include
  - Different doses (but only licensed dose can be recommended)
  - Other (related) outcomes
  - Other (related) populations (children vs adults)
  - Different study types (observational as well as RCTs??)

13

Making best use of evidence

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

14

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

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

15

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

Generic NMA RE model

Recap

THE UNDERLYING MODEL IS

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- θ_{ik}: continuous measure of the treatment effect
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Priors

$$\sigma \sim U(0,5)$$

$$d_{1k} \sim N(0,100^2) \quad k>1$$

$$\mu_i \sim N(0,100^2) \quad i=1,\ldots,N$$

Set $\delta_{i1} = 0$

$$\delta_{ik} \sim N\left(d_{t_{i1},t_{ik}}, \sigma^2\right), k>1$$

$$d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$$

RE: random effects

MBNMA dose-response model

$$\theta_{ik} = \mu_i + \delta_{ik}$$

- θ_{ik}: continuous measure of the treatment effect
- μ_i: effect of baseline treatment in trial i
- δ_{ik}: trial-specific treatment effect of treatment in arm k relative to the treatment in arm 1

treatement $t_{i,k} = \left(x_{i,k}, a_{i,k}\right)$

defined by dose $x_{i,k}$ of agent $a_{i,k}$

$$\delta_{i,k} \sim N\left(d_{(x_{i,1},a_{i,1}),(x_{i,k},a_{i,k})}, \sigma^2\right)$$

We define the relative effect of treatment (x_k, a_k) relative to reference (x_1, a_1) via a dose-response curve:

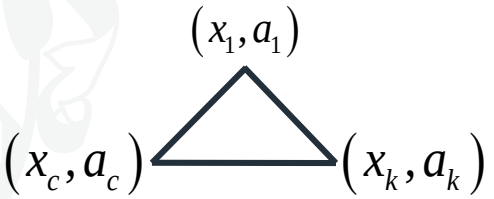
$$d_{(x_1,a_1),(x_k,a_k)} = f\left(x_k, \beta_{a_k}\right)$$

Treatment Level Consistency

FOR ALL TREATMENTS

- Apply consistency equation at the level of the dose response curve

$$d_{(x_c,a_c),(x_k,a_k)} = d_{(x_1,a_1),(x_k,a_k)} - d_{(x_1,a_1),(x_c,a_c)}$$



- Methods to check consistency available
  Pedder et al. (2022) https://doi.org/10.1002/sim.9270

19

Dose-response: Emax model

Dose-response function:

$$E_0 + f(x, \beta_a)$$

= 0 for placebo

treatement defined by dose x of agent a

$$f(x, \beta_a) = \frac{Emax_a \, x}{ED50_a + x}$$

20

Dose-response MBNMA

Dose-response function:

$$E_0 + f(x, \beta_a)$$

treatement defined by dose *x* of agent *a*

$$\theta_{i,k} = \begin{cases} \mu_i & k = 1 \\ \mu_i + \delta_{i,k} & k \geq 2 \end{cases}$$

i = study
k = arm

Dose-response function on relative effects

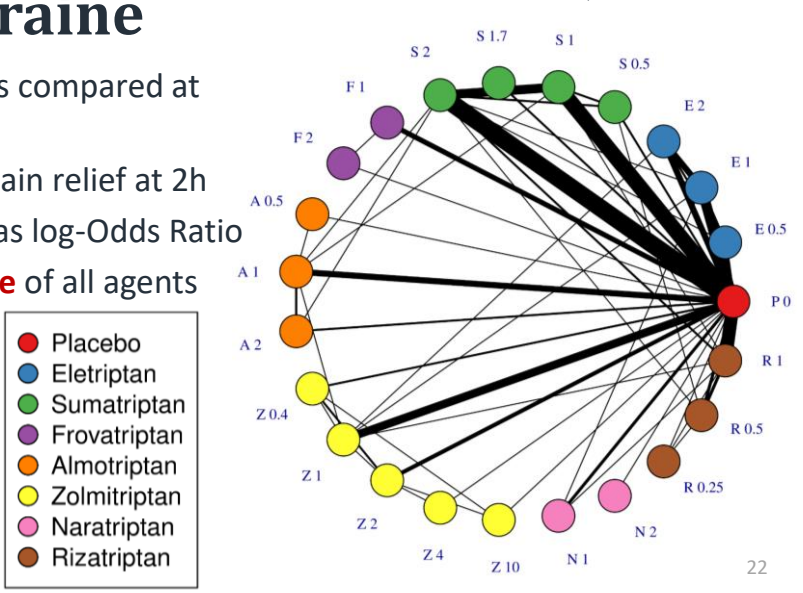
$$\delta_{i,k} = (E_{0,i} + f(x_{i,k}, a_{i,k})) - (E_{0,i} + f(x_{i,1}, a_{i,1}))$$

$$\delta_{i,k} = f(x_{i,k}, a_{i,k}) - f(x_{i,1}, a_{i,1})$$

21

Illustrative dataset: Triptans in migraine

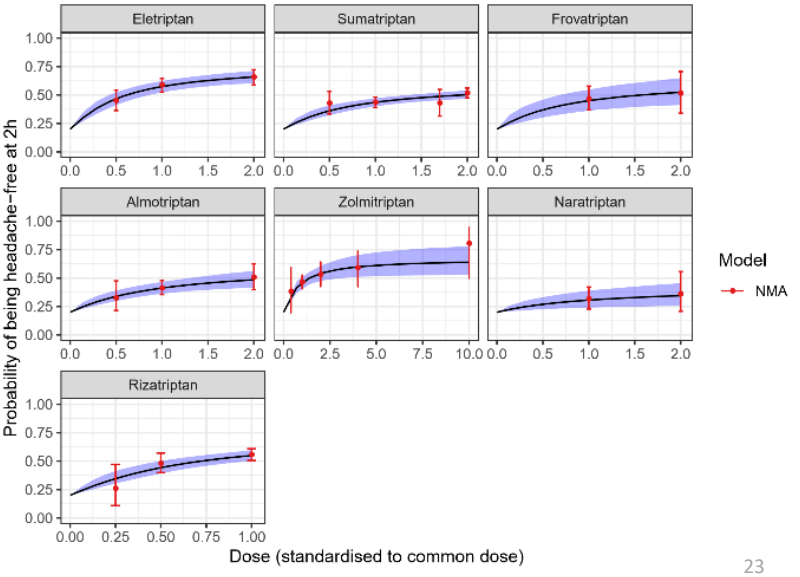
- 70 studies of 8 interventions compared at multiple doses
- Outcome: % patients with pain relief at 2h
- Treatment effect modelled as log-Odds Ratio
- Placebo treated as **zero dose** of all agents



22

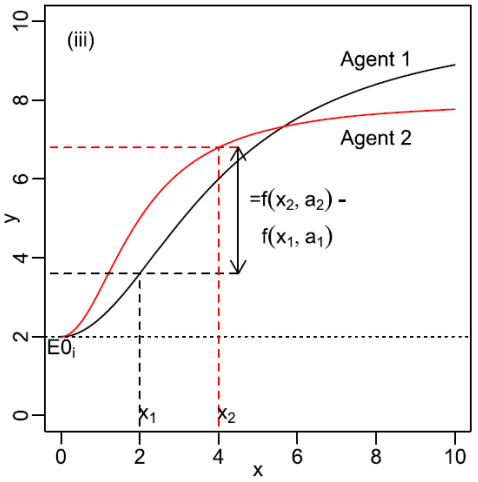
Triptans: connected network

- 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



23

Relative effect at any dose



Dose x_2 of Agent a_2 compared to Dose x_1 of Agent a_1

$$\delta = f(x_2, a_2) - f(x_1, a_1)$$

24

Implementation

- Compare:
  - Lumped NMA: all doses assumed to have same effect (ignore dose)
  - Split NMA: no relationship assumed across doses of the same agent
  - Different model-based NMA
    - E.g. linear, Emax, others
- Assess goodness of fit (e.g. using DIC or similar), residual deviance and heterogeneity
- Check consistency

25

MBNMAdose

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

- Fits Bayesian dose-response MBNMA
- Models 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
  - Outputs for comparing results from two models e.g. MBNMA vs NMA
  - Outcome predictions at different doses
- Includes several example networks, including the triptans network
- **Models also relevant for non-drug interventions**
  - E.g. physical activity: dose is exercise intensity

26

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)

- Dose response not monotonic
- User-specified function

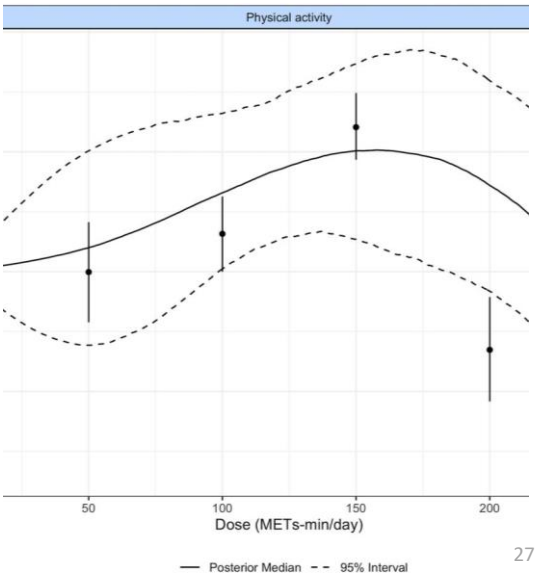


Figure 3 Dose-response relationship between physical activity dosage and functional capacity.

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

British Journal of Sports Medicine

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

27

Comments

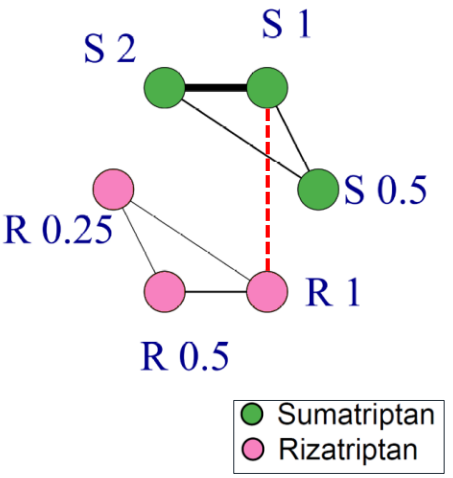
- Sharing of information via dose-response relationship can:
  - improve precision
- Uses relevant evidence on the interventions of interest
  - If there is a dose-response relationship, then evidence on an agent at one dose provides evidence that is relevant for other doses
- Availability of evidence 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

28

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

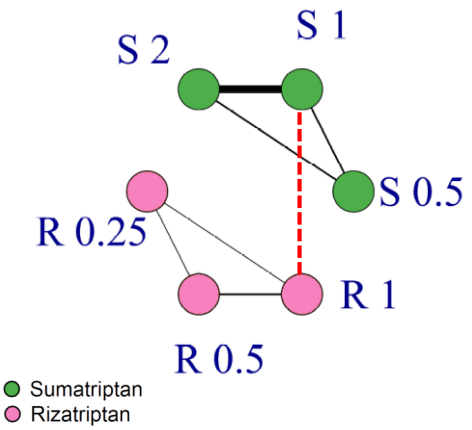


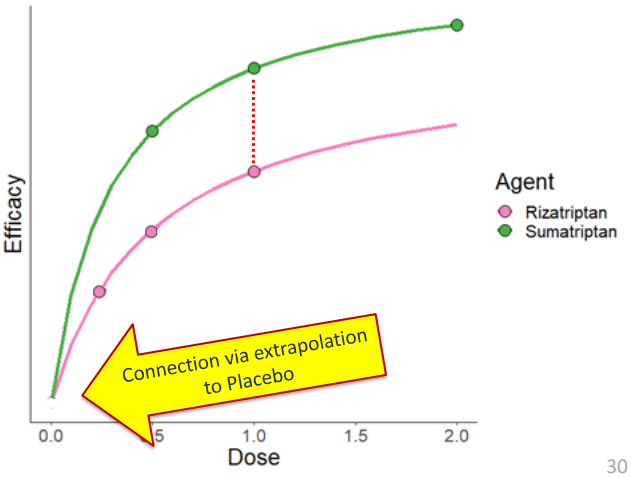
Pedder et al. (2021) https://doi.org/10.1177/0272989X20983315

29

Joining the dots via Placebo

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





30

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
- 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.

31

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

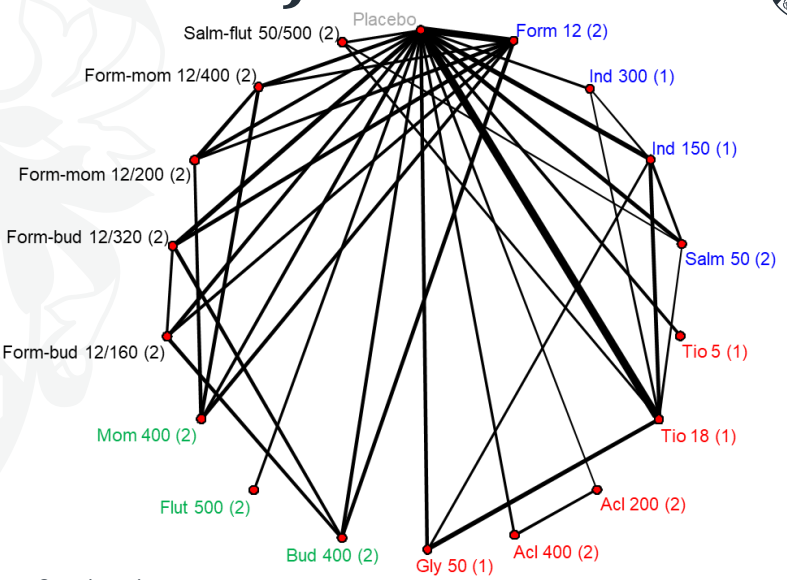
32

Example: COPD

- Treatments for chronic obstructive pulmonary disease (COPD)
  - Cochrane Review: Kew at al 2014
    http://dx.doi.org/10.1002/14651858.CD010844.pub2
- Outcome: mean difference on St George's Respiratory Questionnaire (SGRQ) total score at 6 months
- 25 trials, 18 treatments compared
  - 39 pairwise comparisons made
- Treatments belong to 5 classes: Placebo, Long-active β_2-agonists (LABA), Long-acting muscarinic antagonists (LAMA), Inhaled corticosteroids (ICS) and LABA+ICS.

33

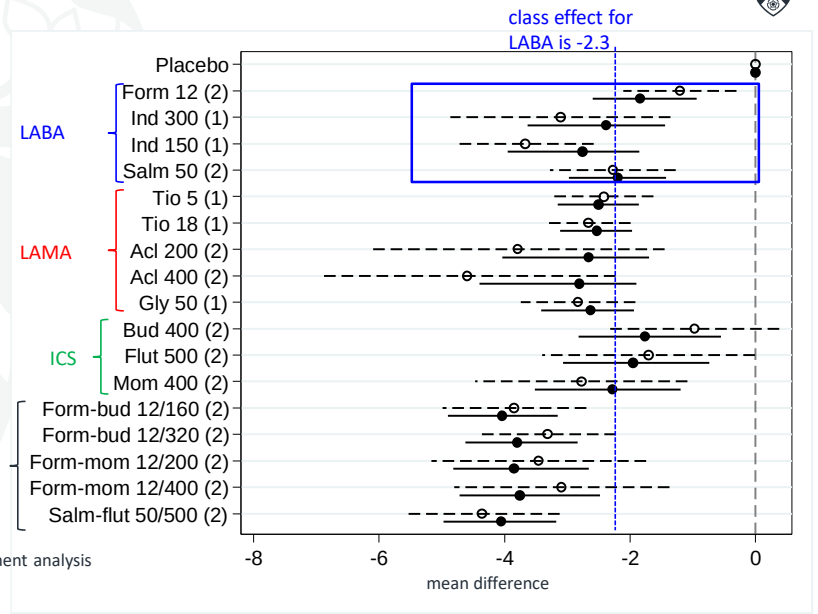
SGRQ (6 months)



SGRQ: St George's Respiratory Questionnaire

34

NMA with and without class effects



Dashed lines: individual treatment analysis
Solid lines: class analysis

35

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) https://doi.org/10.1177/0272989X221097081

36

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?

37

Thank you

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